المجلس الصحي السعودي
Saudi Health Council
الأمانة العامة ١٥٧

تماشيا مع رؤية المملكة ٢٠٣٠ والتي تهدف لدعم تحول القطاع الصحي، وإدراكًا لدور الأدلة السريرية المبنية على البراهين في تحسين جودة الممارسة الصحية والمساهمة في تعزيز صحة المرضى. وسعيا لتوحيد معايير الممارسات الصحية المقدمة في القطاع الصحي في المملكة، تم إعداد سلسلة من الأدلة السريرية الوطنية المبنية على البراهين.

يقدم لكم المجلس الصحي السعودي ممثلا بالمركز الوطني للطب المبني على البراهين ووزارة الصحة ممثلة بشركة الصحة القابضة مسودة الإصدار الأول لدليل سريري وطني مبني على البراهين بعنوان **" الدليل السريري السعودي ٢٠٢٢ لأمراض الكلى المزمنة: علاج ارتفاع ضغط الدم وزراعة الكلى للبالغين والأطفال"** والذي تم إعداده من قبل خبراء محليين وعالميين. وكجزء من آلية اعتماده كدليل وطني، نطرح للعموم هذه المسودة لإبداء الملاحظات والمقترحات.

علما بأن آخر موعد لاستقبال مقترحاتكم وملاحظاتكم بتاريخ ١٤٤٣/١١/٢٩ هـ

نرجو إرسال الملاحظات على الإيميل التالي: ncebhp@shc.gov.sa

Aiming to support the healthcare transformation pillar of Vision 2030, recognizing the role of evidence-based guidelines in improving quality of care and enhancing patients' outcomes and striving to unify the standard of healthcare across the kingdom, a series of national evidence-based guidelines will be developed to support that ultimate aim.

Under the auspice of the Saudi Health Council (SHC) represented by the National Center of Evidence-Based Medicine (NCEBM) and the Ministry of Health and its Health Holding Company (HHC) presented to you this draft version of the first national evidence-based guideline titled as **"2022 Saudi Guideline for Chronic Kidney Disease: Blood Pressure Management and Kidney Replacement Therapy in Adults and Children"** which is developed by local and international experts in the field.

As part of the approval process to make it a national guideline we would like to project this guideline for public consultation. Please feel free to comment and give feedback considering the following questions as an example:

- Has all of the relevant evidence been considered?
- Are there errors in the content?
- Are the recommendations demonstrate reasonable interpretations of the evidence?
- Are the recommendations a suitable basis for a national standard?

Note that the last date for receiving your feedback is on **28/06/2022**

Please send your feedback to the following email: ncebhp@shc.gov.sa

2022 Saudi Guideline for Chronic Kidney Disease: Blood Pressure Management and Kidney Replacement Therapy in Adults and Children

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1. Summary table

Main ICD-10 code	N18 Chronic kidney disease (CKD)
Related ICD-10 codes	N18.1 CKD, stage 1 N18.2 CKD, stage 2 (mild) N18.3 CKD, stage 3 (moderate) N18.30 CKD, stage 3 unspecified N18.31 CKD, stage 3a N18.32 CKD, stage 3b N18.4 CKD, stage 4 (severe) N18.5 CKD, stage 5 N18.6 End stage kidney disease N18.9 CKD, unspecified
Guideline publication date	May 2022
Expected review date	May 2027
Target audience	• Healthcare professionals who care for children and adult patients with CKD. • Providers of kidney replacement therapy and conservative management. • People with CKD, their families, and caregivers. • Policy makers involved in developing national health population programs.
	This guideline adapted a prioritized subset of clinical questions from the following two clinical guidelines: • KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD (Cheung et al., 2021): Clinical questions 1-4. • Renal replacement therapy and conservative management from The National Institute for Health and Care Excellence guideline (NICE-NG107, 2018): Clinical questions 5-12.

2. Executive summary

2.1. Introduction

This guideline was developed by a chronic kidney disease (CKD) Task Force of local experts under the auspices of the National Guidelines Center in Saudi Arabia. This new Center was commissioned in 2021 by the Saudi Arabian Ministry of Health and its Health Holding Company to support the healthcare transformation pillar of Vision 2030 (https://www.vision2030.gov.sa/).

CKD is a major health problem globally and in Saudi Arabia, with its incidence and prevalence having significantly increased over the last several decades. Kidney disease has been reported as the 3rd leading cause of death in Saudi Arabia, and the country's age-adjusted death rate from kidney disease is the 5th highest one in the world (World Health Rankings, n.d.).

2.2. Methods

The CKD Task Force included adult and pediatric nephrologists, and kidney transplant (KT) specialists from across the Kingdom as well as a clinical pharmacist and a patient representative.

In order to make the best use of recent high-quality efforts locally and internationally, guideline development followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE)-ADOLOPMENT methodology, an internationally accepted approach for adoption, adaptation, and de novo guideline development (Schünemann et al., 2017).

Using a systematic approach, the following two guidelines were selected as starting points for guideline adaptation:

- KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD (Cheung et al., 2021).
- Renal replacement therapy and conservative management from the (National Institute for Health and Care Excellence guideline (NICE-NG107, 2018).

The CKD Task Force prioritized 4 clinical questions from the KDIGO guideline on blood pressure management, and another 8 questions on modalities of kidney replacement therapy (KRT) together with associated clinical outcomes. The evidence base for each question was updated in October 2021 in line with the source guidelines' search strategies, and the quality of the new body of evidence evaluated using the GRADE approach (Schünemann et al., 2013). Additional literature searches were run on local contextual factors (epidemiology, values and preferences, equity, acceptability, feasibility, implementation, and cost). The evidence summaries informed the creation of GRADE Evidence-to-

Decision (EtD) frameworks for each question and in turn the formulation of associated guideline recommendations. For the list of questions and recommendations, see section 2.4, and for more details on the guideline's methodology, see section 9.

2.3. What does this guideline add?

This guideline adds new, updated, and localized evidence to previous recommendations for blood pressure management and KRT in adults and children with CKD in Saudi Arabia. The aim of this guideline is to facilitate decision-making in clinical practice, to improve specific outcomes, and to guide healthcare systems, taking into account local considerations and expertise. In line with previous guidelines from Saudi Arabia (Albarrak et al., 2021), the target audience includes adult and pediatric general practitioners and kidney specialists, as well as other providers who care for people with CKD.

Compared to previous efforts, this guideline follows the rigorous GRADE-ADOLOPMENT methodology, aimed at assessing not only the quality of the evidence, but also the numerous factors that influence healthcare decisions, such as locally available intervention options, the balance of benefits and harms, certainty of the evidence, impact of patient characteristics, circumstances, values, and preferences on clinical decisions, and of social, economic, or other practical considerations on the outcome of a particular care option.

2.4. Questions and recommendations

#	Question	Recommendation
1	Should ACEi or ARBs versus other antihypertensive agents be used for hypertension treatment in children with CKD?	In children with CKD, the CKD Task Force suggests using ACEi or ARBs rather than other antihypertensive agents for hypertension treatment ***(conditional recommendation, very low certainty in the evidence of effects)***. This recommendation applies to all children with CKD stages 1-3 and to those with advanced CKD (stages 4-5) who are not receiving KRT.
2	Should non-RASi versus RASi be used for hypertension treatment in adults with CKD?	In adults with CKD, the CKD Task Force suggests using RASi over non-RASi for hypertension treatment ***(conditional recommendation, low certainty in the evidence of effects)***. This recommendation

		applies to all adults with CKD stages 1-3 and to those with advanced CKD (stages 4-5) who are not receiving KRT.
3	Should intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets versus standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets be used for hypertension treatment in children with CKD?	In children with CKD, the CKD Task Force suggests using intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets rather than standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets for hypertension treatment ***(conditional recommendation, low certainty in the evidence of effects)***.
4	Should intensive (SBP <120 mm Hg) blood pressure targets versus standard (SBP <140mm Hg) blood pressure targets be used for hypertension treatment in adults with CKD?	In adults with CKD, the CKD Task Force suggests using intensive (SBP <120 mm Hg) blood pressure targets rather than standard (SBP <140mm Hg) blood pressure targets for hypertension treatment ***(conditional recommendation, low certainty in the evidence of effects)***.
5	Should early assessment (i.e., eGFR 20 mL/min/1.73m2) versus late assessment (i.e., eGFR <20 mL/min/1.73m2) be used for KRT in patients with CKD?	In patients with CKD, the CKD Task Force suggests using early assessment (i.e., eGFR 20 mL/min/1.73m2) for KRT rather than late assessment (i.e., eGFR <20 mL/min/1.73m2) for KRT ***(conditional recommendation, very low certainty in the evidence of effects)***.
6	Should any late preparation strategy* (based on eGFR or by anticipated time to start of KRT) versus any early preparation strategy (based on eGFR or by anticipated time to start of KRT) be used in patients with CKD stage 4 to 5 to prepare the patient for the start of KRT?	In patients with CKD stage 4 to 5, the CKD Task Force suggests using an early preparation strategy* (based on eGFR or by anticipated time to start of KRT) rather than a late preparation strategy (by eGFR or by anticipated time to start of KRT) to prepare the patient for the start of KRT **(conditional recommendation, very low certainty in the evidence of effects).**

	*eGFR 20 mL/min/1.73m2; anticipated time for PD (2-4 weeks); hemodialysis (4-8 weeks for AVF to heal).	
7	Should a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms that he/she is experiencing versus not using such strategy be used in patients who are undergoing or being assessed for KRT or conservative management of established kidney failure?	In patients who are undergoing or being assessed for KRT or conservative management of established kidney failure, the CKD Task Force suggests using a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms he/she is experiencing rather than not using such a strategy ***(conditional recommendation, very low certainty in the evidence of effects)***.
8	Should initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms versus initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms* be used in previously KRT-naive adults requiring KRT for deteriorating CKD?	In previously KRT-naive adults requiring KRT for deteriorating CKD, the CKD Task Force suggests initiating KRT late (i.e., eGFR 5-7 mL/min/1.73m2) or based on severe symptoms* rather than initiating KRT early (i.e., eGFR 10-15 mL/min/1.73m2) or based on moderate symptoms ***(conditional recommendation, very low certainty in the evidence of effects)***.
	* Severe uremic symptoms and/or uncontrollable fluid overload	
9	Should any KRT modality versus conservative management be used in certain groups* of patients requiring KRT for CKD?	In certain groups* of patients requiring KRT for CKD, the CKD Task Force suggests using conservative management rather than any KRT modality for CKD treatment ***(conditional recommendation, very low certainty in the evidence of effects)***.
	***i.** those that choose not to undergo dialysis, **ii.** those who choose to withdraw from dialysis after a period of treatment, **iii.** those who are coming to the end of their lives while already on long-term dialysis, **iv.** those who have a failing transplant and decide not to return to dialysis.	
10	Should transferring between KRT modalities or discontinuing KRT based on suitable	In patients with CKD currently receiving KRT, the CKD Task Force suggests transferring

	clinical indicators* versus not transferring between modalities of KRT or discontinuing KRT based on suitable clinical indicators* or doing either at a later stage be used in patients with CKD currently receiving KRT?	between KRT modalities or discontinuing KRT based on suitable clinical indicators* rather than not transferring between modalities of KRT or discontinuing KRT based on suitable clinical indicators* or doing either at a later stage ***(conditional recommendation)***.
	*Vascular access failures, peritoneal membrane failure or failure of kidney graft.	
11	Should any frequency of regular review for any KRT modality or conservative management versus any other frequency of regular review be used in patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice?	In patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice, the CKD Task Force suggests regular review at a frequency tailored to the KRT modality or conservative management ***(conditional recommendation)***.
12	Should any type of information, education, or support versus any other type of information, education, or support be used in patients requiring KRT or conservative management (and their families or caregivers as appropriate)?	In patients requiring KRT or conservative management (and their families or caregivers as appropriate), the CKD Task Force suggests using individualized information, education, or support rather than other types of information, education, or support) ***(conditional recommendation, moderate certainty in the evidence of effects)***.

ACEi: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin receptor blockers; AVF: arteriovenous fistula; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; KRT: kidney replacement therapy; MAP: mean arterial pressure. Non-RASi: non-renin angiotensin system inhibition; PD: peritoneal dialysis; RASi: renin angiotensin system inhibition; SBP: systolic blood pressure.

3. Table of Contents

4. Introduction

Chronic Kidney Disease (CKD) is defined as "abnormalities of kidney structure or function, present for >3 months, with implications for the health of an individual, which can occur abruptly and either resolve or become chronic. The most serious outcome of CKD is end-stage kidney disease (ESKD) (Cheung et al., 2021).

CKD is classified based on cause, glomerular filtration rate category (G1–G5), and albuminuria category (A1-A3). The term CKD encompasses a range of disorders that affect kidney structure and/or function. Clinical presentation depends on the underlying cause, severity, and rate of progression.

Patients with early-stage kidney disease are often asymptomatic, causing delays in the diagnosis and early management of the underlying cause. Despite all attempts to optimize the management of CKD, many patients will progress to ESKD and require KRT.

4.1. Kidney damage

Damage to the kidney is most often inferred from markers rather than from direct examination of the kidney tissue. Analysis of these markers can give clues regarding the origin or localization of the damage, whether it's the parenchyma, large blood vessels or collecting systems. Two of these markers are proteinuria, a general term for the presence of increased amounts of protein in the urine, and albuminuria, which refers to abnormal loss of albumin in the urine.

Adult normative values for albuminuria and proteinuria are generally expressed as the urinary loss rate. The urinary loss rate of albumin and protein has commonly been referred to albumin excretion rate (AER) and protein excretion rate. Based on AER, CKD is identified by a threshold of ≥30 mg/24 hours sustained for >3 months (approximately equivalent to an albumin:creatinine ratio [ACR] in a random untimed urine sample of ≥30 mg/g or ≥3mg/mmol) (KDIGO, 2013a).

In children, normal protein excretion is defined as <4 mg/m2/hour, abnormal proteinuria is defined as 4-40 mg/ m2/hour, and nephrotic proteinuria is defined as protein excretion of >40 mg/m2/hour or >1 gm/m2/day in a 24 hour-urine collection or a spot urine protein:creatinine ratio of >2 mg/mg (Ariceta, 2011; Singh et al., 2019).

For the initial detection of proteinuria in adults, children, and young people urine ACR rather than protein:creatinine ratio should be used because of the greater sensitivity for low levels of proteinuria. In a subsequent early morning sample, an ACR between 3 mg/mmol and 70 mg/mmol should be checked to confirm the result. A repeat sample is not needed if the initial ACR is 70 mg/mmol or more. A confirmed ACR of ≥3 mg/mmol is regarded as clinically important proteinuria (NICE-NG203, 2021).

4.2. Classification

Classification of CKD is based on the presence or absence of systemic disease and location of pathologic-anatomic findings within the kidney (Rovin et al., 2021).

Classification of chronic kidney disease by glomerular filtration rate category	
G1: normal or high kidney function	GFR: greater than 90 mL/minute/1.73 m²
G2: mildly decreased kidney function	GFR: 60 to 89 mL/minute/1.73 m²
G3a: mildly to moderately decreased kidney function	GFR: 45 to 59 mL/minute/1.73 m²
G3b: moderately to severely decreased kidney function	GFR: 30 to 44 mL/minute/1.73 m²
G4: severely decreased kidney function	GFR: 15 to 29 mL/minute/1.73 m²
G5: kidney failure	GFR: less than 15 mL/minute/1.73 m²
Patients receiving dialysis are indicated with a "D" (for example, G5D)	

G: grade; GFR: Glomerular filtration rate.

Classification of chronic kidney disease by albuminuria category*	
A1: normal to mildly increased	ACR: less than 30 mg/g
	AER: less than 30 mg/24 hours
A2: moderately increased	ACR: 30 to 300 mg/g
	AER: 30 to 300 mg/24 hours
A3: severely increased	ACR: greater than 300 mg/g
	AER: greater than 300 mg/24 hours
*Combined GFR and albuminuria stage more accurately denotes risk of progression of CKD.	

ACR: albumin:creatinine ratio; AER: albumin excretion rate; GFR: glomerular filtration rate.

Current Chronic Kidney Disease nomenclature used by KDIGO (reproduced with permission from (Rovin et al., 2021)**).**

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1,73 m²) Description and range	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: Low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: High risk; Red: Very high risk; GFR: glomerular filtration rate

4.3. Epidemiology

The incidence and prevalence of CKD have reportedly increased in Saudi Arabia over the last several decades. However, nationwide population-based registries reflecting the true burden of CKD and ESKD are not readily available, and it is possible that real estimates surpass what is reflected in this current guideline. Therefore, current estimates mostly source from either single-center observational studies, or studies conducted almost or over a decade ago (Ahmed et al., 2014a; Al-Homrany and Abolfotoh, 1998; Alsuwaida et al., 2010; Mitwalli et al., 1995).

In a community-based screening program in commercial centers in Riyadh, participants were screened for CKD based on creatinine levels and eGFR. In the study, comprising 491 volunteers, the overall CKD all-stage prevalence was 5.7% (Alsuwaida et al., 2010). The prevalence of CKD stages 1, 2 and 3 was 3.5%, 1.6% and 0.6%, respectively. In another cross-sectional, community-based study involving 13 cities and 2800 volunteers from around the city of Hail, the estimated overall prevalence of CKD was 7.8% (Ahmed et al., 2014a). Even though the prevalence of CKD does not appear to be very high, kidney disease accounts for 6.19% of deaths due to all causes, making it the 3rd leading cause of death

in Saudi Arabia according to WHO estimates from 2018. The age-adjusted death rate is 45.22 per 100,000 of population, placing Saudi Arabia in 5th position in the world (World Health Rankings, n.d.).

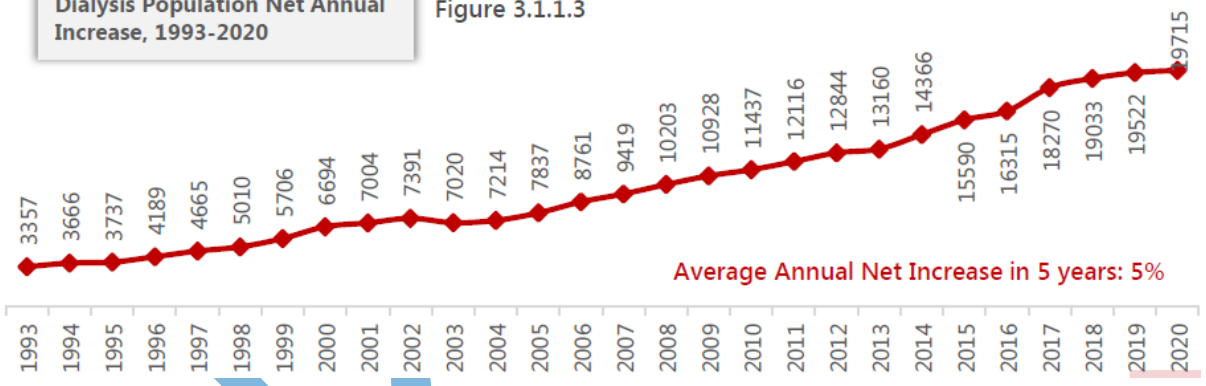
Kidney replacement therapy

According to the Saudi Center for Organ Transplantation (SCOT), diabetic nephropathy and population ageing have been identified as the two major factors behind the development of CKD (Saudi Center for Organ Transplantation, 2020). Since the number of people diagnosed with diabetes in Saudi Arabia has quadrupled in the last 10 years according to data from the International Diabetes Federation, the incidence of diabetic nephropathy and CKD is only expected to increase in Saudi Arabia (International Diabetes Federation, n.d.).

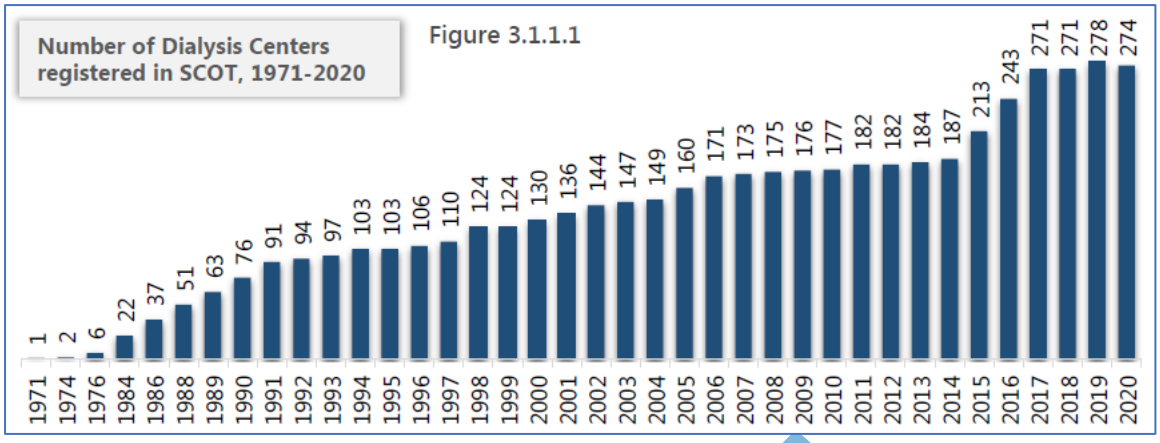
The high burden of kidney disease is also reflected by the growing number of people requiring KRT. According to SCOT estimates, as of 2020, there were a total of 21,496 patients requiring dialysis in Saudi Arabia, of which 19,715 patients were on hemodialysis (92%) and 1,781 patients on peritoneal dialysis (PD) (8%). Every year, the number of patients undergoing dialysis, both modalities combined, increases by a net 5%, as shown by the figure below (reproduced with permission from (Saudi Center for Organ Transplantation, 2020)).

Dialysis Population Net Annual Increase, 1993-2020

Figure 3.1.1.3



Consequently, the number of centers providing dialysis services has also increased, growing by almost 50% in the last 10 years. The number of available centers in the Saudi Arabia is shown in the figure below (reproduced with permission from (Saudi Center for Organ Transplantation, 2020)).

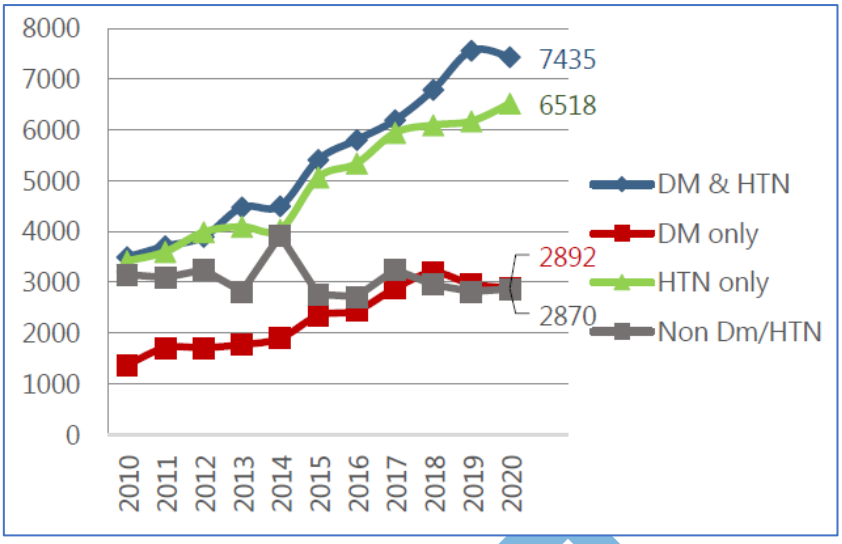


Hypertension and chronic kidney disease

High blood pressure is one of the major causes of CKD. At the same time, kidney disease can cause or worsen hypertension secondary to increased systemic vascular resistance and volume expansion (Tedla et al., 2011). In a cross-sectional survey conducted in 13 cities around the northwestern city of Hail, the prevalence of hypertension was found to be 33.4% (Ahmed et al., 2014b). According to SCOT, by far the two most common causes of ESKD among patients undergoing hemodialysis are diabetic nephropathy (42%) and hypertensive nephropathy (34%). These and other causes of ESKD in Saudi Arabia are shown in the image below (reproduced with permission from (Saudi Center for Organ Transplantation, 2020)).

Cause of Renal Failure	N	%
Diabetic Nephropathy	8294	42%
Hypertensive Nephropathy	6713	34%
Unknown Etiology	1693	9%
Glumerulonephritis	849	4%
Others	478	2%
Obstructive Uropathy	489	2%
Congenital Malformation	411	2%
Heredofamilial Disease	465	2%
Vasculitis	208	1%
Pregnancy Related	115	1%
Total	**19715**	**100%**

In addition, the number of patients with concomitant diabetes mellitus and hypertension, or hypertension alone, has been shown to increase progressively in the last 10 years as observed in the image below (reproduced with permission from (Saudi Center for Organ Transplantation, 2020)).



Children and chronic kidney disease

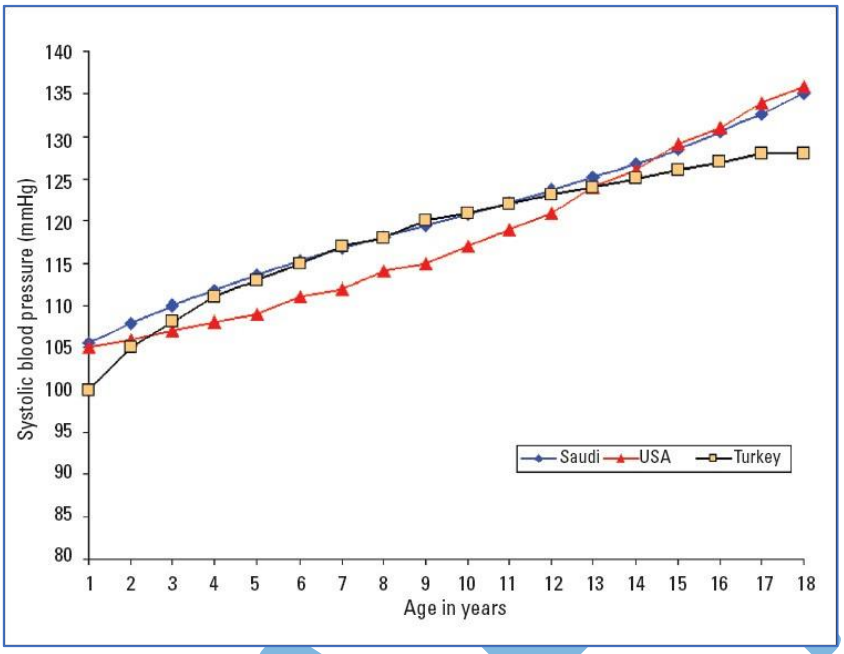
In many countries, including Saudi Arabia, literature on the etiology, rate, and risk factors for progression, comorbidities, and outcomes in children with CKD is remarkably scarce. The consequences of this lack of evidence include delays in diagnosis and timely treatment, impacting the child's quality of life and survival. Moreover, reports indicate that mortality among children who progress to ESKD is 30 to 50 times higher compared to that in the general population (Harambat et al., 2012; Mitsnefes et al., 2013). Hence, research and evidence-based recommendations are greatly needed for this population.

A small retrospective chart review of 66 children (35 boys and 31 girls) followed up over a four-year period showed that 76% had a severely decreased kidney function (Grade 4-5), with half of them in frank ESKD (Grade 5). The main causes of CKD in this population were congenital abnormalities of the renal system (50%), neurogenic bladder (nearly 20%), acquired causes (14%), and hereditary conditions (12%). The study also exposed the considerable delay in referring children CKD to a pediatric nephrologist as well as in the management of preventable causes such as neurogenic bladder associated with spina bifida (Kari, 2006).

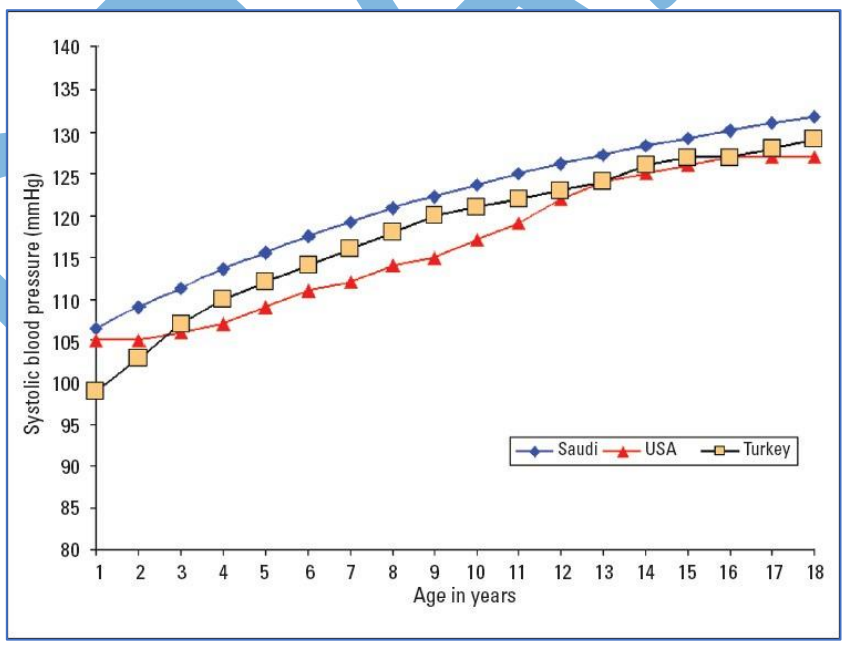
Blood pressure values for Saudi children and adolescents from birth to 18 years are shown in Appendix 14.3.

A comparison of blood pressures for children in KSA, Turkey and the United States are found in the four figures below (Al Salloum et al., 2009).

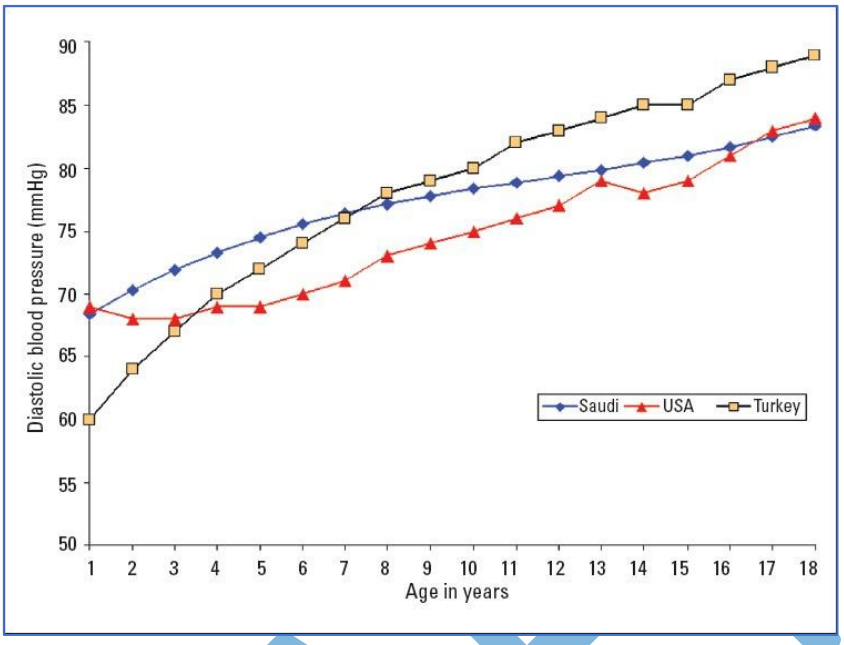
Comparison of the 90th percentile of systolic blood pressure levels of Saudi Arab boys with the values of American and Turkish boys



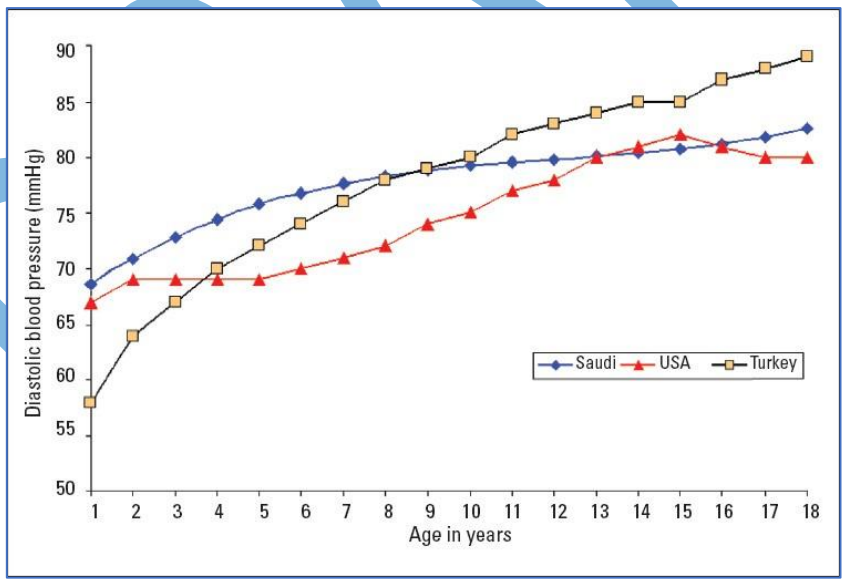
Comparison of the 90th percentile of systolic blood pressure levels of Saudi Arab girls with the values of American and Turkish girls



Comparison of the 90th percentile of diastolic blood pressure levels of Saudi Arab boys with the values of American and Turkish boys



Comparison of the 90th percentile of diastolic blood pressure levels of Saudi Arab girls with the values of American and Turkish girls



4.4. What do other guidelines say?

The table below contains a comparison of recommendations for blood pressure management from the 2021 KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD (Cheung et al., 2021) and NICE CKD: assessment and management guideline (NICE-NG203, 2021).

	KDIGO 2021	NICE 2021	Comments
Blood pressure targets: adults	Based on standardized measurement	ACR <70 mg/mmol: clinic blood pressure goal <140/90 mm Hg	KDIGO and NICE were in general agreement about blood pressure management except for blood pressure targets in adults. KDIGO relied on a subgroup analysis from the SPRINT trial to support a lower blood pressure target in adults with CKD and used only SBP for its target. However, KDIGO emphasized that standardized blood pressure was used rather than clinic or office blood pressure measurement
	Goal SBP <120 mm Hg	ACR ≥70 mg/mmol: clinic blood pressure <130/80 mm Hg	
Blood pressure targets: children and young people	24-hour MAP by ambulatory blood pressure monitoring: <50th percentile for age, sex, and height	ACR ≥70 mg/mmol: clinic SBP <50th percentile for height	KDIGO added as practice point that ABPM should be performed annually, supplemented by standardized auscultatory office blood pressure every 3-6 months in children with CKD; however, if this is not possible, a reasonable approach is to obtain a manual office-based auscultatory or oscillometric blood pressure measurement in a standardized manner, targeting achieved SBP at <90th percentile for age, sex, and height of normal children
Renin-angiotensin system inhibition: initiation	Titrate ACEi or ARB to highest tolerated approved dose	Optimal tolerated licensed dose for adults, children and young people with CKD and hypertension with ACR category A3 or above	KDIGO and NICE were in agreement to not combine renin-angiotensin system antagonists
	Monitor blood pressure, serum creatinine, serum potassium within 2-4 weeks of initiation or change in dose	Adults with diabetes: ACEi or ARB if ACR is ≥3 mg/mmol	
		Monitor eGFR and serum potassium 1-2 weeks after	

		initiation and after each dose increase	
Renin-angiotensin system inhibition: management of hyperkalemia	Continue ACEi/ARB unless serum creatinine rises >30% within 4 weeks of initiation or change in dosage	Assess and treat for any factors that promote hyperkalemia; frequent monitoring may be needed	These guidelines were in general agreement that an attempt at medical management of mild hyperkalemia should be made before discontinuing an ACEi/ARB
	Consider discontinuing ACEi/ARB if symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment	Do not start ACEi/ARB if serum potassium >5.0 mmol/L After starting, do not modify dose if baseline GFR decreases <25% OR baseline serum creatinine increases <30%; repeat test in 1-2 weeks	

		If adult eGFR decreases >25% or serum creatinine increases >30%: investigate possible causes such as volume depletion or other medication (e.g., NSAIDs) If no cause of hyperkalemia is found, stop or lower ACEi/ARB dose and add alternate antihypertensive if needed Stop ACEi/ARB if serum potassium >6.0 mmol/L and exacerbating medicines have been discontinued	

ABPM: ambulatory blood pressure monitoring; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blockers; ACR: albumin-creatinine ratio; NSAIDs: non-steroidal anti-inflammatory drugs; KDIGO: Kidney Disease Improving Global Outcomes; MAP: mean arterial pressure. NICE: National Institute for Health and Care Excellence; SBP: systolic blood pressure; SPRINT: The Systolic Blood Pressure Intervention Trial.

The table below shows a comparison for kidney replacement therapy recommendations between KDIGO and NICE guidelines:

	KDIGO	NICE
Timing of kidney replacement therapy	Recommends timely referral for planning KRT in people with progressive CKD in whom the risk of kidney failure within 1 year is 10-20% or higher, as determined by validated risk prediction tools (KDIGO, 2013b)	Provide adults with CKD and their family members or caregivers information about their 5-year risk of needing KRT (NICE-NG203, 2021) (measured using the 4-variable Kidney Failure Risk Equation) (Major et al., 2019)

		Adults with CKD are at increased risk of progression to end-stage kidney disease if they have a sustained decrease of GFR of either of the following over 12 months: ≥25% or ≥15 mL/min/1.73 m^2 (NICE-NG203, 2021). Extrapolate the current rate of decline of GFR and take into account when planning intervention strategies, particularly if it suggests that the person might need KRT in their lifetime (NICE-NG203, 2021) Start assessment for KRT or conservative management at least one year before therapy is likely to be needed, including for those with a failing transplant (NICE-NG107, 2018)
Dialysis	Suggests that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment (KDIGO, 2013b) This often but not always occurs in the GFR range of 5-10 mL/min/1.73 m^2 (KDIGO, 2013b) Recommends a goal of encouraging and supporting patients to select a home-based therapy (PD or home hemodialysis) or self-care dialysis and to identify ways of overcoming barriers to this goal, but recognizes that many patients in many parts of the world will need or prefer in-center hemodialysis and that available dialysis modalities in some countries may depend upon local circumstances (Chan et al., 2019)	Consider starting dialysis when indicated by the impact of symptoms of uremia on daily living, or biochemical measures or uncontrollable fluid overload, or at an estimated glomerular filtration rate (eGFR) of about 5-7 mL/min/1.73 m^2 without symptoms (NICE-NG107, 2018) Offer a choice of dialysis modalities at home or in a center, ensuring that the decision is informed by clinical considerations and patient preferences (NICE-NG107, 2018)
Kidney transplantation	Recommends preemptive transplantation with a living kidney donor as the preferred treatment for transplant-eligible CKD patients (Chadban et al., 2020)	Offer a preemptive living donor transplant (when there is a suitable living donor) or preemptive listing for deceased donor transplantation to people considered eligible after a full assessment (NICE-NG107, 2018)

	Preemptive transplantation (living or deceased donor) recommended for adults when the estimated glomerular filtration rate (eGFR) is <10mL/min/1.73 m^2 or earlier with symptoms (Chadban et al., 2020) Preemptive transplantation (living or deceased donor) recommended for children when the eGFR is <15mL/min/1.73 m^2 or earlier with symptoms (Chadban et al., 2020)	
Conservative management	An option for people who choose not to pursue KRT that should be supported by a comprehensive and culturally appropriate management program (KDIGO, 2013b)	Offer a choice of KRT or conservative management to people who are likely to need KRT (NICE-NG107, 2018) Conservative management for children should only be considered within appropriate regulatory frameworks (NICE-NG107, 2018)

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blockers; KDIGO: Kidney Disease Improving Global Outcomes; NICE: National Institute for Health and Care Excellence; PD: peritoneal dialysis.

5. Scope and purpose

Stakeholders across the healthcare spectrum prioritized CKD as an initial subject for guideline development during a comprehensive engagement in the first phase of the new National Guidelines Center. The participants recognized the condition's high disease burden in Saudi Arabia and the need for localized recommendations.

This guideline covers the care and management of people with CKD regarding blood pressure and KRT. Patients with any degree of CKD but without significant comorbidities requiring adjustment or modification of the recommendations were included.

The purpose of this guideline is to provide evidence-based recommendations for blood pressure management and KRT in adults and children with CKD. Important outcomes related to the 12 clinical questions selected will be included, such as mortality, adverse events, quality of life, transplantation rates, development of ESKD, and nutritional status.

This guideline is aimed at adult and pediatric nephrologists, and members of the caregiving team, including dialysis nurses, therapists, and technicians, clinical pharmacists, as well as policy makers involved in developing national health population programs.

6. Prioritized questions

Q1	Should ACEi or ARBs versus other antihypertensive agents be used for hypertension treatment in children with CKD?
Q2	Should non-RASi versus RASi be used for hypertension treatment in adults with CKD?
Q3	Should intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets versus standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets be used for hypertension treatment in children with CKD?
Q4	Should intensive (SBP <120 mm Hg) blood pressure targets compared to standard (SBP <140mm Hg) blood pressure targets be used for hypertension treatment in adults with CKD?
Q5	Should early assessment (i.e., eGFR 20 mL/min/1.73m2) versus late assessment (i.e., eGFR <20 mL/min/1.73m2) be used for KRT in patients with CKD?
Q6	Should any late preparation strategy* (based on eGFR or by anticipated time to start of KRT) versus any early preparation strategy (based on eGFR or by anticipated time to start of KRT) be used in patients with CKD stage 4 to 5 to prepare the patient for the start of KRT?
Q7	Should a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms that he/she is experiencing versus not using such strategy be used in patients who are undergoing or being assessed for KRT or conservative management of established kidney failure?
Q8	Should initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms versus initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms be used in previously KRT-naive adults requiring KRT for deteriorating CKD?
Q9	Should any KRT modality versus conservative management be used in certain groups* of patients requiring KRT for CKD?
Q10	Should transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators* versus not transferring between modalities of KRT or discontinuing KRT based on suitable clinical indicators* or doing either at a later stage be used in patients with CKD currently receiving KRT?
Q11	Should any frequency of regular review for any KRT modality or conservative management versus any other frequency of regular review be used in patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice?
Q12	Should any type of information, education, or support versus any other type of information, education, or support be used in patients requiring KRT or conservative management (and their families or caregivers as appropriate)?

ACEi: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin receptor blockers; AVF: arteriovenous fistula; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; KRT: kidney replacement therapy; MAP: mean arterial pressure. Non-RASi: non-renin angiotensin system inhibition; PD: peritoneal dialysis; RASi: renin angiotensin system inhibition; SBP: systolic blood pressure.

7. General issues for the correct interpretation and implementation of recommendations

7.1. Assumed values and preferences

Patient values and preferences were considered via 4 approaches:

1) Obtaining relevant content from the source guidelines used for adaptation.
2) Systematic literature searches in PubMed to summarize the best available evidence published in the last 10 years.
3) Clinical experience of the CKD Task Force members with direct patient contact.
4) Input by the patient representative.

The evidence summaries for values were provided as part of the EtD framework for each question to the CKD Task Force prior to the Recommendations Workshops.

7.2. Recommendations for children

Recommendations apply to pediatric populations in the following questions:

- Directly addressed: Question 1, Question 3
- Included: Question 5 to Question 12.

The age cut-off for children in the clinical studies in the evidence summaries in this guideline was 18 years, and this is also the age threshold the CKD Task Force have used for their recommendations. With regards to the management of young people with CKD aged 15 to 18 years (usually treated as adults in the Saudi health system), the Saudi CKD Guideline's recommendations applicable to this age group are those aimed at children; whereas those targeted at adults are applicable to patients aged 18 years and older only.

According to the KDIGO 2021 guideline, blood pressure should be measured in children's right arm, similar to the method used for adults (Cheung et al., 2021).

The 2017 American Academy of Pediatrics Clinical Practice guidelines provide considerable detail on correct blood pressure measurement methods but note that randomized controlled trials (RCTs) data targeting either oscillometric or auscultatory blood pressure measurements obtained in the clinic setting in children are lacking (Flynn et al., 2017).

In a clinic setting the initial blood pressure measurement may be oscillometric using a calibrated machine that has been validated for use in the pediatric population. Values obtained via oscillometric

measurements may be slightly higher, and conversion from oscillometric to auscultatory measurement on an individual basis is difficult (Flynn et al., 2017). Therefore, in patients with a high risk for elevated blood pressure, such as those with glomerular disease, the readings should be confirmed by auscultation (Warady et al., 2015). When conducting the blood pressure measurement with an oscillometric device, make sure the appropriate cuff size is used and that the upper-arm cuff monitor has been clinically validated in children. The validation status for oscillometric blood pressure devices in the pediatric age group can be checked at https://stridebp.org/ (n.d.).

Home blood pressure monitoring (HBPM) is useful for the initial evaluation of untreated children with suspected hypertension and for children with treated hypertension before each follow-up visit to the healthcare provider (Stergiou et al., 2019). The advantages of HBPM include the ability to obtain multiple blood pressure measurements outside the office setting, its relative ease of use, and a higher acceptance by patients and families (Cheung et al., 2021).

If home blood pressure monitoring is going to be performed, the following recommendations should be followed:

- It should be performed for a total of 7 days, and not less than 3 days, resulting in at least 6-12 readings per week.
- Morning and evening measurements should be performed after 5 minutes of sitting at rest and with 1 minute between readings.

At the time of publication of this guideline, the use of home blood pressure monitoring in children has not yet been endorsed for the diagnosis of hypertension by the American Academy of Pediatrics Clinical Practice Guideline due to lack of evidence (prospective, RCTs targeting HBPM) and a reliable method for converting standardized office blood pressure to home blood pressure or ambulatory blood pressure monitoring (ABPM) in children (Cheung et al., 2021).

For locally applicable tables of percentile values of SBP and diastolic blood pressure (DBP) according to age and sex, please use those developed by Al Salloum and team as part of the Health Profile of the Saudi Arabian Children and Adolescents project, see Appendix 14.3 (Al Salloum et al., 2009).

8. Recommendations

8.1. Question 1 – Antihypertensive agents in children with CKD

Should ACEi or ARBs versus other antihypertensive agents be used for hypertension treatment in children with CKD?

Recommendation

In children with CKD, the CKD Task Force suggests using ACEi or ARBs rather than other antihypertensive agents for hypertension treatment ***(conditional recommendation, very low certainty in the evidence of effects)***. This recommendation applies to all children with CKD stages 1-3 and to those with advanced CKD (stages 4-5) who are not receiving KRT.

Additional considerations

The CKD Task Force noted that hyperkalemia and progression of CKD (decrease in GFR) were known complications of antihypertensive medications and that the recommendation did not apply to children with advanced CKD who are not receiving dialysis in view of the increased risk of hyperkalemia in this population. They recommended that serum potassium levels be monitored 7-10 days after initiation of therapy and—in addition to GFR and albuminuria—during annual check-ups (more frequently in CKD stages G3b-G5).

Evidence summary

The literature search for the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure (BP) in CKD* (Cheung et al., 2021) identified one open-label RCT evaluating the effectiveness of enalapril compared to no enalapril (Hari et al., 2013). Our update search conducted in October 2021 found no additional studies for inclusion.

Benefits and harms: The included RCT of 41 children aged 2 to 18 years, with GFR between 15-60 mL/min/1.73 m2 compared enalapril at 0.4 mg/kg /day versus no enalapril (Hari et al., 2013). The evidence is very uncertain about the effect of enalapril on kidney failure (relative risk [RR], 0.45; 95% confidence interval [CI], 0.13-1.50; very low certainty in the evidence of effects]. At 12 months, the study found no difference in the rate and speed of GFR decline (mL/min/1.73 m2) (mean difference [MD], -1.2; 95% CI, -4.05 - 1.65; very low certainty in the evidence of effects) but a significantly greater mean proteinuria (urine protein/creatinine [mg/mg]) reduction with enalapril (MD, -1.13; 95% CI -1.82 - -0.44; very low certainty in the evidence of effects). Systolic (mmHg) (MD, -0.6; 95% CI -1.12 - 0.08; very low certainty in the evidence of effects) and diastolic blood pressure (mmHg) (MD, -0.64; 95% CI

-1.10 - 0.18; very low certainty in the evidence of effects) over the study period were significantly lower with enalapril. The RCT did not evaluate all-cause or cardiovascular mortality, cardiovascular morbidity, doubling serum creatinine, acute kidney injury, left ventricular hypertrophy, or encephalopathy. The CKD Task Force concluded that the balance between desirable and undesirable effects probably favors the use of antihypertensive agents.

Certainty in the evidence: We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, owing to very serious risk of bias, and serious imprecision of the estimates.

Values: A nominal group technique SONG-Kids study (Hanson et al., 2019) cited in the 2021 KDIGO guideline (Cheung et al., 2021) aimed to identify important outcomes for young people with CKD and their caregivers. It reported that both children with kidney disease and their caregivers rated kidney function as an important outcome, and blood pressure control was also rated as an important outcome by caregivers. The guideline's Work Group noted that most patients would value these clinical benefits despite the inconvenience and potential risk of side effects from blood pressure management. The CKD Task Force concluded that due to the insufficient evidence there was possibly important uncertainty about how much people value the main outcomes, so input about their preferences would need to be sought from individual patients or caregivers before initiation of therapy.

Resource use and cost-effectiveness: We did not identify direct evidence on resource requirements for blood pressure treatment but received information from the Saudi Health Technology Agency about cost per package of antihypertensive agents (see Cost table in Appendix 14.9). A microsimulation model applied to SPRINT showed that intensive blood pressure control prevented cardiovascular disease events and prolonged life regardless of whether benefits were reduced after 5 years or persisted for the patient's remaining lifetime, at levels below the willingness-to-pay thresholds (51 to 79% below the threshold of $50000 per quality-adjusted life-years and 76 to 93% below the threshold of $100000 per quality-adjusted life-years) (Bress et al., 2017).

The 2021 KDIGO Work Group (Cheung et al., 2021) noted that in particular when treating patients with CKD (G1–G4, A2) where the indication for antihypertensive therapy was not strong, consideration should be given to the clinical impact on the patient and the costs of starting RASi, including the need for additional clinic visits and lab testing. The CKD Task concluded that blood pressure treatment probably leads to moderate savings as the costs of antihypertensive agents were low compared with those of future complications of CKD, they might prevent such as prevention of future KT or dialysis, as well as possible improvement in future quality of life. They also judged that cost-effectiveness

probably favored the intervention given the indirect evidence from the cost-effectiveness study (Bress et al., 2017).

Other contextual factors:

- *Equity*: We did not identify direct evidence to address equity for this question. The CKD Task Force concluded that given Saudi Arabia's comprehensive health coverage, there would probably be no disadvantages associated with the use of antihypertensive treatment in children with CKD on equity from implementing the recommendation.
- *Acceptability*: We did not identify direct evidence to address acceptability for this question. The CKD Task Force used their collective experience with antihypertensive therapy to judge that this pharmacological therapy was acceptable to stakeholders in Saudi Arabia, such as providers and decision-makers.
- *Feasibility*: We did not identify direct evidence to address feasibility for this question. The CKD Task Force judged that there was no reason to suspect differences in feasibility regarding the availability of antihypertensive treatments in Saudi Arabia.
- *Implementation*: The 2021 KDIGO guideline (Cheung et al., 2021) reported that implementing ABPM for monitoring the treatment of hypertension is challenging (Halbach, 2020). For instance, blood pressure monitors are not always available when needed; they require time from a parent or other adult to return the monitor to the clinic; they are expensive; and in certain situations, there is a low probability of finding elevated blood pressure using ABPM, such as children with clinic blood pressure at <25th percentile.

For additional details, please see the EtD framework and Summary of Findings (SoF) table in Appendix 14.8.

Research needs

The 2021 KDIGO guideline listed as research recommendation to ascertain when antihypertensive medications should be initiated, and identify the best blood pressure measurement technique and setting to define hypertension and blood pressure targets for pediatric CKD patients (Cheung et al., 2021). The CKD Task Force did not add any further research needs and pointed out the difficulties of performing large RCTs in the pediatric population.

8.2. Question 2 – Non-RASi vs RASi in adults with CKD

Should non-RASi versus RASi be used for hypertension treatment in adults with CKD?

Recommendation

In adults with CKD, the CKD Task Force suggests using RASi over non-RASi for hypertension treatment ***(conditional recommendation, low certainty in the evidence of effects)***. This recommendation applies to all adults with CKD stages 1-3 and to those with advanced CKD (stages 4-5) who are not receiving KRT.

Additional considerations

The RASi used commonly in Saudi Arabia include ACEi and ARBs, whereas non-RASi drug classes include beta blockers, calcium channel blockers (CCBs) and aldosterone antagonists.

Evidence summary

The literature search for the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure (BP) in CKD* (Cheung et al., 2021) identified 3 RCTs with a total of 330 participants comparing beta blockers vs RASi (Agarwal et al., 2014; Hannedouche et al., 1994; PROCOPA Study Group, 2002) and 5 RCTs with a total of 2,992 participants comparing CCBs vs RASi (Herlitz et al., 2001; Saruta et al., 2009; Yilmaz et al., 2010; Zucchelli et al., 1992). Our update search conducted in October 2021 found 1 additional RCT with 269 participants comparing non-RASi vs ramipril (Ruggenenti et al., 2005).

Benefits and harms: Betablockers compared with RASi results in no difference in cardiovascular mortality (RR, 0.67; 95% CI, 0.11-3.90; low certainty in the evidence of effects), corresponding to 57 fewer events (102 fewer to 17 more); cardiovascular morbidity (RR, 0.59; 95% CI, 0.28-1.22; low certainty in the evidence of effects), corresponding to 70 fewer events (122 fewer to 37 more), kidney failure (RR, 1.84; 95% CI, 0.94-3.62; low certainty in the evidence of effects), corresponding to 162 fewer events (12 fewer to 504 more), systolic blood pressure (MD, 2.12; 95% CI, -6.70 – 10.94; low certainty in the evidence of effects); and proteinuria (n/M) (RR, 1.27; 95% CI, 0.31-5.19; low certainty in the evidence of effects), corresponding to 64 more events (165 fewer to 1000 more). The evidence also suggests that betablockers compared to RASi results in a slight increase in diastolic blood pressure (MD, 1.93; 95% CI, 1.32 – 2.53; low certainty in the evidence of effects; and may result in a reduction in hyperkalemia and hyperkalemia (OR, 0.26; 95% CI, 0.08-0.89.; low certainty in the evidence of effects), corresponding to 57 fewer more events (72 fewer to 8 fewer).

Calcium Channel Blockers compared with RASi may result in no difference in cardiovascular mortality, (RR, 1.05; 95% CI, 0.81-1.38; low certainty in the evidence of effects), corresponding to 4 more events (14 fewer to 27 more); cardiovascular morbidity, (RR, 0.93; 95% CI, 0.61-1.42; low certainty in the evidence of effects), corresponding to 2 more events (12 fewer to 13 more); systolic blood pressure,

(MD, 0.32; 95% CI, -5.34 - 5.97; low certainty in the evidence of effects); diastolic blood pressure, (MD, -1.33; 95% CI, -4.51 - 1.85; low certainty in the evidence of effects); eGFR change from baseline (MD, 0.02; 95% CI, -0.33 – 0.37; low certainty in the evidence of effects); proteinuria assessed as g/g creatinine (MD, 0.08; 95% CI, -1.42 - 1.58; low certainty in the evidence of effects); and proteinuria assess as g/24 (OR, 4.33; 95% CI, 0.71-26.53; low certainty in the evidence of effects), corresponding to 266 more events (35 fewer to 670 more).

Non RASi compared with RASi (ramipril) may result in no difference in cardiovascular mortality (RR, 1.97; 95% CI, 0.98-3.96; low certainty in the evidence of effects), corresponding to 76 more events (2 fewer to 233 more); cardiovascular morbidity, (RR, 0.54; 95% CI, 0.10-2.91; low certainty in the evidence of effects), corresponding to 13 fewer events (26 fewer to 55 more); and hyperkalemia (OR, 1.10; 95% CI, 0.54-2.2; low certainty in the evidence of effects), corresponding to 11 more events (55 fewer to 118 more) (Agarwal et al., 2014; Hannedouche et al., 1994; Herlitz et al., 2001; Ruggenenti et al., 2021; Saruta et al., 2009; Yilmaz et al., 2010; Zucchelli et al., 1992). No other critical outcomes were reported in the body of evidence (Cheung et al., 2021). The CKD Task Force concluded that based on the available evidence, the balance between desirable and undesirable effects probably favors RASi.

Certainty in the evidence: We rated the overall certainty in the evidence of effects as low based on the lowest certainty in the evidence for the critical outcomes, owing to serious risk of bias, and very serious imprecision of the estimates.

Values: We did not identify primary studies addressing the relative importance of the outcomes for this question. In the opinion of the 2021 KDIGO Work Group (Cheung et al., 2021), most well-informed patients with CKD and severely increased albuminuria would place emphasis on preventing cardiovascular outcomes in addition to preventing CKD progression despite the inconvenience and potential risk of side effects from blood pressure management. The CKD Task Force judged that this also applied to adults in Saudi Arabia and that there was probably no important variability in patients' values and preferences.

Resource use and cost effectiveness: We did not identify direct evidence on resource requirements for blood pressure treatment but received information from the Saudi Health Technology Agency about cost per package of antihypertensive agents (see Cost table in Appendix 14.9). The 2021 KDIGO Work Group (Cheung et al., 2021) noted that in particular when treating patients with CKD (G1–G4, A2) where the indication for antihypertensive therapy was not strong, consideration should be given to the clinical impact on the patient and the costs of starting RASi, including the need for additional clinic visits and lab testing. The CKD Task Force discussed the issue of immediate costs (cost of antihypertensive agents), considering possible long-term savings such as prevention of future KT or

dialysis, as well as possible improvement in future quality of life. They noted that blood pressure treatment led to moderate savings as the costs of antihypertensive agents were low compared with those of future complications of CKD they might prevent and concluded that cost-effectiveness probably favored the comparison. This, added to the fact that average cost of RASi is lower than non-RASi, would favor the recommendation.

Other contextual factors:

- *Equity*: We did not identify direct evidence to address equity for this question. The CKD Task Force concluded that in view of Saudi Arabia's comprehensive health coverage, there would probably be no disadvantages associated with the use of antihypertensive treatment in adults with CKD on equity from implementing the recommendation.
- *Acceptability* We did not identify direct evidence to address acceptability for this question. The CKD Task Force used their collective experience with antihypertensive therapy in Saudi Arabia to judge that this pharmacological therapy was acceptable to stakeholders in Saudi Arabia, such as providers and decision-makers.
- *Feasibility*: We did not identify direct evidence to address feasibility for this question.
- *Implementation*: We did not identify direct evidence to address implementation for this question.

For additional details, please see the EtD framework and SoF table in Appendix 14.8.

Research needs

The 2021 KDIGO Guideline identified as research needs the undertaking of adequately powered RCT to evaluate cardiovascular and kidney effects of ARB versus dihydropyridine CCB among patients with KT (Cheung et al., 2021). Also, since RASi in patients with CKD G3–G4, A1 and A2 with or without diabetes have not been adequately studied, future studies should examine if RASi, in the presence or absence of other reno-protective agents such as SGLT2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, provide kidney, cardiovascular, and survival benefits to this important subgroup (Cheung et al., 2021). Finally, there is insufficient evidence on the role of diuretics as first line therapy for the treatment of high blood pressure in patients with CKD. Therefore, it would be helpful to clarify the role of diuretics as initial therapy in this population (Cheung et al., 2021).

The NICE Guideline, identified as research need understanding the clinical effectiveness of RASi in patients with CKD older than 75 years (NICE-NG203, 2021).

8.3. Question 3 – Intensive vs standard blood pressure targets in children with CKD

Should intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets versus standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets be used for hypertension treatment in children with CKD?

Recommendation

In children with CKD, the CKD Task Force suggests using intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets rather than standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets for hypertension treatment ***(conditional recommendation, low certainty in the evidence of effects)***.

Additional considerations

Based on the available evidence and in line with the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure (BP) in CKD* (Cheung et al., 2021), the CKD Task Force suggests targeting 24-hour MAP <50th percentile for intensive blood pressure control. Please see section 7.2 for additional details on measuring blood pressure in children.

Evidence summary

The literature search for the 2021 KDIGO guideline (Cheung et al., 2021) identified one RCT compared intensive blood pressure control (targeting 24-hour MAP <50th percentile of normal children) versus standard blood pressure control (targeting 24-hour MAP 50th-99th percentile of normal children) (ESCAPE Trial Group et al., 2009). Our update search conducted in October 2021 found no additional studies for inclusion.

Benefits and harms: The included RCT (the "Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CKD in Pediatric Patients" [ESCAPE] trial of 385 children aged 3 to 18 years) showed that intensive blood pressure control significantly slowed CKD progression (time to a decline of 59% in GFR, progression to ESKD), with no statistically significant difference in the type or incidence of adverse events or rates of withdrawal (ESCAPE Trial Group et al., 2009). Children with glomerular disorders, GFR <45 ml/min per 1.73 m2, and PCR >1.5 g/g (150 mg/mmol) seemed to benefit the most.

The evidence suggests that intensive blood pressure does not reduce mortality (RR, 0.34; 95% CI, 0.01-8.39; low certainty in the evidence of effects); this corresponds to 3 fewer (5 fewer to 38 more) death per 1000 patients based on a baseline risk of 0.5%, and 220 fewer (331 fewer to 1000 more) per 1000 patients based on a baseline risk of 33.4% from observational data (ref). There is no difference in

decreasing kidney failure (RR, 0.67; 95% CI, 0.41-1.10; low certainty in the evidence of effects), corresponding to 57 fewer events (102 fewer to 17 more); systolic blood pressure (MD, -2.00; 95% CI, -4.97- 0.97; low certainty in the evidence of effects); and diastolic blood pressure (MD, -1.0; SD, -3.7 - 1.7; low certainty in the evidence of effects). Intensive blood pressure may reduce glomerular filtration rate slightly (MD, -1.4; 95% CI, -2.79 - 0.00; low certainty in the evidence of effects). Mean Targeting the intensified blood pressure control required a larger number of antihypertensive agents than the conventional target, and systolic blood pressure (SBP) was found to be higher in the group of participants with higher blood pressure targets. The study was not powered for and did not demonstrate statistically significant effects for all-cause mortality or kidney failure. Neither did it report data on other critical outcomes such as cardiovascular mortality, cardiovascular morbidity, doubling serum creatinine, acute kidney injury, proteinuria, or left ventricular hypertrophy. The CKD Task Force concluded that the balance between desirable and undesirable effects probably favored intensive blood pressure control.

Certainty in the evidence: We rated the overall certainty in the evidence of effects as low based on the lowest certainty in the evidence for the critical outcomes, owing to serious risk of bias, and serious imprecision of the estimates.

Values: We did not identify primary studies evaluating the values and preferences of patients (or their families / caregivers) for this question. The SONG-Kids study cited in the 2021 KDIGO guideline (Cheung et al., 2021) reported that both children with kidney disease and their caregivers rated kidney function as an important outcome, and blood pressure control was also rated as an important outcome by caregivers (Hanson et al., 2019). In the judgment of the Work Group, most patients would value the clinical benefits associated with intensive blood pressure control despite the inconvenience and potential risk of harms associated with it (such as multiple medications, more frequent dosing, possible adverse events if dehydrated, and the burden of monitoring with 24-hour ABPM. Patients for whom medication burden or the burden of ABPM monitoring are particularly important concerns may be more inclined not to follow this recommendation. The CKD Task Force concluded that in the absence of direct evidence there was possibly important uncertainty about how much people value the main outcomes, so input about their preferences would need to be sought from individual patients or caregivers before initiation of intensive blood pressure control.

Resource use and cost effectiveness: We did not identify direct evidence on resource requirements for blood pressure treatment but received information from the Saudi Health Technology Agency about cost per package of antihypertensive agents (see Cost table in Appendix 14.9). Indirect evidence from a cost-effectiveness study determining the lifetime health benefits and health care cost of

intensive versus standard blood pressure management in adults suggests that intensive blood pressure is cost-effective (Bress et al., 2017).The 2021 KDIGO Work Group (Cheung et al., 2021) judged that the potential benefits associated with ABPM outweighed the costs and inconvenience associated with its implementation. Patients and families in areas where ABPM is less affordable will be less inclined to follow this recommendation and may choose to use clinic-based auscultatory blood pressure monitoring instead.

Other contextual factors:

- *Equity*: We did not identify direct evidence to address equity for this question. The CKD Task Force concluded that given Saudi Arabia's comprehensive health coverage, there would probably be no disadvantages associated with the use of antihypertensive treatment in children with CKD on equity from implementing the recommendation.
- *Acceptability*: We did not identify direct evidence to address acceptability for this question. The ESCAPE trial suggests that lower blood pressure targets are usually acceptable to patients and health care providers (ESCAPE Trial Group et al., 2009). The CKD Task Force used their collective experience with antihypertensive therapy in Saudi Arabia to judge that this pharmacological therapy was acceptable to stakeholders in Saudi Arabia, such as providers and decision-makers.
- *Feasibility*: We did not identify direct evidence to address feasibility for this question.
- *Implementation*: The 2021 KDIGO guideline (Cheung et al., 2021) reported that implementing ABPM for monitoring the treatment of hypertension is challenging (Halbach, 2020). For instance, blood pressure monitors are not always available when needed; they require time from a parent or other adult to return the monitor to the clinic; they are expensive; and there are certain situations where there is a low probability of finding elevated blood pressure by ABPM such as children with clinic blood pressure at <25th percentile.

For additional details, please see the EtD framework and SoF table in Appendix 14.8.

Research needs

The research need identified in the source guideline, and accepted by the CKD Task Force, was the undertaking of RCTs that define targets for treatment when ABPM cannot be obtained repeatedly, for example, with home-based or office-based auscultatory or oscillometric blood pressure, with kidney disease progression and cardiovascular disease as outcomes (Cheung et al., 2021). The CKD Task Force also noted that there was insufficient evidence about the effects of intensive lowering blood target compared to higher blood pressure target in children with CKD.

The CKD Task Force considers there is a need for developing and conducting new RCTs to justify blood pressure targets, and that also includes assessment of outcomes that do not yet provide evidence and to make the data available to other countries. They also describe the need to set up a National Research Center that collects all the research done in Saudi Arabia and to encourage independent research centers of each university to exchange information and prevent wastage of research and duplication of efforts.

8.4. Question 4 – Intensive vs standard blood pressure targets in adults with CKD

Should intensive (SBP <120 mm Hg) blood pressure targets compared to standard (SBP <140mm Hg) blood pressure targets be used for hypertension treatment in adults with CKD?

Recommendation

In adults with CKD, the CKD Task Force suggests using intensive (SBP <120 mm Hg) blood pressure targets rather than standard (SBP <140mm Hg) blood pressure targets for hypertension treatment ***(conditional recommendation, low certainty in the evidence of effects)***.

Evidence summary

The 2021 KDIGO guideline (Cheung et al., 2021) identified nine RCTs (Agarwal et al., 2019; Appel et al., 2010; Cheung et al., 2017; Ku et al., 2017; Pahor et al., 1998; Ruggenenti et al., 2005; Sarnak et al., 2005) and conducted a meta-analysis comparing the effects of introducing intensive (SBP <120 mm Hg) versus standard (SBP <140 mm Hg) blood pressure target on blood pressure control in adults with CKD. Our update search conducted in October 2021 found no additional studies for inclusion.

Benefits and harms: Intensive blood pressure targets likely reduces mortality (RR, 0.85; 95% CI, 0.76-0.96; moderate certainty in the evidence of effects), corresponding to 17 fewer events per 1000 patients (27 fewer to 4 fewer), kidney failure (RR, 0.90; 95% CI, 0.82-0.99; moderate certainty in the evidence of effects), corresponding to 18 fewer events (32 fewer to 2 fewer), SBP (MD, -8.12; SD, -13.13 - -3.1; moderate certainty in the evidence of effects), DBP (MD, -4.30; SD, -6.46 - -2.15; moderate certainty in the evidence of effects), and hyperkalemia (RR, 1.34; 95% CI, 1.01-1.78; low certainty in the evidence of effects), corresponding to 20 more events (1 more to 4 more (Agarwal et al., 2019; Cheung et al., 2017; Ku et al., 2017; Pahor et al., 1998; Ruggenenti et al., 2005; Sarnak et al., 2005; The SPRINT Research Group, 2015). There is no difference between intensive blood pressure targets compared to standard blood pressure targets on cardiovascular mortality (RR, 0.96; 95% CI, 0.44-2.08; low certainty in the evidence of effects), corresponding to 1 fewer event (15 fewer to 29 more) cardiovascular morbidity (RR, 0.89; 95% CI, 0.73-1.09; low certainty in the evidence of effects),

corresponding to 26 fewer events (63 fewer to 21 more), and eGFR change from baseline (MD, 1.60; 95% CI, -0.72 - 3.92; low certainty in the evidence of effects) (Agarwal et al., 2019; Appel et al., 2010; Cheung et al., 2017; ESCAPE Trial Group et al., 2009; Klahr et al., 1994; Ruggenenti et al., 2005). None of the included studies had reported information on doubling serum creatinine, acute kidney injury left ventricular hypertrophy and encephalopathy.

Certainty in the evidence: We rated the overall certainty in the evidence of effects as low based on the lowest certainty in the evidence for the critical outcomes, owing to very serious risk of bias, and serious imprecision of the estimates.

Values: We did not find primary evidence addressing the relative importance of the outcomes for this question. In the opinion of the 2021 KDIGO Work Group, most well-informed patients with CKD and severely increased albuminuria would place emphasis on preventing cardiovascular outcomes in addition to preventing CKD progression despite the inconvenience and potential risk of side effects from blood pressure management. The CKD Task Force concurred that this also applied to adults in Saudi Arabia and that there was probably no important variability in patients' values and preferences.

Resource use and cost effectiveness: We did not identify direct evidence on resource requirements for blood pressure treatment but received information from the Saudi Health Technology Agency about cost per package of antihypertensive agents (see Cost table in Appendix 14.9). The 2021 KDIGO Work Group (Cheung et al., 2021) noted that in particular when treating patients with CKD (G1–G4, A2) where the indication for antihypertensive therapy was not strong, consideration should be given to the clinical impact on the patient and the costs of starting RASi, including the need for additional clinic visits and lab testing. The CKD Task Force discussed the issue of immediate costs (cost of antihypertensive agents), considering possible long-term savings such as prevention of future KT or dialysis, as well as possible improvement in future quality of life. They noted that overall, blood pressure treatment led to moderate savings as the costs of antihypertensive agents were low compared with those of future complications of CKD they might prevent and concluded that cost-effectiveness probably favored the intervention.

Other contextual factors:

- *Equity*: We did not identify direct evidence to address equity for this question. The CKD Task Force concluded that given Saudi Arabia's comprehensive health coverage, there would probably be no disadvantages associated with the use of antihypertensive treatment in children with CKD on equity from implementing the recommendation.

- *Acceptability* We did not identify direct evidence to address acceptability for this question. The CKD Task Force used their collective experience with antihypertensive therapy in Saudi Arabia to judge that this pharmacological therapy was acceptable to stakeholders in Saudi Arabia, such as providers and decision-makers.
- *Feasibility*: We did not identify direct evidence to address feasibility for this question.
- *Implementation:* We did not identify direct evidence to address implementation for this question.

For additional details, please see the EtD framework and SoF table in Appendix 14.8.

Research needs

The 2021 KDIGO guideline listed as research recommendation adequately powered RCTs to evaluate cardiovascular and kidney effects of targeting SBP <120 mm Hg versus <130 mm Hg SBP among patients with KTs (Cheung et al., 2021). Also, the undertaking of RCTs comparing treatment based on ABPM or HBPM versus standardized office blood pressure measurements. Treatment based on ABPM or HBPM includes not treating patients with "white-coat" hypertension, not intensifying treatment for the "white-coat" effect, treatment of masked hypertension, and intensifying treatment for masked uncontrolled hypertension.

Finally, information is needed on how patient values and preferences influence decisions related to blood pressure-lowering therapy. This would be an ideal topic for the Standardized Outcomes in Nephrology (SONG) initiative (Cheung et al., 2021).

8.5. Question 5 – Early vs late assessment for KRT in patients with CKD

Should early assessment (i.e., eGFR 20 mL/min/1.73m2) versus late assessment (i.e., eGFR <20 mL/min/1.73m2) be used for KRT in patients with CKD?

Recommendation

In patients with CKD, the CKD Task Force suggests using early assessment (i.e., eGFR 20 mL/min/1.73m2) for KRT rather than late assessment (i.e., eGFR <20 mL/min/1.73m2) for KRT ***(conditional recommendation, very low certainty in the evidence of effects)***.

Additional considerations

The NICE guideline (NICE-NG107, 2018) recommended to start assessment for KRT or conservative management at least one year before therapy was likely to be required, including for patients with a failing KT.

Evidence summary

The NICE guideline (NICE-NG107, 2018) included one retrospective cohort study involving 3,014 participants comparing early and late nephrologist referral (Winkelmayer et al., 2003). Our update search conducted in October 2021 found no additional studies for inclusion addressing this clinical question.

Benefits and harms: Early referral compared to late referral may reduce mortality at 90 days (RR, 0.67; 95% CI, 0.60-0.76; very low certainty in the evidence of effects], corresponding to 115 fewer events per 1000 patients (140 fewer to 84 fewer), but there is no difference on mortality from 91 days to 1 year (RR, 0.07; 95% CI, 0.84-1.13; very low certainty in the evidence of effects), corresponding to 8 fewer events (45 fewer to 37 more). However, the evidence is very uncertain. (Winkelmayer et al., 2003). The study did not report any other critical outcomes such as patient/family/caregiver health related quality of life, impact late referral rates, pre-emptive transplantation rates, proportion of patients receiving KRT after assessment, symptom scores, cognitive impairment, growth, malignancy, or adverse events. The NICE committee noted that when considering the timing of referral for assessment, allowing sufficient time to prepare for KRT needs to be balanced with minimizing referral of those that will never receive it.

Certainty in the evidence: We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, owing to very serious risk of bias, and serious imprecision of the estimates. The NICE committee (NICE-NG107, 2018) and CKD Task Force also noted that referral to a nephrologist is only a proxy for the full multidisciplinary assessment required. Whereas a nephrology referral may happen for a variety of reasons other than assessment for KRT (such as investigating the etiology of the condition and actions to treat and monitor the condition, and preserve renal function), the assessment for KRT often requires transfer of patient care from an individual nephrology consultant-led review to a multidisciplinary review. This usually follows recognition that the person with kidney disease has reached a stage that requires planning of how to manage the progressive nature of their condition, and the multidisciplinary team is needed to cover all aspects of the person's care and future care plans.

Values: We did not find primary evidence addressing the relative importance of the outcomes for this question. Patient representatives and advocates presenting at the KDIGO Controversies Conference on Early Identification & Intervention in CKD in October 2019 expressed a strong belief that patients prefer earlier CKD screening and diagnosis ("Controversies Conference on Early Identification & Intervention in CKD," 2019). They also emphasized that the decisions concerning age to initiate testing, the frequency of repeat testing and time to forgo or end testing should be personalized based on risk

factors, preferences, and life expectancy. A systematic review found that hemodialysis had the lowest utility value (ranging from 0.44 to 0.72), with higher utility value for PD (ranging from 0.53 to 0.81), and the highest utility value calculated for KT (ranging from 0.57 to 0.90) (NICE-NG107, 2018; Yang et al., 2021).

Resource use and cost effectiveness: We did not identify primary studies addressing the resources required to manage CKD patients with KRT.

- Cost of condition: CKD affects about 10 percent of the population worldwide, with over 2 million people worldwide reported to have ESKD (Gadelkarim et al., 2019). In higher-income countries, treatment costs are enormous: a 2010 report from the United Kingdom (UK) National Health Service estimates its annual CKD spending at £1.45 billion, more than half of which was for KRT (Jha et al., 2013). Australia has estimated it will spend over $12 billion on ESKD patients through 2020 (Cass et al., 2010). At the same time, KRT remains entirely unaffordable to the majority of ESKD patients in low- and middle-income countries throughout the world, with over 1 million people dying annually from lack of treatment (Couser et al., 2011).
- Cost of interventions: According to a report estimating unit and annual cost for KTs in the UK, the initial assessment clinic costs include annual cost per patient £2,537 (Saudi Riyals [SAR] 13,137), and annual expenditure of £6,421,018 (SAR 33,238,174). A study conducted at a Saudi dialysis center assessed the health services cost of hemodialysis based on data gathered over 3.5 years (Al Saran and Sabry, 2012). The mean total cost per hemodialysis session came to US $297 (1,114 SAR), and the mean total cost of dialysis per patient per year was US $46,332 (173,784 SAR). Another study conducted in Saudi Arabia compared medical cost of transplantation following desensitization versus maintenance hemodialysis over a 4-year period (Al-Jedai et al., 2012). The average annual cost of medical care per transplant patient was US $133,291, US $14,233, US $5,536, and US $4,402 in the first, second, third, and fourth year respectively. The average 4-year actual total cost per patient was significantly lower in the KT group compared to the hemodialysis group (US $210,779 vs US $317,186.3; p=0.017). A systematic review evaluating dialysis cost in low and middle-income countries found the annual cost per patient for hemodialysis to be lower compared to PD (ranging from international dollars (Int$) 3,424 to Int$ 42,785 with hemodialysis vs Int$ 7,974 to Int$ 47,971 with PD) (Mushi et al., 2015). The main cost drivers for hemodialysis were direct medical cost (especially drugs and consumables) and dialysis solutions and tubing for PD. A systematic review of cost-effectiveness of KRT modalities also reported that KT was the most cost-effective KRT modality, but that PD was more cost-effective than hemodialysis (Yang et al., 2021). Most studies suggested that KT held a dominant position over hemodialysis and PD in terms of both lower costs and higher effectiveness. Five studies suggested that increased uptake of KT

and PD by new ESKD patients would reduce costs and improve health outcomes or would be more cost-effective than current practice patterns.

Other contextual factors:

- *Equity*: We did not identify direct evidence to address equity or feasibility for this question.
- *Acceptability*: We did not identify direct evidence to address acceptability for this question but found indirect evidence from a study evaluating the implementation of a multidisciplinary care (MDC) clinic for patients with advanced CKD (Kwek et al., 2021). The study suggested possible improvement in adherence to CKD intervention targets and good participants' acceptability of the MDC program consisting of clinical outcomes assessment, self-care advice, and KRT options.
- *Feasibility*: We did not identify direct evidence to address feasibility for this question.
- *Implementation*: The CKD Task Force suggested using doubling serum creatinine as an indicator for early assessment of CKD, especially in the remote areas of Saudi Arabia, where hospital infrastructure and proper laboratory facilities may be limited, and the use of GFR may not be possible.

For additional details, please see the EtD framework and SoF table in Appendix 14.8.

Research needs

No research recommendations were reported in the NICE guideline (NICE-NG107, 2018) for this question, and the CKD Task Force did not add any research needs.

8.6. Question 6 – Late vs early preparation strategy for KRT in patients with CKD

Should any late preparation strategy* (based on eGFR or by anticipated time to start of KRT) versus any early preparation strategy (based on eGFR or by anticipated time to start of KRT) be used in patients with CKD stage 4 to 5 to prepare the patient for the start of KRT?

Recommendation

In patients with CKD stage 4 to 5, the CKD Task Force suggests using an early preparation strategy* (based on eGFR or by anticipated time to start of KRT) rather than a late preparation strategy (by eGFR or by anticipated time to start of KRT) to prepare the patient for the start of KRT **(conditional recommendation, very low certainty in the evidence of effects).**

*eGRF: 20 mL/min/1.73m2; anticipated time for PD (2-4 weeks); hemodialysis (4-8 weeks for arteriovenous fistula [AVF] to heal).

Additional considerations

The NICE guideline recommended (NICE-NG107, 2018) to aim to create access via a catheter placed by an open surgical technique around two weeks prior to anticipated start of PD. When planning hemodiafiltration or hemodialysis via an AVF, it recommended to use ultrasound scanning to determine vascular access sites for creating the AVF, and to create the arteriovenous graft (AVG) around 6 months before the anticipated start of dialysis to allow for maturation and to allow for the possibility of the first fistula failing or needed further interventions before use.

Evidence summary

The literature search conducted for the NICE guideline (NICE-NG107, 2018) on early versus late preparation strategy included one RCT (Ranganathan et al., 2017) and two non-randomized studies assessing maturation requirements of AVF for hemodialysis (Ishani et al., 2014; Ravani et al., 2004). The RCT compared initiation of PD 1 week vs 2 weeks vs 4 weeks after PD insertion in 122 adults over 18 years of age. One of the observational studies included 14,459 adults >70 years of age and focused on AVF placement one or one-two months before initiation of KRT (Ishani et al., 2014). The other study evaluated the time from AVF creation to use <30 days versus >30 days among 414 adults over the age of 18 years (Ravani et al., 2004). Our update search conducted in October 2021 found no further studies for inclusion addressing the clinical question.

Benefits and harms: Any late preparation strategy (based on eGFR or by anticipated time to start of KRT) may result in a slight increase in mortality (HR, 1.26; 95% CI, 1.03-1.54; very low certainty in the evidence of effects); AVF failure in hemodialysis access (HR, 1.94; 95% CI, 1.344-2.82; very low certainty in the evidence of effects); leak in PD access between 1 to 4 weeks (RR, 11.56; 95% CI, 1.57-85.42; low certainty in the evidence of effects), corresponding to 258 more events (14 more to 1000 more); and leak in PD access between 1 to 2 weeks (RR, 2.96; 95% CI, 1.03-8.53; low certainty in the evidence of effects), corresponding to 187 more events (3 more to 717 more).

The evidence suggests that any late preparation strategy (based on eGFR or by anticipated time to start of KRT) results in no difference in modality failure in PD access between 1 to 4 weeks (RR, 0.15; 95% CI, 0.02-1.17; low certainty in the evidence of effects), corresponding to 145 fewer events (167 fewer to 29 more); infections in PD access between 1 to 4 weeks (RR, 5.26; 95% CI, 0.64-43.00; low certainty in the evidence of effects), corresponding to 104 more events (9 fewer to 1000 more); modality failure in PD access between 1 to 2 weeks (RR, 1.08; 95% CI, 0.07-16.63; low certainty in the evidence of effects), corresponding to 2 more events (22 fewer to 372 more); infections in PD access between 1 to 2 weeks (RR, 5.38; 95% CI, 0.66-44.07; low certainty in the evidence of effects),

corresponding to 104 more events (8 fewer to 1000 more); modality failure in PD access between 2 to 4 weeks (RR, 0.14; 95% CI, 0.02-1.08; low certainty in the evidence of effects), corresponding to 147 fewer events (167 fewer to 14 more); infections in PD access between 2 to 4 weeks (RR, 0.98; 95% CI, 0.66-15.09; low certainty in the evidence of effects), corresponding to 0 fewer events (23 fewer to 344 more), and leak in PD access between 2 to 4 weeks (RR, 3.90; 95% CI, 0.46-33.48; low certainty in the evidence of effects), corresponding to 71 more events (13 fewer to 792 more).

Certainty in the evidence: We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, owing to very serious risk of bias, and serious imprecision of the estimates.

Values: We did not identify primary studies addressing the relative importance of the outcomes for this question. Indirect evidence from a systematic review found that patients highly value the benefits of hemodialysis, PD, and KT (Yang et al., 2021). Hemodialysis had the lowest utility value (ranging from 0.44 to 0.72), with higher utility value for PD (ranging from 0.53 to 0.81), and the highest utility value calculated for KT (ranging from 0.57 to 0.90). In seven of the nine studies included in the review, KT utility was higher than PD utility, and PD utility was higher than hemodialysis utility. In two of the nine studies, KT utility was higher than PD and hemodialysis utility, with PD and hemodialysis utility being equal. One study suggested that conflicting results of utility valuations existed among different valuation methods. For example, continuous ambulatory PD patients' European Quality of Life five-dimension scale (EQ-5D) scores were higher than those of center hemodialysis patients, while continuous ambulatory PD patients' Standard Gamble and Time Trade-Off scores were lower than those of center hemodialysis patients.

Resource use and cost effectiveness: We did not identify primary studies addressing the resources required to manage CKD patients with KRT.

- Cost of interventions: According to a report estimating unit and annual cost for KT in the UK, the initial assessment clinic costs include annual cost per patient £2,537 (SAR 13,137), and annual expenditure of £6,421,018 (SAR 33,238,174). A study conducted at a Saudi dialysis center assessed the health services cost of hemodialysis based on data gathered over 3.5 years (Al Saran and Sabry, 2012). It found that the mean total cost per hemodialysis session came to US $297 (1,114 SAR), and the mean total cost of dialysis per patient per year was US $46,332 (173,784 SAR). Another study conducted in Saudi Arabia compared medical cost of transplantation following desensitization versus maintenance hemodialysis over a 4-year period (Al-Jedai et al., 2012). The average annual cost of medical care per transplant patient was US $133,291, US $14,233, US $5,536, and US $4,402 in the first, second, third, and fourth year respectively. The average 4-year

actual total cost per patient was significantly lower in the KT group compared to the hemodialysis group (US $210,779 vs US $317,186.3; p=0.017). A systematic review evaluating dialysis cost in low and middle-income countries found the annual cost per patient for hemodialysis to be lower compared to PD (ranging from international dollars (Int$) 3,424 to Int$ 42,785 with hemodialysis vs Int$ 7,974 to Int$ 47,971 with PD) (Mushi et al., 2015). It reported that the main cost drivers for hemodialysis were direct medical cost (especially drugs and consumables) and dialysis solutions and tubing for PD. A systematic review of cost-effectiveness of KRT modalities also reported that KT was the most cost-effective KRT modality but that PD was more cost-effective than hemodialysis (Yang et al., 2021). Most studies suggested that KT held a dominant position over hemodialysis and PD in terms of both lower costs and higher effectiveness. Five studies suggested that increased uptake of KT and PD by new ESKD patients would reduce costs and improve health outcomes or would be more cost-effective than current practice patterns.

Other contextual factors:

- *Equity*: We did not identify evidence to address equity for this question. (Bello et al., 2017)(Alharbi and Enrione, 2012)Two studies suggest that there are local geographical barriers to access to hemodialysis. The reason for the disadvantage is a distribution of resources (Kiani et al., 2018, 2017).
- *Acceptability*: We did not identify direct evidence to address acceptability for this question (Kwek et al., 2021).
- *Feasibility*: We did not identify direct evidence to address feasibility for this question.
- *Implementation:* We did not identify direct evidence to address implementation for this question.

For additional details, please see the EtD framework and SoF table in Appendix 14.8.

Research needs

With regard to research needs, the CKD Task Force identified:

- The timing of creating percutaneous and laparoscopic PD access for different KRT options.
- The clinical and cost-effectiveness of initial hemodialysis versus initial peritoneal dialysis for people who start dialysis in an unplanned approach.
- The best timing for transplant listing for those on KRT considering transplantation.

The CKD Task Force also accepted the following research needs listed in the NICE guideline (NICE-NG107, 2018): What is the most clinical and cost-effective strategy for timing of preemptive transplantation, and what is the optimum timing of listing for transplantation?

8.7. Question 7 – CKD symptoms during assessment for KRT or conservative management

Should a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms that he/she is experiencing versus not using such strategy be used in patients who are undergoing or being assessed for KRT or conservative management of established kidney failure?

Recommendation

In patients who are undergoing or being assessed for KRT or conservative management of established kidney failure, the CKD Task Force suggests using a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms he/she is experiencing rather than not using such a strategy ***(conditional recommendation, very low certainty in the evidence of effects)***.

Additional considerations

This recommendation is in line with NICE guidance to ask patients throughout the course of KRT and conservative management about any symptoms they have, explore whether their symptoms are due to CKD, their treatment or another cause, and to explain the likely cause of the symptoms to the patient (and/or family/caregivers) including how well treatment may be expected to control them. Patients may feel uncomfortable talking about some symptoms (for example sexual dysfunction) and may not associate them with CKD or its treatment.

Evidence summary

The literature search conducted for the NICE guideline on symptom recognition did not find any studies on the effectiveness of symptom identification but reported thirty-four qualitative studies on symptoms reported by patients and caregivers (NICE-NG107, 2018). Twenty-eight of these explored the views of adult patients on KRT. One study provided the views of adolescent patients; four studies focused on the views of patients and caregivers on KT, and one study dealt with views of parents whose children were on KRT or considering KRT. Twenty-nine studies conducted in-depth semi-structured interviews with transcripts analyzed using a phenomenological reduction or thematic analysis. Four studies used focus group sessions, while one study conducted an open-ended survey distributed online. Our update search conducted in October 2021 found two additional observational studies using a survey and questionnaires to capture the views of patients undergoing hemodialysis to explore symptom experiences and symptom clusters respectively (Cervantes et al., 2018; Chaiviboontham et al., 2020).

Benefits and harms: The qualitative review reported in the NICE guideline identified no critical themes but symptoms or the impact of symptoms. The major symptoms identified were fatigue, breathlessness, pain, depression, immobility, itching, nausea, anxiety, cognitive fluctuations, dizziness, insomnia, weakness, weight gain and infection. The two studies identified on update of evidence also delineated gastrointestinal, musculoskeletal, neurological, irritation of skin, depression, sleep disturbances and anemia as important symptoms.

Certainty in the evidence: We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, owing to methodological limitations and concerns regarding adequacy for the assessment of outcomes. ***Values:*** We did not identify direct evidence to address the relative importance of the outcomes for this question.

Resource use and cost effectiveness: We did not identify direct evidence to address resources use and cost effectiveness for this question.

Other contextual factors:

- *Equity:* We did not identify direct evidence to address equity for this question.
- *Acceptability:* We did not identify direct evidence to address acceptability for this question. However, we found indirect evidence on acceptability from a study evaluating the implementation of a MDC clinic for patients with advanced CKD (Al-Jedai et al., 2012). The study suggested possible improvement in adherence to CKD intervention targets and good participants' acceptability of the MDC program consisting of clinical outcomes assessment, self-care advice, and KRT options.
- *Feasibility:* We did not identify direct evidence to address feasibility for this question.
- *Implementation:* We did not identify direct evidence to address implementation for this question.

(Kwek et al., 2021)For additional details, please see the EtD framework and SoF table in Appendix 14.8.

Research needs

No research recommendations were reported in the NICE guideline (NICE-NG107, 2018) for this question, and the CKD Task Force did not add any research needs.

8.8. Question 8 – Initiation of KRT in patients with deteriorating CKD

Should initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms versus initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms* be used in previously KRT-naive adults requiring KRT for deteriorating CKD?

Recommendation

In previously KRT-naive adults requiring KRT for deteriorating CKD, the CKD Task Force suggests initiating KRT late (i.e., eGFR 5-7 mL/min/1.73m2) or based on severe symptoms* rather than initiating KRT early (i.e., eGFR 10-15 mL/min/1.73m2) or based on moderate symptoms ***(conditional recommendation, very low certainty in the evidence of effects)***.

*Severe uremic symptoms and/or uncontrollable fluid overload.

Additional considerations

The NICE guideline (NICE-NG107, 2018) noted that the decision when to start KRT should consider the patient's presence and severity of uremic symptoms (refractory pruritus, and nausea and vomiting, in particular in the morning) and fluid overload (edema, weight gain, and breathlessness), preference, biochemistry, and eGFR, and made on an individual basis. Some patients may prefer an agreed starting point based on eGFR but may need dialysis before this because symptoms are affecting normal daily activities. On the other hand, some patients with slowly progressing CKD may not recognize and report symptoms that indicate that dialysis is needed. It is important to establish whether more general symptoms such as fatigue and depression are due to uremia or not, and to discuss their impact on daily life.

Evidence summary

The literature search conducted for the NICE guideline (NICE-NG107, 2018) identified three studies—one RCT and two non-randomized study—addressing this question (Akkina et al., 2008; Cooper et al., 2010; Ishani et al., 2003). The RCT known as the IDEAL trial was conducted across 32 centers in New Zealand and Australia among 828 adults with CKD (including patients with a failing transplant) and compared planned initiation of dialysis with eGFR 10-14 mL/min/1.73m^2 (early start) versus with eGFR 5-7 mL/min/1.73m^2 (late start) (Cooper et al., 2010). The first non-randomized study was a cohort study with 671 adults aged 18 and older who had their first pre-emptive transplant between 1984 and 2006 (Akkina et al., 2008). The second study evaluated the records of 4,046 adults who had undergone a living donor KT as initial form of KRT (Ishani et al., 2003). Our update search conducted in October 2021 found two additional retrospective cohort studies among children (<18 years of age), with one study (Preka et al., 2019) including 2,963 children from 21 European countries and the other (Winnicki et al., 2019) evaluating 15,170 children who started KRT between 1995 and 2015.

Benefits and harms: For hemodialysis or PD, early preparation compared with late preparation may result in no difference in mortality based on eGFR (RR, 1.04; 95% CI, 0.87-1.24; low certainty in the

evidence of effects), corresponding to 15 more events (48 fewer to 88 more); mortality in age <18 years (HR, 1.25; 95% CI, 0.96-1.64; very low certainty in the evidence of effects); growth <18 years (MD, -0.03; 95% CI, -0.15 - 0.09; very low certainty in the evidence of effects); patient, family/caregiver health related quality of life (MD, 0.00; 95% CI, -0.03 - 0.03; very low certainty in the evidence of effects); pre-emptive transplantation rates at age <18 years, (HR, 0.97; 95% CI, 0.89-1.06; very low certainty in the evidence of effects); and adverse events (RR, 0.89; 95% CI, 0.75-1.06; low certainty in the evidence of effects), corresponding to 45 more events (103 fewer to 25 more).

For patients undergoing kidney transplant with an eGFR ≥15ml/min vs <10ml/min, early preparation compared with late preparation may result in no difference in mortality (HR, 1.35; 95% CI, 0.89-2.05; very low certainty in the evidence of effects).

For transplant at eGFR 10 -14.9 ml/min vs <10ml/min, early preparation compared with late preparation may result in no difference in mortality (HR, 0.99; 95% CI, 0.69-1.42; very low certainty in the evidence of effects) (Cooper et al., 2010) (Winnicki et al., 2019) (Preka et al., 2019)(Akkina et al., 2008; Ishani et al., 2003).

Certainty in the evidence: We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, owing to very serious risk of bias, and serious imprecision of the estimates.

Values: We did not identify primary studies addressing the relative importance of the outcomes for this question. Indirect evidence from a systematic review found that patients highly value the benefits of hemodialysis, PD, and KT (Yang et al., 2021). Hemodialysis had the lowest utility value (ranging from 0.44 to 0.72), with higher utility value for PD (ranging from 0.53 to 0.81), and the highest utility value calculated for KT (ranging from 0.57 to 0.90). In seven of the nine studies included in the review, KT utility was higher than PD utility, and PD utility was higher than hemodialysis utility. In two of the nine studies, KT utility was higher than PD and hemodialysis utility, with PD and hemodialysis utility being equal. One study suggested that conflicting results of utility valuations existed among different valuation methods. For example, continuous ambulatory PD patients' EQ-5D scores were higher than those of center hemodialysis patients, while continuous ambulatory PD patients' standard gamble (SG) and time tradeoff (TTO) scores were lower than those of center hemodialysis patients.

Resource use and cost effectiveness: A systematic review of cost-effectiveness of KRT modalities reported that KT was the most cost-effective KRT modality but that PD was more cost-effective than hemodialysis (Yang et al., 2021). Most studies suggested that KT held a dominant position over hemodialysis and PD in terms of both lower costs and higher effectiveness. Five studies suggested that

increased uptake of KT and PD by new ESKD patients would reduce costs and improve health outcomes or would be more cost-effective than current practice patterns.

Other contextual factors:

- *Equity:* We did not identify direct evidence to address equity for this question.
- *Acceptability:* We did not identify direct evidence to address acceptability for this question.
- *Feasibility:* We did not identify direct evidence to address feasibility for this question.
- *Implementation:* We did not identify direct evidence to address implementation for this question.

(Kwek et al., 2021)For additional details, please see the EtD framework and SoF table in Appendix 14.8.

Research needs

The NICE guideline (NICE-NG107, 2018) identified a research need for the following question: What is the most clinical and cost-effective strategy for timing of pre-emptive transplantation? A question raised by the CKD Task Force was whether initiation of dialysis can be delayed safely with aggressive medical management (Chan et al., 2019).

8.9. Question 9 – Choice of KRT modality or conservative management in certain groups of CKD patients

Should any KRT modality versus conservative management be used in certain groups* of patients requiring KRT for CKD?

Recommendation

In certain groups* of patients requiring KRT for CKD, the CKD Task Force suggests using conservative management rather than any KRT modality for CKD treatment ***(conditional recommendation, very low certainty in the evidence of effects)***.

***i.** those that choose not to undergo dialysis,

ii. those who choose to withdraw from dialysis after a period of treatment,

iii. those who are coming to the end of their lives while already on long-term dialysis,

iv. those who have a failing transplant and decide not to return to dialysis.

Additional considerations

The NICE guideline (NICE-NG107, 2018) recommended to offer a choice of KRT or conservative management (supportive management including symptom and complications control, and advance care planning) to patients who are likely to need KRT, with the decision to be based on individual factors (such as frailty, cognitive impairment and multimorbidity) and patient preference. Especially in the later stages of CKD, patients may decide against KRT. Conservative management is generally (although not always) less appropriate for younger, healthier people, and rarely an option for children.

Evidence summary

The literature search conducted for the NICE guideline (NICE-NG107, 2018) identified one non-randomized study addressing this question. This UK study reviewed the records of 844 patients attending a Nephrology clinic based on data from a hospital database from 1990 – 2008, including 106 patients with KRT and 77 patients with conservative management (Chandna et al., 2011). Our update search conducted in October 2021 found no further studies for inclusion addressing the clinical question.

Benefits and harms: The evidence is very uncertain about the effect of any KRT (hemodialysis and/or peritoneal dialysis and/or transplant) on mortality in over 75 years in a follow up period from 1 to 18 years (HR, 0.85; 95% CI, 0.57-1.27; very low certainty in the evidence of effects). Dialysis may result in a slight increase in mortality in over 75 years in a median follow up period of 2 years (HR, 2.94; 95% CI, 1.56-5.53; very low certainty in the evidence of effects) (Chandna et al., 2011). There was insufficient evidence on other outcomes such as cognitive impairment, growth, impact late referral rates, patient and caregiver health related quality of life, pre-emptive transplantation rates, proportion receiving KRT after assessment, symptom scores, or adverse events.

Certainty in the evidence: We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, owing to very serious risk of bias, and serious imprecision of the estimates.

Values: We did not identify primary studies addressing the relative importance of the outcomes for this question.

Indirect evidence suggests patient representatives and advocates described that there is a strong belief that patients overwhelmingly prefer earlier CKD screening and diagnosis and that patient education has the potential to improve self-management and disease prognosis 70 (Cheung et al., 2021).

One systematic review described the following regarding the relative importance of outcomes and patients' preferences for hemodialysis, PD, and KT. Patients highly value the benefits of hemodialysis, PD, and KT (Yang et al., 2021). The utility values for hemodialysis ranged from 0.44 to 0.72; for PD from 0.53 to 0.81; for KT from 0.57 to 0.90. In seven of the nine studies, KT utility was higher than PD utility, and PD utility was higher than hemodialysis utility. In two of the nine studies, KT utility was higher than PD and hemodialysis utility, with PD and hemodialysis utility being equal. One study suggests that conflicting results of utility valuations existed among different valuation methods. For example, continuous ambulatory PD patients' EQ-5D scores were higher than those of center hemodialysis patients, while continuous ambulatory PD patients' SG and TTO scores were lower than those of center hemodialysis patients (Yang et al., 2021).

Resource use and cost effectiveness: We did not identify primary studies addressing the resources required to manage CKD patients with conservative management or renal replacement therapy.

- Cost of interventions: initial assessment clinic has an annual cost per patient of £2,537 (SAR 13,137), and an annual expenditure of £6,421,018 (SAR 33,238,174). The mean total cost per hemodialysis session was calculated as 297 US dollars (USD) (1,114 SAR), and the mean total cost of dialysis per patient per year was 46,332 USD (173,784 SAR) (Al Saran and Sabry, 2012). One study conducted in Saudi Arabia described that an average annual cost of medical care per patient after transplantation in the first, second, third, and fourth year was USD $133,291, USD $14,233, USD $5,536, and USD $4,402, respectively. The average 4-year actual total cost per patient was USD $210,779 and USD $317,186.3 in the kidney transplant group and the hemodialysis group; respectively (p=0.017) (Al-Jedai et al., 2012).
- In terms of cost effectiveness, one study assessed the value for money and budget impact of offering hemodialysis as a first-line treatment, or the hemodialysis-first policy, and the PD first policy compared to a supportive care option in patients with ESKD in Indonesia (Afiatin et al., 2017). The PD-first policy was found to be more cost-effective compared to the hemodialysis-first policy. Budget impact analysis provided evidence on the enormous financial burden for the country if the current practice, where hemodialysis dominates PD, continues for the next five years.
- Costs:
    - Life years saved
        - Supportive care option: 0.21
        - PD first option: 5.93
        - Hemodialysis first option: 5.93
    - Quality-adjusted life years (QALY)

        - Supportive care option: 0.076
        - PD first option: 4.40
        - Hemodialysis first option: 4.34
    - Incremental cost-effectiveness ratio
        - Supportive care: Not reported
        - PD first option: 193.2 million IDR
        - Hemodialysis first option: 2017.4 million IDR
    - Cost-effectiveness acceptability
        - At the threshold of willingness to pay 43 million IDR (1 GDP), supportive care was the best option. (probability = 1.00)
        - At willingness to pay >190million IDR, PD first was the most cost-effective option (probability >0.5)
        - Hemodialysis first was not the best cost-effective option at any level of willingness to pay.

A CADTH Review (Subramonian and Frey, 2020) demonstrated the results from the cost effectiveness acceptability curve. Supportive care remained the most cost-effective option up to a threshold of <200 million IDR, after which PD first option was the most cost effective. Hemodialysis first option was not the best cost-effective option at any level of willingness to pay (43 million IDR equates roughly to $4,000 CAD).

Other contextual factors:

- *Equity:* We did not identify direct evidence to address equity for this question.
- *Acceptability:* We did not identify direct evidence to address acceptability for this question. However, the included study provided information on the survival of patients who have chosen to forego dialysis and demonstrated that in patients aged >75 years with high extra-renal comorbidity, the survival advantage conferred by KRT over conservative management is likely to be small (Chandna et al., 2011). Our update search conducted in October 2021 identified a protocol for a pilot RCT aiming to explore the feasibility and acceptability of Conservative Kidney Management Options and Advance Care Planning Education—COPE, change in communication of preferences and differences in the intervention's effects on knowledge and communication of preferences by race (Stallings et al., 2021).
- *Feasibility:* We did not identify direct evidence to address feasibility for this question.
- *Implementation:* We did not identify direct evidence to address implementation for this question.

For additional details, please see the EtD framework and SoF table in Appendix 14.8.

Research needs

The research needs identified by the NICE guideline (NICE-NG107, 2018), and confirmed by the CKD Task Force, were as follows:

- What is the clinical and cost-effectiveness of conservative management versus dialysis in frail, older people? (NICE-NG107, 2018).
- Can a CKD Frailty Index be used to inform patient decision-making? (Chan et al., 2019).
- What would constitute the index—could it be based on the Integrated Palliative Care Outcome Scale (IPOS)-Renal index? (Chan et al., 2019) And finally,
- Could a CKD Frailty Index be combined with traditional and novel biomarkers and clinical scoring systems (serial assessments of fluid status, nutritional status and/or body composition) to guide initiation of dialysis? (Chan et al., 2019).

8.10. Question 10 – Transferring between KRT modalities or discontinuing KRT

Should transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators* versus not transferring between modalities of KRT or discontinuing KRT based on suitable clinical indicators* or doing either at a later stage be used in patients with CKD currently receiving KRT?

Recommendation

In patients with CKD currently receiving KRT, the CKD Task Force suggests transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators* rather than not transferring between modalities of KRT or discontinuing KRT based on suitable clinical indicators* or doing either at a later stage ***(conditional recommendation)***.

*Vascular access failures, peritoneal membrane failure or failure of kidney graft.

Additional considerations

The NICE guideline (NICE-NG107, 2018) recommended to offer information on all medically appropriate treatment options when discussing switching KRT modality. Switching treatment modality or stopping KRT should be considered if medically indicated or if the patient (or, where appropriate, the family/caregiver) asks for this, and planned wherever possible. The guideline advised against routinely switching patients on PD to a different modality in anticipation of potential future complications (e.g., encapsulating peritoneal sclerosis) but rather to monitor risk factors (such as loss of ultrafiltration). It recommended to seek specialist advice on the need for switching modality when

women become pregnant or wish to become pregnant. The need for a switch in these situations would depend on the adequacy of dialysis, the health of the fetus and the control of urea.

Evidence summary

Neither the literature search conducted for the NICE guideline (NICE-NG107, 2018) nor our update search identified any evidence addressing this question.

Benefits and harms: Insufficient evidence to inform what are the benefits and harms of any particular strategy for transferring between KRT modalities or for discontinuing KRT.

Certainty in the evidence: We did not rate the overall certainty in the evidence of effects for all reported outcomes due to insufficient evidence.

Values: We did not identify primary studies addressing the relative importance of the outcomes for this question. A review summarizing the literature on the transition between different KRT modalities noted that transitioning from one KRT modality to another can have a huge impact on the well-being and lifestyle of patients and their caregivers (INTEGRATED group consists of (in alphabetical order) et al., 2019). One study defined six categories of transitions of care during advanced CKD: (1) transition from non-dialysis-dependent CKD to de novo dialysis therapy; (2) transition from non-dialysis dependent CKD to pre-emptive transplantation; (3) transition among or across dialysis modalities, formats and frequency (hemodialysis to PD or vice versa, in-center to home; (4) transition from dialysis therapy to KT; (5) transition from a gradually failing KT back to dialysis therapy; and (6) transition from any of the above stages to partial or full transitions can be present in patients with CKD (Kalantar-Zadeh et al., 2017). There is uncertainty regarding what factors make patients' transition and their caregivers' experiences successful, stressful, or even unsuccessful. Moreover, data are lacking on how patients and their caregivers perceive such a transition, what their ideas and emotions are, and how they cope with them (Chan et al., 2019).

Resource use and cost effectiveness: We did not identify primary studies addressing the resources required and cost effectiveness to manage CKD patients with KRT. We report indirect evidence regarding the cost of the disease and different CKD interventions.

- Cost of disease

CKD affects about 10 percent of the population worldwide, including an estimated 1 in 7 adult Americans. In the US, Medicare spending totals more than $64 billion each year to care for Americans with CKD and an additional $34 billion to care for patients with ESKD (Initiative, 2018).

The impact of kidney disease extends well beyond the United States; over 2 million people worldwide have ESKD. In higher-income countries, treatment costs are enormous: a 2010 report from the UK National Health Service estimates its annual CKD spending at £1.45 billion—more than half of which was for KRT (Jha et al., 2013)—while Australia has estimated it will spend over $12 billion on ESKD patients through 2020 (Cass et al., 2010). At the same time, KRT remains entirely unaffordable to the majority of ESKD patients in low- and middle-income countries throughout the world, with over 1 million people dying annually from lack of treatment (Couser et al., 2011).

- Cost of interventions

Initial assessment clinic: annual cost per patient £2,537 (SAR 13,137), annual expenditure £6,421,018 (SAR 33,238,174). The mean total cost per hemodialysis session was calculated as 297 US USD (1,114 SAR), and the mean total cost of dialysis per patient per year was 46,332 USD (173,784 SAR) (Al Saran and Sabry, 2012). One study conducted in Saudi Arabia described that an average annual cost of medical care per patient after transplantation in the first, second, third, and fourth year was US $133,291, US $14,233, US $5,536, and US $4,402; respectively. The average 4-year actual total cost per patient was US $210,779 and US $317,186.3 in the kidney transplant group and the hemodialysis group; respectively (p=0.017) (Al-Jedai et al., 2012). One systematic review reported annual costs of hemodialysis and PD in low and middle-income countries. The annual cost per patient for hemodialysis ranged from Int$ 3,424 to Int$ 42,785, and PD ranged from Int$ 7,974 to Int$ 47,971. Direct medical cost especially drugs and consumables for hemodialysis and dialysis solutions and tubing for PD were the main cost drivers (Mushi et al., 2015).

In terms of cost effectiveness, one systematic review directly addresses the cost-effectiveness of different KRT. KT was the most cost-effective KRT modality and PD was more cost-effective than hemodialysis. Most studies suggested that KT held a dominant position over hemodialysis and PD with both lower costs and higher effectiveness. Five studies suggested that increased uptake of KT and PD by new ESKD patients would reduce costs and improve health outcomes or would be more cost-effective than current practice patterns (Yang et al., 2021).

Other contextual factors:

- *Equity:* We did not identify direct evidence to address equity for this question.
- *Acceptability:* We did not identify direct evidence to address acceptability for this question. Indirect evidence from one study provided information on the survival of patients who have chosen to forego dialysis. The study demonstrated that in patients aged >75 years with high

extra-renal comorbidity, the survival advantage conferred by KRT over conservative management is likely to be small (Chandna et al., 2011).

- *Feasibility:* We did not identify direct evidence to address feasibility for this question.
- *Implementation:* We did not identify direct evidence to address implementation for this question.

Our update search conducted in October 2021 identified a protocol for a pilot RCT aiming to explore the feasibility and acceptability of Conservative Kidney Management Options and Advance Care Planning Education—COPE, change in communication of preferences and differences in the intervention's effects on knowledge and communication of preferences by race (Stallings et al., 2021).

For additional details, please see the EtD framework and SoF table in Appendix 14.8.

Research needs

The NICE guideline (NICE-NG107, 2018) identified the following research need, confirmed by the CKD Task Force: What is the clinical and cost effectiveness of strategies for switching KRT modality?

The review summarizing the literature on the transition between different KRT modalities (INTEGRATED group consists of (in alphabetical order) et al., 2019) reported a number of unanswered questions related to transition of care in CKD, including whether the transition to KRT and the type and modality of the transition should be selected based on pre-dialysis patient data; regarding the outcome predictability of pre-ESKD conditions with selection of dialysis modality (hemodialysis versus PD), format (in-center versus home), frequency (daily versus infrequent) and vascular access (pre-emptive AVF or PD catheter placement versus no access placement until dialysis starts); regarding what factors make patients' transition and their caregivers' experiences successful, stressful, or even unsuccessful; and how patients and their caregivers perceive such a transition, what their ideas and emotions are, and how they cope with them.

8.11. Question 11 – Review frequency for KRT or conservative management

Should any frequency of regular review for any KRT modality or conservative management versus any other frequency of regular review be used in patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice?

Recommendation

In patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice, the CKD Task Force suggests regular review at a frequency tailored to the KRT modality or conservative management ***(conditional recommendation).***

Additional considerations

The NICE guideline committee (NICE-NG107, 2018) noted that what is reviewed will vary according to clinical circumstances but may include serum biochemistry, blood pressure and weight. Some reviews will need to be carried out face to face, whereas others can be done remotely. Increasing the frequency of review may allow for faster recognition of deterioration in the health state of patients on KRT and conservative management, and may improve communication, adherence with treatment and the prevention of complications. These benefits must be weighed against the potential harms of treatment burden for the patient and healthcare services, in particular those related to KRT where patients may have many different healthcare contacts and multiple weekly hospital visits due to the severity of their condition and comorbidities.

- Transplant: Practice for assessing transplant function can vary between centers but commonly involves eGFR measurement every 3 months and eGFRs being reviewed by the renal team on a 3-6 monthly basis. Children are usually assessed at least every 3 months. The general health of people with a stable KT is typically assessed at least once a year and includes the assessment of cardiovascular risk factors.
- Dialysis: In the absence of any evidence, it is difficult to make any specific recommendations about the ideal frequency of review in people on dialysis. Patients receiving in-center dialysis may be reviewed too frequently as it is logistically easy to do.
- Conservative management: Frequency of review in this patient group is highly dependent on the prognosis of the patient and stage of treatment. The frequency of review will increase as the person's condition deteriorates, based on individual circumstances and preferences. Face-to-face review is likely to be particularly important for patients receiving conservative management to assess current functional status.

Evidence summary

Neither the literature search conducted for the NICE guideline (NICE-NG107, 2018) nor our update search identified any evidence addressing this question.

Benefits and harms: Insufficient evidence to inform what are the benefits and harms on how frequently patients on different forms of KRT should be reviewed.

Certainty in the evidence: We did not rate the overall certainty in the evidence of effects for all reported outcomes due to insufficient evidence.

Values: We did not find primary studies addressing the relative importance of the outcomes for this question. Patient representatives and advocates presenting at the KDIGO Controversies Conference on Early Identification & Intervention in CKD in October 2019 expressed a strong belief that patients prefer earlier CKD screening and diagnosis ("Controversies Conference on Early Identification & Intervention in CKD," 2019). They also emphasized that the decisions concerning age to initiate testing, the frequency of repeat testing and time to forgo or end testing should be personalized based on risk factors, preferences, and life expectancy.

One systematic review described the following regarding the relative importance of outcomes and patients' preferences for hemodialysis, PD, and KT. Patients highly value the benefits of hemodialysis, PD, and KT (Yang et al., 2021). The utility values for hemodialysis ranged from 0.44 to 0.72; for PD from 0.53 to 0.81; for KT from 0.57 to 0.90. In seven of the nine studies, KT utility was higher than PD utility, and PD utility was higher than hemodialysis utility. In two of the nine studies, KT utility was higher than PD and hemodialysis utility, with PD and hemodialysis utility being equal. One study suggests that conflicting results of utility valuations existed among different valuation methods. For example, continuous ambulatory PD patients' EQ-5D scores were higher than those of center hemodialysis patients, while continuous ambulatory PD patients' SG and TTO scores were lower than those of center hemodialysis patients (Yang, 2021).

Resource use and cost effectiveness: We did not identify primary studies addressing the resources required and cost effectiveness to address this specific question. We report indirect evidence regarding the cost of different CKD interventions. The NICE guideline pointed out that more frequent review will be associated with more healthcare appointments leading to higher costs.

- Cost of interventions

Initial assessment clinic: annual cost per patient £2,537 (SAR 13,137), annual expenditure £6,421,018 (SAR 33,238,174). The mean total cost per hemodialysis session was calculated as 297 USD (1,114 SAR), and the mean total cost of dialysis per patient per year was 46,332 USD (173,784 SAR) (Al Saran and Sabry, 2012). One study conducted in Saudi Arabia described that an average annual cost of medical care per patient after transplantation in the first, second, third, and fourth year was US $133,291, US $14,233, US $5,536, and US $4,402; respectively. The average 4-year actual total cost

per patient was US $210,779 and US $317,186.3 in the kidney transplant group and the hemodialysis group; respectively (p=0.017) (Al-Jedai et al., 2012).

In terms of cost effectiveness, one study assessed the value for money and budget impact of offering hemodialysis as a first-line treatment, or the hemodialysis-first policy, and the PD first policy compared to a supportive care option in patients with ESKD in Indonesia (Afiatin et al., 2017). The PD-first policy was found to be more cost-effective compared to the hemodialysis-first policy. Budget impact analysis provided evidence on the enormous financial burden for the country if the current practice, where hemodialysis dominates PD, continues for the next five years.

- Costs:
    - Life years saved
        - Supportive care option: 0.21
        - PD first option: 5.93
        - Hemodialysis first option: 5.93
    - Quality-adjusted life years
        - Supportive care option: 0.076
        - PD first option: 4.40
        - Hemodialysis first option: 4.34
    - Incremental cost-effectiveness ratio
        - Supportive care: Not reported
        - PD first option: 193.2 million IDR
        - Hemodialysis first option: 2017.4 million IDR
    - Cost-effectiveness acceptability
        - At the threshold of willingness to pay 43 million IDR (1 GDP), supportive care was the best option (probability = 1.00)
        - At willingness to pay >190million IDR, PD first was the most cost-effective option (probability >0.5)
        - Hemodialysis first was not the best cost-effective option at any level of willingness to pay.

A CADTH Review (Subramonian and Frey, 2020) demonstrated the results from the cost effectiveness acceptability curve. Supportive care remained the most cost-effective option up to a threshold of < 200 million IDR, after which PD first option was the most cost effective. Hemodialysis first option was not the best cost-effective option at any level of willingness to pay (43 million IDR equates roughly to $4,000 CAD).

Other contextual factors:

- *Equity:* We did not identify direct evidence to address equity for this question.
- *Acceptability:* We did not identify direct evidence to address acceptability for this question. Indirect evidence from one study provided information on the survival of patients who have chosen to forego dialysis. The study demonstrated that in patients aged >75 years with high extra-renal comorbidity, the survival advantage conferred by KRT over conservative management is likely to be small (Chandna et al., 2011).
- *Feasibility:* We did not identify direct evidence to address feasibility for this question.
- *Implementation:* We did not identify direct evidence to address implementation for this question.

Our update search conducted in October 2021 identified a protocol for a pilot RCT aiming to explore the feasibility and acceptability of Conservative Kidney Management Options and Advance Care Planning Education—COPE, change in communication of preferences and differences in the intervention's effects on knowledge and communication of preferences by race (Stallings et al., 2021).

For additional details, please see the EtD framework and SoF table in Appendix 14.8.

Research needs

The NICE guideline (NICE-NG107, 2018) identified the following research needs, confirmed by the CKD Task Force:

- What is the most clinical and cost-effective frequency of review for people on PD, hemodiafiltration, hemodialysis or conservative management? (NICE-NG107, 2018)
- Could a CKD Frailty Index be used to identify clinically important changes over time in individuals before dialysis and after initiation of dialysis? (Chan et al., 2019)
- Are the changes different with hemodialysis versus PD? (Chan et al., 2019)
- Is it possible to predict which patients improve and which get worse? (Chan et al., 2019)
- To what extent do uremic symptoms change after initiation of dialysis? (Chan et al., 2019)

8.12. Question 12 – Information, education and support

Should any type of information, education, or support versus any other type of information, education, or support be used in patients requiring KRT or conservative management (and their families or caregivers as appropriate)?

Recommendation

In patients requiring KRT or conservative management (and their families or caregivers as appropriate), the CKD Task Force suggests using individualized information, education, or support rather than other types of information, education, or support) ***(conditional recommendation, moderate certainty in the evidence of effects)***.

Additional considerations

In order to enable patients, their families and caregivers to make informed decisions, the NICE guideline recommended to offer balanced and accurate information about

1. Treatments including KRT, conservative management and dietary intervention:
    - What they involve, for example, availability of assistance, time that treatment takes place, and number of sessions per day/week
    - Potential benefits
    - The benefits of adherence to treatment regimens and the potential consequences of non-adherence
    - Potential adverse effects, their severity and how they may be managed
    - The likely prognosis on dialysis, after transplant or with conservative management
    - The transplant listing process (when appropriate)
    - Switching the modality of KRT and the possible consequences (that is, the impact on the person's life or how this may affect future treatment or outcomes)
    - Reviewing treatment decisions
    - Stopping treatment and planning end of life care.
2. Information about how treatments may affect lifestyle:
    - The person or caregiver's ability to carry out and adjust the treatment themselves
    - The possible impact of dietary management and management of fluid allowance
    - How treatment may fit in with daily activities such as work, school, hobbies, family commitments and travel for work or leisure
    - How treatment may affect sexual function, fertility, and family planning
    - Opportunities to maintain social interaction
    - How treatment may affect body image
    - How treatment may affect physical activity (for example, whether contact sports should be avoided after transplantation, whether swimming should be avoided with PD)
    - Whether a person's home will need to be modified to accommodate treatment

- How much time and travel treatment or training will involve
- The availability of transport
- The flexibility of the treatment regimen
- Whether any additional support or services might be needed.

The guideline also advised to offer oral and written information in an accessible format early enough to allow time for patients to fully understand their treatment options and make informed decisions; to direct patients to other sources of information and support such as online resources, pre-dialysis classes and peer support; to remember that some decisions must be made months before KRT is needed (e.g. fistula creation); to take into account information the patient has obtained from other sources such as family members and caregivers, and how this has influenced their decision; to ensure that healthcare professionals offering information have specialist knowledge about late-stage CKD and the skills to support shared decision making; and to offer patients who have presented late, or who started dialysis in an unplanned way, the same information as to those presenting at an earlier stage.

Evidence summary

The literature search conducted for the NICE guideline (NICE-NG107, 2018) identified thirty-nine qualitative studies (2018). Four of these studies were in children between the ages of 2 and 16 (and their parents), thirty-three studies included people aged 25 to 70 and two studies evaluated people aged 70 and over. Two studies focused on the pre-KRT population, two studies involved a mix of people before and during KRT. Five studies involved patients with any form of KRT, eight studies those undergoing either hemodialysis or PD (two with the input of caregivers) and eight studies patients who had received a transplant. Twelve studies involved patients undergoing hemodialysis only (two with the input of caregivers). One study involved those who had opted for conservative management. In our update search conducted in October 2021, we found an additional nineteen studies relevant to this question that dealt with the content of information, preferred format of information, decision making, psychological support, barriers and facilitators to good care, and modality of KRT.

Benefits and harms:

Themes identified from the qualitative studies:

- Content of Information: Content of information should cover symptoms, prognosis, mode of access, benefits, and harms of different modalities of KRT and conservative management, services, adherence, how to approach living donors, acute situations, kidney function and CKD, Information around transitions between forms of KRT, and end-of-life care.

- Format of information provision: Patients reported the depth and timing of information, personalized information, delivery via classes and tours, and in multiple formats, and the target of education/information as important themes to be addressed. Decision making was also identified as an important topic for education.
- Stress/support: People noted that the availability of transport affected their ability to engage with KRT and was a significant psychological stressor during KRT. Psychological support was identified as one of the support systems.
- Barriers/problems: Barriers to home dialysis were lack of a care partner, lack of home space, and patient preference (El Shamy et al., 2021). Some of the participants encountered periods of limited funds. Some of the participants experienced the effects of the hidden costs of dialysis, such as specific dietary requirements including specific, more costly food groups (Small, 2010). Further problems described by patients included lack of information and dissatisfaction with their healthcare providers regarding perceptions of their care, lack of explanation of results, not being completely honest, kept in the dark about the seriousness of the problem, and not being clear about when dialysis would occur (Harwood et al., 2005).
- Facilitators of good care: Patients thought 1:1 time with transplant team members was helpful, and they wanted additional information sources as well, without losing 1:1 time (Korus et al., 2011).
- Impact of treatment on lifestyle: Patients mentioned that information on any modality choice, including limitations on travel, and sexual activity as areas they appreciated or would have appreciated.
- Information sources: These include sources other than healthcare professionals such as support groups and online resources.

Certainty in the evidence: We rated the overall certainty in the evidence of effects as moderate based on the lowest certainty in the evidence for the critical outcomes, owing to methodological limitations and concerns regarding adequacy for the assessment of outcomes.

Values: A retrospective cohort study evaluated whether a pre-dialysis education program (PDEP) was an acceptable tool for increasing the rates of PD in ESKD patients (Alghamdi et al., 2020). It showed that PDEP significantly reduced hemodialysis rates [OR (95% CI) = 0.11 (0.05-0.24); P-value < 0.001]. The PDEP positively impacted the rate of PD, while PD was associated with favorable outcomes and lower infection rates, emphasizing the importance of the educational program. Another study found that a series of structured PDEP sessions for the patients progressing to ESKD facilitated their selection of KRT (Mirza et al., 2020). Two studies showed that educating health promotion strategies were

effective in improving self-esteem and quality of life in patients undergoing hemodialysis (Ghadam et al., 2015; Poorgholami et al., 2015).

Resource use and cost effectiveness: We did not identify primary studies addressing the resources required to provide information, education and support to CKD patients.

Other contextual factors:

- *Equity*: We did not identify direct evidence to address equity for this question.
- *Acceptability*: One study reported that quality-of-life issues for people with CKD include depression and anxiety, which are prevalent among people undergoing hemodialysis (Musa et al., 2018). Several small studies addressed whether screening, counseling or education might support social interactions (Kazemi et al., 2011), self-esteem (Poorgholami et al., 2015), or the families of children undergoing PD (Alhameedi and Collier, 2016).
- *Feasibility*: We did not identify direct evidence to address feasibility for this question. Studies that examined areas for improvement in the delivery of care included a cross-sectional study in Palestine that found self-reported adherence to diet, fluid restriction, medications, and hemodialysis sessions to be optimal in about 56% of 220 people with end-stage renal disease (Naalweh et al., 2017). A record review in New York found that lack of motivation, dialysis dependence, and comorbidities predicted failure to complete pre-transplantation preparation (Siskind et al., 2014). The authors suggested that interventions such as timely referral, educational resources, counseling, and support might increase workup completion rates or improve therapeutic outcomes.
- *Implementation:* We did not identify direct evidence to address implementation for this question.

For additional details, please see the EtD framework and SoF table in Appendix 14.8.

Research needs

The NICE guideline (NICE-NG107, 2018) identified the following research needs, confirmed by the CKD Task Force, were:

- What is the clinical and cost effectiveness of having keyworkers present in the context of KRT? (NICE-NG107, 2018)
- What is the clinical and cost effectiveness of using decision aids in the context of KRT? (NICE-NG107, 2018).
- Can an integrated care model improve quality and decrease costs for patients with kidney disease as they transition from CKD G5 to G5D? (Chan et al., 2019).

- What is the preferred timing for educating patients regarding dialysis modalities? Does the optimal time vary based on patient characteristics? (Chan et al., 2019).
- What is the optimal content and format for educating patients regarding the advantages and disadvantages of each modality? How do we check their understanding? (Chan et al., 2019)

The CKD Task Force proposes that researchers develop studies (RCTs) to assess the impact of interventions, namely education and support to patients, families, and caregivers to evaluate the effectiveness and impact on outcomes like morbidity and mortality.

9. Methods

9.1. Organization, Task Force composition, and coordination

Chronic Kidney Disease Task Force

This guideline was developed by a multidisciplinary local group of 10 experts led by a Clinical Lead. This Task Force included adult and pediatric nephrologists, and KT specialists, a clinical pharmacist, and a patient representative. Members represented a range of Ministry of Health, University, Military, and National Guard institutions, geographical regions, and medical societies, with several participants trained in epidemiology and guideline methodology.

Name	Affiliation	Role
Dr Khalid A. Alhasan	1Department of Pediatrics, College of Medicine, King Saud University Medical City. Riyadh, Saudi Arabia Saudi Society of Nephrology and Transplantation. Riyadh, Saudi Arabia	Clinical Lead; Pediatric Nephrologist
Dr Sumayah Askandarani	King Fahad Specialist Hospital. Dammam, Saudi Arabia	Adult Transplant Nephrologist
Dr Yasser Sami Amer	Department of Pediatrics, College of Medicine, King Saud University Medical City. Riyadh, Saudi Arabia Clinical Practice Guidelines and Quality Research Unit, Corporate Quality Management Department, King Saud University Medical City, Riyadh, Saudi Arabia Adaptation Working Group, Guidelines International Network, Perth, Scotland	Pediatrician, Guideline Methodologist
Muneera Rashid Al-Jelaify	Pharmacy Services, King Saud University Medical City. Riyadh, Saudi Arabia	Clinical pharmacist
Dr Khalid Ibrahim Almatham	King Fahad Medical City. Riyadh, Saudi Arabia	Adult Nephrology Lead
Dr Mohammed Al-Ghonaim	Nephrology Division, Department of Medicine, College of Medicine, King Saud University. Riyadh, Saudi Arabia	Adult Nephrologist
Dr Sultan K. Al Dalbhi	Department of Nephrology, Prince Sultan Military Medical City. Riyadh, Saudi Arabia	Adult nephrologist; Director of Nephrology & Renal Transplantation
Prof Jameela A Kari	Department of Pediatrics, Faculty of Medicine, King Abdulaziz University. Jeddah, Saudi Arabia	Pediatric Nephrologist
Prof Ahmed H Mitwalli	Dallah Hospital. Riyadh, Saudi Arabia	Adult Nephrologist
Prof Mohammed Alrasheed	King Saud University Medical City	Patient Representative (dialysis patient); Assistant Professor of Mechanical Engineering

Guideline Support Team

The work of the CKD Task Force was supported by an international team based at (or contracted by) Elsevier. This Guideline Support Team was responsible for:

- Recruitment and onboarding of the Clinical Lead based on local expert nominations.
- Onboarding of Task Force members.

- Evidence searches to identify source guidelines.
- Creation of online surveys prior to the Scoping Workshops.
- Administrative support for the Scoping, Recommendations and Finalization Workshops
- Extraction of search strategies and outcome definitions from identified source guidelines / systematic reviews.
- Updating of search strategies, running of searches, deduplication and assessment of search results for all clinical questions.
- Developing new search strategies, running of searches, deduplication and assessment of search results for contextual factors.
- Risk of bias assessment of and data extraction from included new studies.
- Synthesis of existing evidence and newly identified study results and grading of the certainty of the evidence per prioritized outcome.
- Summarizing the evidence on contextual factors (patient values & preferences, equity, feasibility, acceptability, implementation, cost).
- Importing of all data into the guideline's development tool GRADEpro to create EtD frameworks.
- Identification of draft performance and quality indicators.
- Drafting of the guideline manuscript.
- Organizing peer review and passing on comments to the CKD Task Force.
- Implementing Task Force feedback and comments to finalize the manuscript.
- Submission of the manuscript for publication in a peer-reviewed journal
- Dissemination of the guideline and its recommendations via online (website, app) and offline channels
- Implementation of the recommendations via localized Order Sets integrated into selected electronic patient record systems at pilot sites across several Saudi Arabian clusters.

Name	Role	Location
Klara Brunnhuber	Project Lead	UK
Juan José Yepes-Nuñez	EBM Co-Chair and Lead Methodologist	Colombia
Hannu Gutt	Project Manager	Germany
Ximena Alvira	Clinical Lead	Spain
Hema Jagota	Workstream Champion	India
Majed Sweis	Middle East Analyst and Products Expert	UAE
Ruchi Chawla	Content Lead	India
Joanna Sara Valson	Guideline Developer	India
Khushnam Bilimoria	Content Manager	India

Jennifer Goldstein	Director, EBM Global Content	USA
Maura Sostack	Global Medical Librarian	USA
Skye Bickett	Lead Evidence Librarian	USA
Sheila Feit	Lead Clinical Writer	USA
Naresh Goli	Evidence Reviewer	India
Sai Prasanna Vangapelly	Evidence Reviewer	India

Communication within and between the CKD Task Force and Guideline Support Team occurred mainly via WhatsApp groups created specifically to share content and files, updates, arrange meetings, share meeting links, and request feedback. Email was mainly used to share meeting invites and attachments.

In all, the CKD Task Force and Elsevier Guideline Team conducted six 2:30-3:00 hour-long, remotely held working sessions to select the PICO questions to be included (guideline scope), conduct outcomes prioritization, and formulation of recommendations. Pre-session surveys were utilized to elicit the views of Task Force members prior to workshops and during the draft finalization phase. The meeting agenda and relevant pre-reading materials were shared with the CKD Task Force before every meeting and minutes circulated following each session.

9.2. Guideline funding and management of conflict of interest

The members of the CKD Task Force including the Clinical Lead and invited peer reviewers did not receive financial incentives for participating in the development of this guideline. The activities of the Guideline Support Team were funded via a contract between the Ministry of Health's Health Holding Company and Elsevier Ltd.

All members of the CKD Task Force, Guideline Support team and peer reviewers were asked ahead of their work to declare any relevant Conflicts of Interest from the previous 4 years using a Declaration of Interest form customized from the form used by the World Health Organization. They were also requested to update the National Guidelines Center's Program Board about any changes to their conflicts of interest.

Declarations covered direct (financial) and indirect (non-financial) conflicts relevant to the guideline topic up to agreed thresholds. They were managed via the guideline development tool GRADEpro and stored securely in line with international best practices and local data retention, confidentiality, and security guidance. Declared conflicts of interest were to be assessed by a Responsible Officer nominated by the Guidelines Center Program Board according to the WHO assessment steps to ensure that only participants without conflicts vote on related recommendations.

Any conflicts of interest were read out at the beginning of each Task Force meeting and checked for updates. A summary of all declarations and actions taken to manage any declared interests is being published in all resulting reports and work products.

All Task Force members confirmed that they had no conflicts of interest to declare. All members of the Guideline Support Team declared that they were salaried or freelance employees of Elsevier, contracted to support the setting up of the National Guidelines Center and the development of its first 12 guidelines.

9.3. Selection of questions and determining outcomes of interest

Identifying the source guideline(s) aligned with local needs

The Guideline Support Team conducted a systematic search for high-quality local (Saudi or Gulf region) or international guidelines as a starting point for guideline adaptation. The identified candidate guidelines were assessed for quality using AGREE II ("AGREE II. https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf," n.d.). The following two guidelines were selected as source of clinical questions:

- KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD (Cheung et al., 2021).
- Renal replacement therapy and conservative management NICE guideline (NICE-NG107, 2018).

From the 20 clinical questions addressed by these 2 source guidelines, the CKD Task Force prioritized those most relevant for the Saudi Arabia setting. First, through an on-line survey, CKD Task Force members rated the clinical questions using a 9-point scale. The clinical questions were ranked based on the median score from all the CKD Task Force members. During the scoping workshop, 11 questions were identified as being the most relevant, with an additional question (Question 12) being suggested by the patient representative.

Quorum threshold for voting was set at 70% of all Task Force members with voting rights attending a session or providing input by email/survey response. The Task Force used consensus-based decision making for key approvals during scoping, recommendations and finalization, with a consensus threshold set at 70%.

List of prioritized questions:

Q1	Should ACEi or ARBs versus other antihypertensive agents be used for hypertension treatment in children with CKD?
Q2	Should non-RASi versus RASi be used for hypertension treatment in adults with CKD?

Q3	Should intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets versus standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets be used for hypertension treatment in children with CKD?
Q4	Should intensive (SBP <120 mm Hg) blood pressure targets compared to standard (SBP <140mm Hg) blood pressure targets be used for hypertension treatment in adults with CKD?
Q5	Should early assessment (i.e., eGFR 20 mL/min/1.73m2) versus late assessment (i.e., eGFR <20 mL/min/1.73m2) be used for KRT in patients with CKD?
Q6	Should any late preparation strategy* (based on eGFR or by anticipated time to start of KRT) versus any early preparation strategy (based on eGFR or by anticipated time to start of KRT) be used in patients with CKD stage 4 to 5 to prepare the patient for the start of KRT?
Q7	Should a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms that he/she is experiencing versus not using such strategy be used in patients who are undergoing or being assessed for KRT or conservative management of established kidney failure?
Q8	Should initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms versus initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms be used in previously KRT-naive adults requiring KRT for deteriorating CKD?
Q9	Should any KRT modality versus conservative management be used in certain groups* of patients requiring KRT for CKD?
Q10	Should transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators* versus not transferring between modalities of KRT or discontinuing KRT based on suitable clinical indicators* or doing either at a later stage be used in patients with CKD currently receiving KRT?
Q11	Should any frequency of regular review for any KRT modality or conservative management versus any other frequency of regular review be used in patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice?
Q12	Should any type of information, education, or support versus any other type of information, education, or support be used in patients requiring KRT or conservative management (and their families or caregivers as appropriate)?

ACEi: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin receptor blockers; AVF: arteriovenous fistula; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; KRT: kidney replacement therapy; MAP: mean arterial pressure. Non-RASi: non-renin angiotensin system inhibition; PD: peritoneal dialysis; RASi: renin angiotensin system inhibition; SBP: systolic blood pressure.

The CKD Task Force selected outcomes of interest for each question a priori, by rating their importance during an online survey. Outcomes included were those reported in the original resources and others that the CKD Task Force considered critical for decision making. The CKD Task Force rated the following outcomes as critical for clinical decision making across questions:

#	Question	Prioritized Outcomes
Blood Pressure Management		
1.	Should ACEi or ARBs versus other antihypertensive agents be used for hypertension treatment in children with CKD?	All-cause mortality
		Cardiovascular morbidity
		Cardiovascular mortality
		Kidney Failure
		Doubling serum creatinine

		Acute kidney injury
		Blood pressure
		eGFR
		Proteinuria
		Left ventricular hypertrophy
		Encephalopathy
2.	Should non-RASi versus RASi be used for hypertension treatment in adults with CKD?	All-cause mortality
		Cardiovascular morbidity
		Cardiovascular mortality
		Kidney failure
		Doubling serum creatinine
		Acute kidney injury
		Blood pressure
		eGFR
		Proteinuria
		Left ventricular hypertrophy
		Encephalopathy
		Hyperkalemia
3.	Should intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets versus standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets be used for hypertension treatment in children with CKD?	All-cause mortality
		Cardiovascular morbidity
		Cardiovascular mortality
		Kidney failure
		Doubling serum creatinine
		Acute kidney injury
		Blood pressure
		eGFR
		Proteinuria
		Left ventricular hypertrophy
4.	Should intensive (SBP <120 mm Hg) blood pressure targets compared to standard (SBP <140mm Hg) blood pressure targets be used for hypertension treatment in adults with CKD?	All-cause mortality
		Cardiovascular morbidity
		Cardiovascular mortality
		Kidney Failure (ESKD)
		Doubling serum creatinine
		Acute kidney injury

		Blood pressure
		eGFR
		Left ventricular hypertrophy
		Encephalopathy
		Hyperkalemia
Kidney replacement therapy		
5	Should early assessment (i.e., eGFR 20 mL/min/1.73m2) versus late assessment (i.e., eGFR <20 mL/min/1.73m2) be used for KRT in patients with CKD?	Adverse events
		Cognitive impairment
		Growth
		Impact Late referral rates
		Mortality
		Patient, family/caregiver health related QoL
		Pre-emptive transplantation rates
		Proportion of patients receiving KRT after assessment
		Symptom scores
6	Should any late preparation strategy* (based on eGFR or by anticipated time to start of KRT) versus any early preparation strategy (based on eGFR or by anticipated time to start of KRT) be used in patients with CKD stage 4 to 5 to prepare the patient for the start of KRT?	Adverse events
		Cognitive impairment
		Growth
		Impact late referral rates
		Mortality
		Patient, family/caregiver health related QoL
		Pre-emptive transplantation rates
		Proportion of patients receiving KRT after assessment
		Symptom scores
7	Should a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms that he/she is experiencing versus not using such strategy be used in patients who are undergoing or being assessed for KRT or conservative management of established kidney failure?	Fatigue
		Itching
		Nausea and vomiting
		Weight loss
		Tiredness
		Psychological distress and mental wellbeing
		Anorexia
8	Should initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate	Adverse events
		Cognitive impairment

	symptoms versus initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms be used in previously KRT-naive adults requiring KRT for deteriorating CKD?	Growth
		Impact late referral rates
		Mortality
		Patient, family/caregiver health related QoL
		Pre-emptive transplantation rates
		Proportion of patients receiving KRT after assessment
		Symptom scores
9	Should any KRT modality versus conservative management be used in certain groups* of patients requiring KRT for CKD?	Adverse events
		Cognitive impairment
		Growth
		Impact late referral rates
		Mortality
		Patient, family/caregiver health related QoL
		Pre-emptive transplantation rates
		Proportion of patients receiving KRT after assessment
		Symptom scores
10	Should transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators* versus not transferring between modalities of KRT or discontinuing KRT based on suitable clinical indicators* or doing either at a later stage be used in patients with CKD currently receiving KRT?	Adverse events
		Cognitive impairment
		Growth
		Impact late referral rates
		Mortality
		Patient, family/caregiver health related QoL
		Pre-emptive transplantation rates
		Proportion of patients receiving KRT after assessment
		Symptom scores
11	Should any frequency of regular review for any KRT modality or conservative management versus any other frequency of regular review be used in patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice?	Adverse events
		Cognitive impairment
		Growth
		Impact late referral rates
		Mortality
		Patient, family/caregiver health related QoL
		Pre-emptive transplantation rates

		Proportion of patients receiving KRT after assessment
		Symptom scores
12	Should any type of information, education, or support versus any other type of information, education, or support be used in patients requiring KRT or conservative management (and their families or caregivers as appropriate)?	Barriers to good care
		Content of information
		Decision-making
		Facilitators of good care
		Impact of transport on care
		Impact of treatment on lifestyle
		Information around transitions between forms of KRT
		Information sources other than healthcare professionals (e.g., support groups, online resources)
		Modality of KRT
		Preferred format of information provision
		Psychological support

ACEi: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin receptor blockers; AVF: arteriovenous fistula; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESKD: end stage kidney disease. KRT: kidney replacement therapy; MAP: mean arterial pressure. Non-RASi: non-renin angiotensin system inhibition; PD: peritoneal dialysis; QoL: quality of life; RASi: renin angiotensin system inhibition; SBP: systolic blood pressure.

9.4. Evidence review and inclusion of local data

The original guidelines included Summary of Findings (SoF) tables or evidence profiles for each of the questions addressed. The Guideline Support Team updated the electronic searches of the systematic reviews included in the original guidelines. They also conducted a comprehensive search of regional evidence about epidemiology, patients' values and preferences, resource use, accessibility, feasibility, and impact on health equity (see Appendix 14.8). Local information on required resources and cost effectiveness was provided by the Center of Health Technology Assessment. The Guideline Support Team created Evidence-to-Decision (EtD) frameworks, summarizing for each the data used on the original guideline as well all relevant regional information identified using the GRADEpro guideline development tool (McMaster University, Hamilton, ON, Canada, and Evidence Prime, Inc., Kraków, Poland). To estimate the absolute effect of the interventions, the team calculated the risk difference by multiplying the pooled risk ratio and the baseline risk of each outcome. The median of the risks observed in control groups of the included trials was used as baseline risk. When possible, the baseline risk observed in large observational studies was considered.

The quality of the evidence was based on judgments regarding risk of bias, precision, consistency, directness, and likelihood of publication bias, and categorized into 4 levels ranging from very low to high according to the GRADE approach (Schünemann et al., 2017).

9.5. Development of recommendations

During four online meetings held between December 03rd to December 17th, 2021, the CKD Task Force reviewed the original guideline recommendations, updated them in view of new evidence, and adapted them to local circumstances based on literature searches conducted in October 2021. These local contextual factors included baseline risks for prioritized outcomes, patient values and preferences, equity, acceptability, cost effectiveness and resource impact, feasibility, and implementation. Additional cost information was provided by the Saudi Health Technology Agency.

The CKD Task Force agreed on the direction and strength of recommendations through group discussion and deliberation, following the GRADE approach (Andrews et al., 2013). Voting took place for each EtD criteria judgments and for the final recommendation with a threshold of 70% for each vote.

The strength of recommendations is expressed as either strong ('guideline CKD Task Force recommends…') or conditional ('guideline CKD Task Force suggests…') and has explicit implications (see the Table below) (Andrews et al., 2013). Understanding the interpretation of these two grades is essential for sagacious clinical decision making.

Interpretation of strong and conditional (weak) recommendations Implications	**Strong recommendation**	**Conditional (weak) recommendation**
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or

	a quality criterion or performance indicator.	her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders.

The overall guideline development process, including funding of the work, CKD Task Force formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by policies and procedures derived from the Guidelines International Network (GIN)–McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) in order to meet recommendations for trustworthy guidelines by the Institute of Medicine and GIN, and approved by the National Guidelines Center Advisory Committee (Institute of Medicine (U.S.) and Graham, 2011; Qaseem et al., 2012; Schünemann et al., 2015, 2014). For details on the process please refer to the Appendix section 14.4.

9.6. Document review

The guideline draft was reviewed and adjusted by the CKD Task Force and the Guideline Support Team in an iterative process, until a final version was signed off by the Task Force during a Guideline Finalization Workshop.

The process was guided by the CKD Task Force Lead. For judgements about EtD criteria, the CKD Task Force used the stepwise approach outlined here:

- The process was carried out on a per-recommendation basis. That is, all judgements were made for each recommendation.
- Judgements were requested on each criterion, first suggested by one CKD Task Force member (unless the answer was already clear: for example, often the process of prioritization highlights whether the problem is a priority or not); or, if similar questions were answered for other recommendations, the CKD Task Force Lead could suggest the respective judgement or answer.
- If it became clear that one or a few members of the CKD Task Force were too opinionated or influential, the CKD Task Force Lead asked other Task Force members for their initial judgement first.
- CKD Task Force members were explicitly requested to express any disagreement.

- If no consensus was reached after discussion, the CKD Task Force resorted to voting:
    - Simple majority rules were implemented (quorum of 70% or more for contextual factors).
- If any CKD Task Force member disagreed, the Task Force Lead asked if the Task Force members wished to note this in the additional considerations' column (either mentioning the Task Force member's name, or without assigning a name to the comment).

For agreement on the final recommendations (conclusion section), the following process was followed:

- The CKD Task Force Lead asked for a suggestion by one member (or made a suggestion).
- The CKD Task Force Lead will ask for any disagreement to be expressed.
- The focus was first made on the direction of the recommendation (decided by simple majority), and then on its strength. A 70% majority was required for a strong recommendation.
- The five paradigmatic situations that were defined for strong recommendations, in the face of low- or very low-quality evidence, were applied to strong recommendations in that context.

9.7. Peer review and Approval

Peer review of the guideline draft was conducted by experts not directly involved in the production of the guideline. All peer reviewers were required to fill in a Conflict of Interest declaration. Peer review was mainly conducted using a survey and the option to provide free-text comments, although some peer reviewers preferred to provide comments directly into the draft manuscript via track changes or comments. The Guideline Support Team evaluate all received comments and discussed resulting changes with the Clinical Lead and members of the CKD Task Force, followed by a finalization workshop to resolve outstanding queries.

Subsequently, the guideline was submitted to nominated members of the Saudi Health Council's (SHC) Scientific Committee for review while the guideline draft was posted on the SHC website for public consultation. Once all feedback had been evaluated and relevant changes made, the guideline was officially approved by the SHC Scientific Committee as a national guideline.

9.8. How to use these guidelines

This guideline is designed to assist in decision-making and not to define a standard of care. Therefore, the recommendations herein should not be interpreted as prescribing a single course of management.

Variations in practice are expected to occur once the clinician takes into consideration the patient's needs and preferences, available resources, and limitations specific to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

9.9. Search results

In our comprehensive search, conducted in October 2021, we identified additional RCTs or observational that provided additional evidence on the efficacy or safety of the interventions of interest, for the following clinical questions:

Q1	Should ACEi or ARBs versus other antihypertensive agents be used for hypertension treatment in children with CKD?
Q2	Should non-RASi versus RASi be used for hypertension treatment in adults with CKD?
Q3	Should intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets versus standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets be used for hypertension treatment in children with CKD?
Q4	Should intensive (SBP <120 mm Hg) blood pressure targets compared to standard (SBP <140mm Hg) blood pressure targets be used for hypertension treatment in adults with CKD?
Q5	Should early assessment (i.e., eGFR 20 mL/min/1.73m2) versus late assessment (i.e., eGFR <20 mL/min/1.73m2) be used for KRT in patients with CKD?
Q6	Should any late preparation strategy* (based on eGFR or by anticipated time to start of KRT) versus any early preparation strategy (based on eGFR or by anticipated time to start of KRT) be used in patients with CKD stage 4 to 5 to prepare the patient for the start of KRT?
Q7	Should a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms that he/she is experiencing versus not using such strategy be used in patients who are undergoing or being assessed for KRT or conservative management of established kidney failure?
Q8	Should initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms versus initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms be used in previously KRT-naive adults requiring KRT for deteriorating CKD?
Q9	Should any KRT modality versus conservative management be used in certain groups* of patients requiring KRT for CKD?
Q12	Should any type of information, education, or support versus any other type of information, education, or support be used in patients requiring KRT or conservative management (and their families or caregivers as appropriate)?

ACEi: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin receptor blockers; AVF: arteriovenous fistula; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; KRT: kidney replacement therapy; MAP: mean arterial pressure. Non-RASi: non-renin angiotensin system inhibition; PD: peritoneal dialysis; RASi: renin angiotensin system inhibition; SBP: systolic blood pressure.

We did not identify any additional randomized trials or observational that provided additional evidence on the efficacy or safety of the interventions of interest, for the following clinical questions:

Q10	Should transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators* versus not transferring between modalities of KRT or discontinuing KRT based on

	suitable clinical indicators* or doing either at a later stage be used in patients with CKD currently receiving KRT?
Q11	Should any frequency of regular review for any KRT modality or conservative management versus any other frequency of regular review be used in patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice?

CKD: chronic kidney disease; KRT: kidney replacement therapy

We did not find studies reporting patients' values and preferences but identified information about the cost of the interventions in different countries of the region as well as evidence of accessibility and potential impact on health equity. This information is summarized for each question in the adapted EtD tables (see Appendix 14.8).

10. Performance measures

Performance measures (or key performance indicators, KPIs) are quantifiable goals that measure structures, processes, and outcomes. They specify definitions of numerator and denominator to assess how well a population of patients adheres to a specific clinical practice guideline (Nothacker et al., 2016).

Developing KPIs in tandem with evidence-based recommendations is a goal in guideline development. Methodological rigor and connection to guideline development have often been limited (Piggott et al., 2021).

As per the GIN standards, it is recommended that clinical practice guidelines-based KPIs be based on strong recommendations (Nothacker et al., 2016). As none of the recommendations in this guideline were rated as strong, the following approach was used to arrive at agreed KPIs:

Searches were conducted to find literature that could potentially provide KPIs relevant to the questions and recommendations in this CKD guideline (for details on the search strategies see section 14.5). The resulting literature was shared with the team at the Corporate Quality Management Department of King Saud University Medical City in Riyadh, who developed a long list of KPI candidates. These were submitted for voting by the CKD Task Force via a survey and using a 1-to-9-point rating scale. In all, the CKD Task Force rated 14 KPIs, of which the following six were selected for inclusion in the CKD guideline:

10.1 Performance measures for children with CKD

10.1.1. Percentage of patients aged 17 years and younger with a diagnosis of CKD (grades 1-3, or grades 4-5 who are not receiving KRT) who were prescribed ACEi or ARB therapy within a 12-month period

<table>
<tr><th colspan="4">DESCRIPTION</th></tr>
<tr><td>Functional Area</td><td>CKD</td><td>ID code</td><td>To be added locally</td></tr>
<tr><td>Name</td><td colspan="3">Percentage of patients aged 17 years and younger with a diagnosis of CKD (grades 1-3, or grades 4-5 who are not receiving KRT) who were prescribed ACEi or ARB therapy within a 12-month period.</td></tr>
<tr><td>Definitions</td><td colspan="3">KRT: For the purposes of this measure, KRT includes hemodialysis, peritoneal dialysis, and kidney transplantation.

Prescribed: May include prescription given to the patient for ACEi or ARB therapy OR patient already taking ACEi or ARB therapy as documented in the current medication list.

Classification CKD by GFR:
<table>
<tr><td>G1: normal or high kidney function</td><td>GFR: greater than 90 mL/minute/1.73 m²</td></tr>
</table></td></tr>
</table>

	G2: mildly decreased kidney function	GFR: 60 to 89 mL/minute/1.73 m²
	G3a: mildly to moderately decreased kidney function	GFR: 45 to 59 mL/minute/1.73 m²
	G3b: moderately to severely decreased kidney function	GFR: 30 to 44 mL/minute/1.73 m²
	G4: severely decreased kidney function	GFR: 15 to 29 mL/minute/1.73 m²
	G5: kidney failure	GFR: less than 15 mL/minute/1.73 m²

Rationale	**Guideline recommendation 1:** In children with CKD, the CKD Task Force suggests using ACEi or ARBs rather than other antihypertensive agents for hypertension treatment *(conditional recommendation, very low certainty in the evidence of effects)*[(1)]. This recommendation applies to all children with CKD grades 1-3 and to those with advanced CKD (grades 4-5) who are not receiving KRT		
Classifications	Process	**Quality dimensions**	Safety, Effectiveness
CALCULATION			
Calculation formula	**(Total number of patients aged 17 years and younger with CKD who were prescribed ACEi or ARB therapy within a 12-month period / Total number of patients aged 17 years and younger with a diagnosis of CKD within the same period) x 100**		
Numerator	• Patients aged 17 years and younger with a diagnosis of CKD who were prescribed ACEi or ARB therapy on their last recorded list of chronic medications during a 12-month period	**Denominator**	• Patients aged 17 years and younger with a diagnosis of CKD within the same period.
Exclusion criteria	• Patients aged 17 years and younger with a diagnosis CKD grades 4-5 who are receiving KRT • Patients aged 18 years and older with a diagnosis of CKD.	**Exclusion criteria**	• Documentation of medical reason(s) for not prescribing ACEi or ARB therapy (e.g., cough or allergy to medication) • Documentation of patient reason(s) for not prescribing ACEi or ARB therapy (patient declined, other patient reasons) • Patients aged 17 years and younger with a diagnosis of CKD grades 4-5 who are receiving KRT • Patients aged 18 years and older with a diagnosis of CKD.
Unit of measure	Percentage (%)		
TARGET SETTING			
Target	*To be agreed locally*	**Data collection**	Monthly *or as agreed locally*
Benchmark	*To be agreed locally*	**Reporting frequency**	Quarterly *or as agreed locally*
DATA COLLECTION AND ADMINISTRATION			
Data source	Patient medical records		

References	1. *Alhasan KA, Askandarani S, Amer YS, et al. 2022 Saudi Guideline for Chronic Kidney Disease: Blood Pressure Management and Kidney Replacement Therapy in Adults and Children.*

ACEi: angiotensin-converting-enzyme inhibitors; ARB: angiotensin receptor blockers; CKD: chronic kidney disease; G: grade; GFR: Glomerular filtration rate; KRT: kidney replacement therapy.

10.1.2. Percentage of patients aged 17 years and younger with a diagnosis of CKD in whom the recent blood pressure was adequately controlled during the measurement period.

DESCRIPTION			
Functional Area	CKD	**ID code**	*To be added locally*
Name	The percentage of patients aged 17 years and younger with a diagnosis of CKD in whom the recent blood pressure was adequately controlled during the measurement period.		
Definition	**Adequately controlled blood pressure:** For the purposes of this measure, 24-hour MAP <50th percentile of normal children. **Measurement period:** The previous 12 months, note: If there are multiple blood pressure readings on the same day, use the lowest systolic and the lowest diastolic reading as the most recent blood pressure reading.		
Rationale	In children with CKD, the CKD Task Force suggests using intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets rather than standard (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets for hypertension treatment [(1)].		
Classifications	Process	**Quality dimensions**	Safety, Effectiveness
CALCULATION			
Calculation formula	**(Total number of patients aged 17 years and younger with a diagnosis of CKD whose recent blood pressure was adequately controlled / Total number of patients aged 17 years and younger with a diagnosis of CKD within the same period) x 100**		
Numerator	• Patients aged 17 years and younger with a diagnosis of CKD whose recent MAP is <50th percentile of normal children.	**Denominator**	• Patients aged 17 years and younger with a diagnosis of CKD.
Exclusion criteria	• Patients aged 18 years and older with a diagnosis of CKD. Do not include blood pressure readings: • Taken during an acute inpatient stay or a visit to the Emergency Department • Taken on the same day as a diagnostic test or diagnostic or therapeutic procedure that requires a change in diet or change in medication on or one day before the day of the test or procedure, except for fasting blood tests • Taken by someone who is not a clinician.	**Exclusion criteria**	• Patients aged 18 years and older with a diagnosis of CKD • Hospice services given to patient any time during the measurement period.
Unit of measure	Percentage (%)		
TARGET SETTING			
Target	*To be agreed locally*	**Data collection**	Monthly *or as agreed locally*

Benchmark	*To be agreed locally*	**Reporting frequency**	Quarterly *or as agreed locally*
DATA COLLECTION AND ADMINISTRATION			
Data source	Patient medical records		
References:	1. *Alhasan KA, Askandarani S, Amer YS, et al. 2022 Saudi Guideline for Chronic Kidney Disease: Blood Pressure Management and Kidney Replacement Therapy in Adults and Children*		

CKD: chronic kidney disease; MAP: mean arterial pressure

10.2 Performance measures for adults with CKD

10.2.1. Percentage of patients aged 18 years and older with a diagnosis of CKD (grades 1-3, or grades 4-5 who are not receiving KRT) who were prescribed RASi or non-RASI therapy within a 12-month period

<table>
<tr><th colspan="4">DESCRIPTION</th></tr>
<tr><td>Functional Area</td><td>CKD</td><td>ID code</td><td>To be added locally</td></tr>
<tr><td>Name</td><td colspan="3">Percentage of patients aged 18 years and older with a diagnosis of CKD (grades 1-3, or grades 4-5 who are not receiving KRT) who were prescribed RASi or non-RASi therapy within a 12-month period.</td></tr>
<tr><td>Definition</td><td colspan="3">KRT: For the purposes of this measure, KRT includes hemodialysis, peritoneal dialysis, and kidney transplantation.

Prescribed: May include prescription given to the patient for RASi or non-RASi therapy OR patients already taking RASi or non-RASi therapy as documented in the current medication list.

Classification CKD by GFR:
<table>
<tr><td>G1: normal or high kidney function</td><td>GFR: greater than 90 mL/minute/1.73 m²</td></tr>
<tr><td>G2: mildly decreased kidney function</td><td>GFR: 60 to 89 mL/minute/1.73 m²</td></tr>
<tr><td>G3a: mildly to moderately decreased kidney function</td><td>GFR: 45 to 59 mL/minute/1.73 m²</td></tr>
<tr><td>G3b: moderately to severely decreased kidney function</td><td>GFR: 30 to 44 mL/minute/1.73 m²</td></tr>
<tr><td>G4: severely decreased kidney function</td><td>GFR: 15 to 29 mL/minute/1.73 m²</td></tr>
<tr><td>G5: kidney failure</td><td>GFR: less than 15 mL/minute/1.73 m²</td></tr>
</table></td></tr>
<tr><td>Rationale</td><td colspan="3">In adults with CKD, the CKD Task Force suggests using a RASi over a non-RASi for hypertension treatment [1]. This recommendation applies to all adults with CKD stages 1-3 and to those with advanced CKD (stages 4-5) who are not receiving KRT.</td></tr>
<tr><td>Classifications</td><td>Process</td><td>Quality dimensions</td><td>Safety, Effectiveness</td></tr>
<tr><th colspan="4">CALCULATION</th></tr>
<tr><td>Calculation formula</td><td colspan="3">((Total number of patients aged 18 years and older who were prescribed RASi therapy within a 12-month period) / (Total number of patients aged 18 years and older with a diagnosis of CKD within the same period)) x 100</td></tr>
<tr><td>Numerator</td><td>• Patients aged 18 years and older with a diagnosis of CKD who were prescribed RASi therapy on their last recorded list of chronic medications during a 12-month period.</td><td>Denominator</td><td>• Patients aged 18 years and older with a diagnosis of CKD within the same period.</td></tr>
<tr><td>Exclusion criteria</td><td>• Patients aged 18 years and older with a diagnosis CKD grades 4-5 who are receiving KRT.
• Patients aged 17 years and younger with a diagnosis of CKD.</td><td>Exclusion criteria</td><td>• Documentation of medical reason(s) for not prescribing RASi therapy (e.g., allergy to medications)
• Documentation of patient reason(s) for not prescribing RASi therapy (patient</td></tr>
</table>

			declined, other patient reasons). • Patients aged 18 years and older with a diagnosis of CKD grades 4-5 who are receiving KRT • Patients aged 17 years and younger with a diagnosis of CKD.
Unit of measure	Percentage (%)		
TARGET SETTING			
Target	*To be agreed locally*	**Data collection**	Monthly *or as agreed locally*
Benchmark	*To be agreed locally*	**Reporting frequency**	Quarterly *or as agreed locally*
DATA COLLECTION AND ADMINISTRATION			
Data source	Patient medical records		
References	1. *Alhasan KA, Askandarani S, Amer YS, et al. 2022 Saudi Guideline for Chronic Kidney Disease: Blood Pressure Management and Kidney Replacement Therapy in Adults and Children.*		

ACR: albumin-to-creatinine ratio; AER: albumin excretion rate; CKD: chronic kidney disease; G: grade; GFR: Glomerular filtration rate; Non-RASi: non-renin angiotensin system inhibition; RASi: renin angiotensin system inhibition; SBP: systolic blood pressure

10.2.2. Percentage of patients aged 18 and older with a diagnosis of CKD in whom the recent blood pressure was adequately controlled during the measurement period.

DESCRIPTION			
Functional Area	CKD	**ID code**	*To be added locally*
Name	Percentage of patients aged 18 years and older with a diagnosis of CKD in whom the recent blood pressure was adequately controlled during the measurement period.		
Definition	**Adequately controlled of blood pressure:** For the purposes of this measure, systolic blood pressure <120 mmHg. **Measurement period:** The previous 12 months, note: If there are multiple blood pressure readings on the same day, use the lowest systolic and the lowest diastolic reading as the most recent blood pressure reading.		
Rationale	In adults with CKD, the CKD Task Force suggests using intensive (SBP <120 mm Hg) blood pressure targets rather than standard (SBP <140mm Hg) blood pressure targets for hypertension treatment [(1)].		
Classifications	Process	**Quality dimensions**	Safety, Effectiveness
CALCULATION			
Calculation formula	**(Total number of patients aged 18 years and older with a diagnosis of CKD whose recent blood pressure was adequately controlled / Total number of patients aged 18 years and older with a diagnosis of CKD within the same period) x 100**		
Numerator	• Patients aged 18 years and older with a diagnosis of CKD whose recent SBP was <120 mm Hg.	**Denominator**	• Patients aged 18 years and older with a diagnosis of CKD.
Exclusion criteria	Do not include blood pressure readings: • Taken during an acute inpatient stay or a visit to the Emergency Department. • Taken on the same day as a diagnostic test or diagnostic or therapeutic procedure that requires a change in diet or change in medication on or one day before the day of the test or procedure, except for fasting blood tests. • Taken by someone who is not a clinician. • Patients aged 17 years and younger	**Exclusion criteria**	• Hospice services given to patient any time during the measurement period. • Patients aged 17 years and younger with a diagnosis of CKD.
Unit of measure	Percentage (%)		
TARGET SETTING			
Target	*To be agreed locally*	**Data collection**	Monthly *or as agreed locally*
Benchmark	*To be agreed locally*	**Reporting frequency**	Quarterly *or as agreed locally*
DATA COLLECTION AND ADMINISTRATION			

Data source	Patient medical records
References:	1. *Alhasan KA, Askandarani S, Amer YS, et al. 2022 Saudi Guideline for Chronic Kidney Disease: Blood Pressure Management and Kidney Replacement Therapy in Adults and Children.*

CKD: chronic kidney disease; MAP: mean arterial pressure; SBP: systolic blood pressure

10.2.3. Percentage of patients aged 18 years and older with a diagnosis of CKD initiating dialysis at eGFR of 5-7 mL/min/1.73 m2.

DESCRIPTION			
Functional Area	CKD	**ID code**	*To be added locally*
Name	Percentage of patients aged 18 years and older with a diagnosis of CKD who are initiating dialysis at an eGFR of 5-7 mL/min/1.73 m2.		
Definition	**Severe symptoms:** Severe uremic symptoms and/or uncontrollable fluid overload.		
Rationale	In previously KRT-naive adults requiring KRT for deteriorating CKD, the CKD Task Force suggests initiating KRT late (i.e., eGFR 5-7 mL/min/1.73m2) or based on severe symptoms rather than initiating KRT early (i.e., eGFR 10-15 mL/min/1.73m2) or based on moderate symptoms[1].		
Classifications	Process	**Quality dimensions**	Safety, Effectiveness
CALCULATION			
Calculation formula	**(Total number of patients aged 18 years and older with a diagnosis of CKD initiating dialysis at an eGFR of 5-7 mL/min/1.73 m2 / Total number of patients aged 18 years and older with a diagnosis of CKD within the same period) x 100**		
Numerator	• Previously KRT-naive patients aged 18 years and older with a diagnosis of CKD who are initiating dialysis at an eGFR of 5-7 mL/min/1.73 m2.	**Denominator**	• Patients aged 18 years and older with a diagnosis of CKD.
Exclusion criteria	• Patients aged 17 years and younger with a diagnosis of CKD.	**Exclusion criteria**	• Patients aged 17 years and younger with a diagnosis of CKD.
Unit of measure	Percentage (%)		
TARGET SETTING			
Target	*To be agreed locally*	**Data collection**	Monthly *or as agreed locally*
Benchmark	*To be agreed locally*	**Reporting frequency**	Quarterly *or as agreed locally*
DATA COLLECTION AND ADMINISTRATION			
Data source	Patient medical records		
References:	1. *Alhasan KA, Askandarani S, Amer YS, et al. 2022 Saudi Guideline for Chronic Kidney Disease: Blood Pressure Management and Kidney Replacement Therapy in Adults and Children.*		

CKD: chronic kidney disease; eGRF: estimated glomerular filtration rate.

10.2.4. Percentage of patients aged 18 years and older with a diagnosis of CKD and an eGFR of less than 5-7 mL/min/1.73m2 (on at least 2 occasions 90 days apart) referred for kidney transplant.

DESCRIPTION			
Functional Area	CKD	**ID code**	*To be added locally*
Name	Percentage of patients aged 18 years and older with a diagnosis of CKD and an eGFR of less than 5-7 mL/min/1.73m2 (on at least 2 occasions 90 days apart) referred for kidney transplant.		
Definition	**Severe symptoms:** Severe uremic symptoms and/or uncontrollable fluid overload.		
Rationale	In previously KRT-naive adults requiring KRT for deteriorating CKD, the CKD Task Force suggests initiating KRT late (i.e., eGFR 5-7 mL/min/1.73m2) or based on severe symptoms rather than initiating KRT early (i.e., eGFR 10-15 mL/min/1.73m2) or based on moderate symptoms[1].		
Classifications	Process	**Quality dimensions**	Effectiveness
CALCULATION			
Calculation formula	**(Total number of patients aged 18 years and older with a diagnosis of CKD and an eGFR of less than 5-7 mL/min/1.73m2 (on at least 2 occasions 90 days apart) who are referred for kidney transplant / Total number of patients aged 18 years and older with a diagnosis of CKD and an eGFR of less than 5-7 mL/min/1.73m2 [on at least 2 occasions 90 days apart]) x 100**		
Numerator	• Patients aged 18 years and older with a diagnosis of CKD with an eGFR of less than 5-7 mL/min/1.73m2 (on at least 2 occasions 90 days apart) who are referred for kidney transplant within a 12-month period.	**Denominator**	• Patients aged 18 years and older with a diagnosis of CKD and an eGFR of less than 5-7 mL/min/1.73m2 (on at least 2 occasions 90 days apart).
Exclusion criteria	• Patients aged 17 years or younger with a diagnosis of CKD an eGFR of less than 5-7 mL/min/1.73m2 (on at least 2 occasions 90 days apart).	**Exclusion criteria**	• Documentation of medical reason(s) for not referring for kidney transplant (e.g., patients undergoing palliative dialysis). • Documentation of patient reason(s) for not referring for kidney transplant (e.g., patient declined). • Documentation of system reason(s) for not referring for kidney transplant (e.g., nearest facility too far away, other systems reasons). • Patients aged 17 years or younger with a diagnosis of CKD an eGFR of less than 5-7 mL/min/1.73m2 (on at least 2 occasions 90 days apart).
Unit of measure	Percentage (%)		
TARGET SETTING			

Target	*To be agreed locally*	**Data collection**	Monthly *or as agreed locally*
Benchmark	*To be agreed locally*	**Reporting frequency**	Quarterly *or as agreed locally*
DATA COLLECTION AND ADMINISTRATION			
Data source	Patient medical records		
References:	1. *Alhasan KA, Askandarani S, Amer YS, et al. 2022 Saudi Guideline for Chronic Kidney Disease: Blood Pressure Management and Kidney Replacement Therapy in Adults and Children.*		

CKD: chronic kidney disease; eGRF: estimated glomerular filtration rate; KRT: kidney replacement therapy

11. Guideline dissemination and implementation

Appropriate dissemination and implementation are key to the success of any guideline.

Dissemination has been defined as the targeted distribution of guideline information and materials, whereas implementation strategies are techniques that enhance guideline adoption, use and sustainability (Tomasone et al., 2020).

The multi-faceted interventions to increase clinical adoption of this guideline consist of:

- Dissemination: Website, app with API-driven content feeds from the associated GRADEpro account.
- Implementation: The guideline recommendations will be used to inform customized computerized provider order entry (CPOE) order sets integrated within the electronic health record systems at selected pilot sites across Saudi Arabia. Additional local guideline implementation strategies/interventions—whether workflow- or provider-focused—may include: leadership commitment and engagement, dissemination and communication, regular training and education, regular audit and feedback to identify facilitators and barriers, and patients as champions for change (Amer et al., 2019; Fischer et al., 2016; Gagliardi et al., 2015; Paksaite et al., 2021).

12. Guideline updating and localization

A review of the guideline by the National Guidelines Center will occur no later than 5 years post publication, with an earlier review prompted by:

- Relevant new evidence, new interventions, changes to the health system, patient values or available resources.
- Internal or external feedback to improve the usability of recommendations without changing the intent, and therefore without the need for an evidence review or Task Force input.
- Clinical review at cluster or institutional level for localization of guideline recommendations (and derived order sets).

The guideline update process will be guided by the Checklist for the Reporting of Updated Guidelines (CheckUp) (Vernooij et al., 2017).

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14. Appendix

14.1. Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACEi	Angiotensin-converting enzyme inhibitor
ACR	Albumin-to-creatinine ratio
AER	Albumin excretion rate
AKI	Acute kidney injury
ARB	Angiotensin II receptor blocker
BP	Blood pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
CAD	Canadian Dollars
CCB	Calcium channel blocker
CoHTA	Center of Health Technology Assessment
CKD	Chronic kidney disease
CKiD	Chronic Kidney Disease in Children Study
CPG	Clinical practice guideline
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
EQ-5D	European Quality of Life Five Dimension
ESKD	End-stage kidney disease
EtD	Evidence-to-Decision
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIN	Guidelines International Network
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GC	Guidelines Center
GDP	Gross domestic product
HBPM	Home blood pressure monitoring
HD	Hemodialysis
HDF	Hemodiafiltration
HHC	Health Holding Company
KDIGO	Kidney Disease: Improving Global Outcomes
MAP	Mean arterial pressure

NICE	National Institute for Health and Care Excellence
Non-RASi	Non-renin-angiotensin system inhibitor
NSAIDS	Non-steroidal anti-inflammatory drugs
PD	Peritoneal dialysis
RASi	Renin-angiotensin system inhibitor
RCT/s	Randomized controlled trial/s
KRT	Kidney replacement therapy
SBP	Systolic blood pressure
UK	United Kingdom
vs	versus

14.2. Glossary of terms

Term	**Definition**
Acute kidney injury	Previously known as acute kidney failure. This is a wide spectrum of injury to the kidneys (not just failure) and is characterized by rapid loss of kidney function.
Advance care plan	A formal care plan that includes details about the person's condition, decisions made with them, and where appropriate their parents or caregivers (for example about managing symptoms), and their wishes and ambitions. This plan is a core element of their palliative care.
Ambulatory blood pressure monitoring	Blood pressure obtained on a frequent intermittent basis (i.e., 15–30 min per 24 h) using an automated wearable device, usually outside the provider's office or medical facilities.
Arteriovenous fistula	A link created between an artery and vein needed for hemodialysis.
Automated office blood pressure	Blood pressure obtained in the provider's office using an automated device that is programmed to start only after a set resting period and measured several times with fixed intervals between measurements. An average reading is then provided as the output. Preparation before measurement and attendance by the provider are not part of the definition.
Chronic kidney disease	Abnormalities of kidney function and/or structure, present for more than three months, with implications for health.
Cognitive impairment	A problem with a person's thinking, communication, understanding or memory. It may be a short-term problem or a permanent condition.
Conservative management	Full supportive management (including the control of symptoms and complications and advance care planning) for those in the later stages of chronic kidney disease who, in conjunction with caregivers and the clinical team, decide against kidney replacement therapy.
Dialysis via vascular access	An umbrella term to incorporate both hemodialysis and hemodiafiltration.

Early strategy	Preparation for kidney replacement therapy by estimated glomerular filtration rate or by time from start of KRT
Encapsulating peritoneal sclerosis	A rare complication of long-term peritoneal dialysis associated with extensive thickening and fibrosis of the peritoneum that can severely affect the bowel such that it becomes partially or even fully obstructed.
End of life care	End of life care includes the care and support given in the final days, weeks and months of life, and the planning and preparation for this.
Estimated glomerular filtration rate	Assessment of how much blood is filtered by the kidneys, estimated using a mathematical formula that compares a person's size, age, sex, and race to serum creatinine levels.
Fluid allowance	Daily allowable fluid intake. This is necessary because the kidneys are unable to regulate the amount of fluid in the body.
Hemodiafiltration	A form of dialysis which removes uremic solutes beyond the usual range of small molecules removed in conventional hemodialysis.
Hemodialysis	A form of dialysis in which the blood is cleaned outside the body in a dialysis machine.
Home blood pressure monitoring	Blood pressure obtained at the patient's home with an automated oscillometric or manual auscultatory device, usually excluding automated office blood pressure. Preparation before measurement, person taking the measurement, and the device used are not part of the definition, although they are often performed by the patient herself/himself with an automated device.
Home hemodialysis	Hemodialysis available for suitable patients with support at home.
Hyperkaliemia	Abnormally high potassium concentration in the blood, most often due to defective kidney excretion, as in kidney disease.
Hyperphosphatasemia	An abnormally elevated level of phosphate in the blood.
Kidney replacement therapy	Hemodialysis and/or peritoneal dialysis and/or kidney transplant.
Intensive blood pressure targeting in children	Targeting 24-hour mean arterial pressure 50th-99th percentile of normal children.
Intensive blood pressure targeting in adults	Systolic blood pressure less than 120 mm Hg
Later stages of chronic kidney disease	Stage 4 or 5 (and stage 3 in the context of initiating planning to the later stages).
Manual blood pressure	Blood pressure obtained using a manual auscultatory blood pressure cuff, instead of an automated method, with either a mercury or aneroid sphygmomanometer. Preparation before the measurement is not part of the definition.
Peritoneal dialysis	A form of dialysis that takes place inside the patient's peritoneal cavity.
Pre-emptive transplant	A kidney transplant before dialysis begins.
Kidney replacement therapy	A term used to encompass life-supporting treatments for severe acute kidney injury or stage 5 chronic kidney disease. It includes hemodialysis, hemofiltration, hemodiafiltration, peritoneal dialysis and kidney transplant. These are collectively

	referred to in the guideline as modalities of kidney replacement therapy.
Routine office blood pressure	Blood pressure measured in the provider's office. Preparation before measurement and the device used are not part of the definition. The values are often inconsistent between providers performing the measurements. In addition, it does not bear a reliable relationship with standardized office blood pressure.
Shared decision making	Shared decision making is an approach where clinicians and patients communicate together using the best available evidence when faced with the task of making decisions, where patients are supported to deliberate about the possible attributes and consequences of options, to arrive at informed preferences in making a determination about the best action and which respects patient autonomy, where this is desired, ethical and legal.
Smoothed percentile	A mathematical formula is applied to raw data to produce charts and graphs of clinical findings, for example for pediatric growth charts.
Standard blood pressure in children	Targeting 24-hour mean arterial pressure 50th-99th percentile of normal children.
Standard blood pressure in adults	Systolic blood pressure less than 140 mm Hg.
Standardized office blood pressure	This is the recommended method for measuring blood pressure. It should be conducted according to the steps outlined in the checklist below. The device used is not part of the definition.
Ultrafiltration	The removal of water in hemodialysis.
Unplanned start	Kidney replacement therapy initiated without prior planning or preparation, often as a result of acute kidney injury.
Uremia	An excess of urea and nitrogen-based wastes in the blood.
Vascular access	Access using a vein for hemodialysis.

Sources: KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD (Cheung et al., 2021) and NICE Guideline Methods, 2018. KRT and conservative management (NICE-NG107, 2018).

14.3. Blood pressure percentiles

Smoothed percentiles of systolic blood pressure for boys (1-18 years) (Al Salloum et al., 2009)

Age (years)	Number	50th	75th	90th	95th
1	598	93	99	106	109
2	403	95	101	108	112
3	453	97	104	110	114
4	502	99	105	112	116
5	545	101	107	114	117
6	497	103	109	115	119
7	555	104	110	117	121

Age (years)	Number	50th	75th	90th	95th
8	508	105	112	118	122
9	501	107	113	120	123
10	557	108	114	121	125
11	536	110	116	122	126
12	472	111	117	124	127
13	458	113	119	125	129
14	439	114	120	127	131
15	389	116	122	129	132
16	374	118	124	130	134
17	293	120	126	133	137
18	218	123	129	135	139

Smoothed percentiles of systolic blood pressure for girls (1-18 years) (Al Salloum et al., 2009)

Age (years)	Number	50th	75th	90th	95th
1	573	93	100	106	110
2	393	95	102	109	113
3	468	98	105	111	115
4	476	100	107	114	117
5	495	102	109	116	119
6	469	104	111	117	121
7	540	105	113	119	123
8	474	107	114	121	125
9	498	109	116	122	126
10	524	110	117	124	128
11	451	111	118	125	129
12	437	112	120	126	130
13	422	113	121	127	131
14	439	114	122	128	132
15	364	115	123	129	133
16	352	116	124	130	134
17	309	117	124	131	135
18	244	118	125	132	136

Smoothed percentiles of diastolic blood pressure for boys (1-18 years) (Al Salloum et al., 2009)

Age (years)	Number	50th	75th	90th	95th
1	598	57	63	68	72
2	403	59	65	70	74
3	453	60	66	72	75
4	502	62	68	73	77
5	545	63	69	74	78
6	497	64	70	76	79
7	555	65	71	76	80
8	508	66	72	77	80
9	501	66	72	78	81
10	557	67	73	78	82
11	536	67	73	79	82
12	472	68	74	79	83
13	458	68	74	80	83
14	439	69	75	80	84
15	389	70	76	81	84
16	374	70	76	82	85
17	293	71	77	82	86
18	218	72	78	83	89

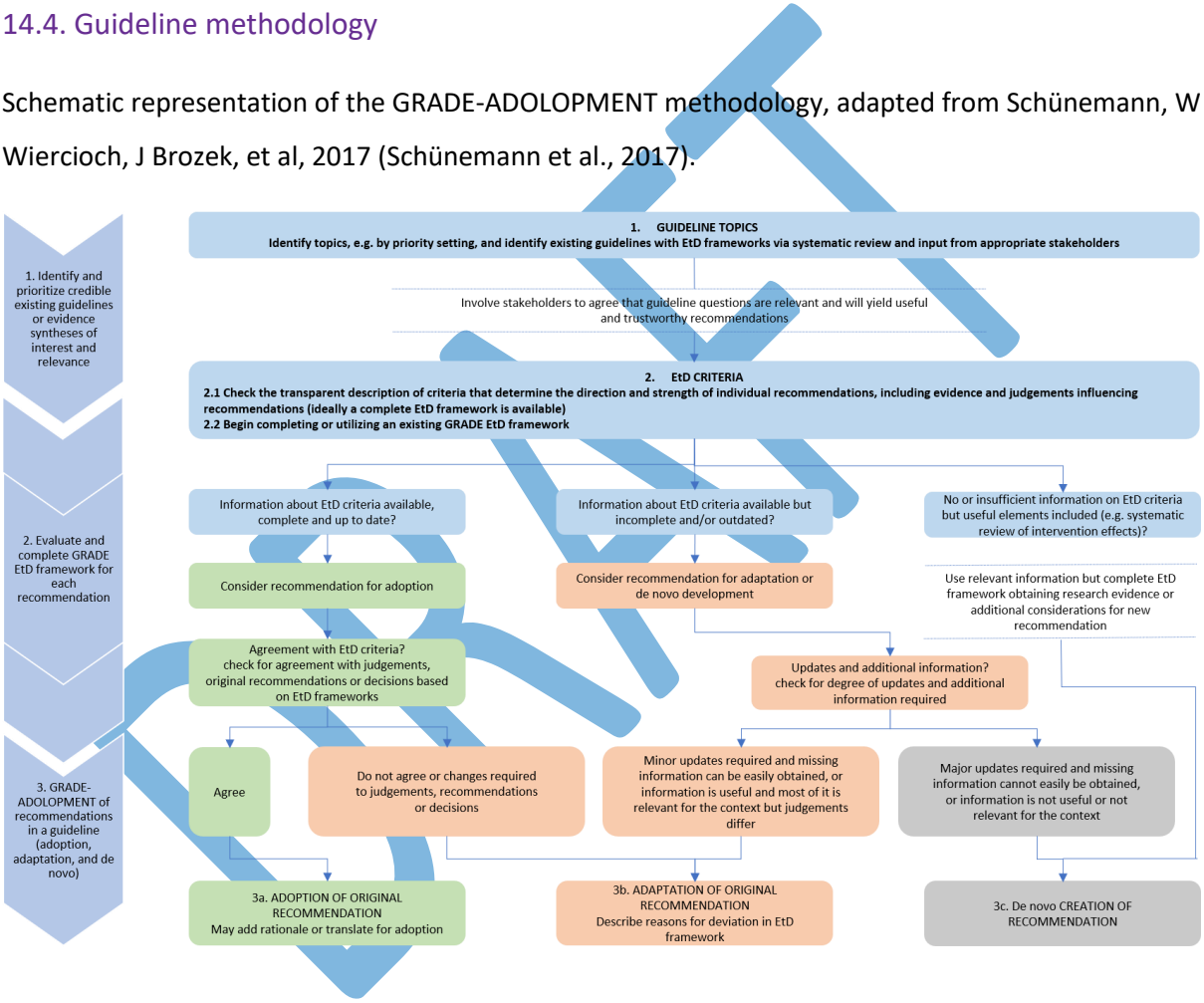
Smoothed percentiles of diastolic blood pressure for girls (1-18 years) (Al Salloum et al., 2009)

Age (years)	Number	50th	75th	90th	95th
1	573	57	63	69	72
2	393	59	65	71	74
3	468	61	67	73	76
4	476	63	69	74	78
5	495	64	70	76	79
6	469	65	71	77	80
7	540	66	72	78	81
8	474	67	73	78	82
9	498	67	73	79	82
10	524	68	74	79	83
11	451	68	74	80	83
12	437	68	74	80	83

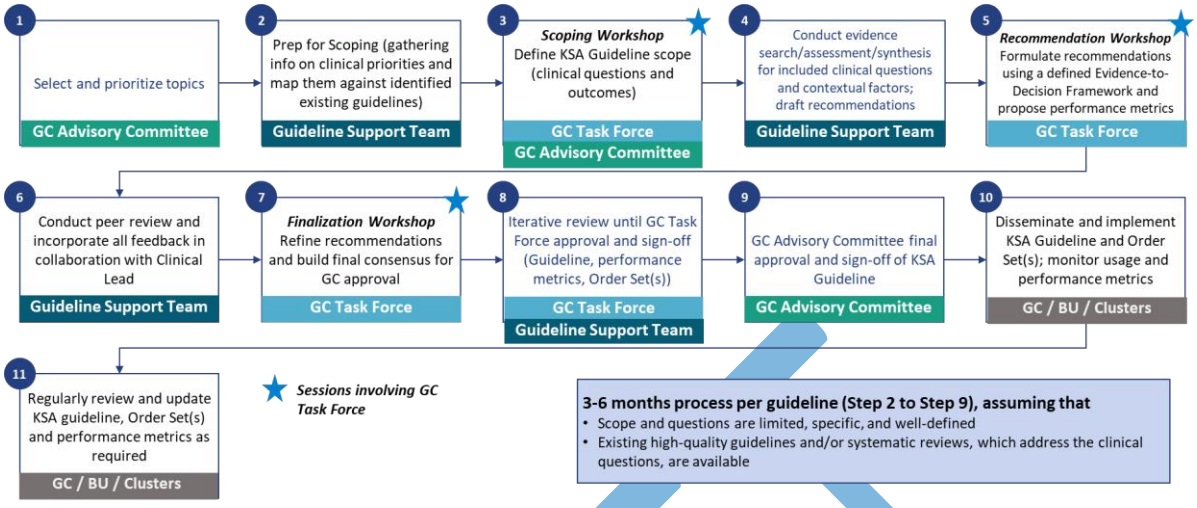
Age (years)	Number	50th	75th	90th	95th
13	422	69	75	80	83
14	439	69	75	80	84
15	364	69	75	81	84
16	352	70	76	81	85
17	309	70	76	82	85
18	244	71	77	83	86

14.4. Guideline methodology

Schematic representation of the GRADE-ADOLOPMENT methodology, adapted from Schünemann, W Wiercioch, J Brozek, et al, 2017 (Schünemann et al., 2017).



The high-level process of guideline development included 10 steps, from topic selection to deployment, with the 11th step to follow guideline dissemination, as indicated below.



GC: Guidelines Center; BU: Business Units.

14.5. Search methods

Search strategies to identify source guidelines

Resources searched:

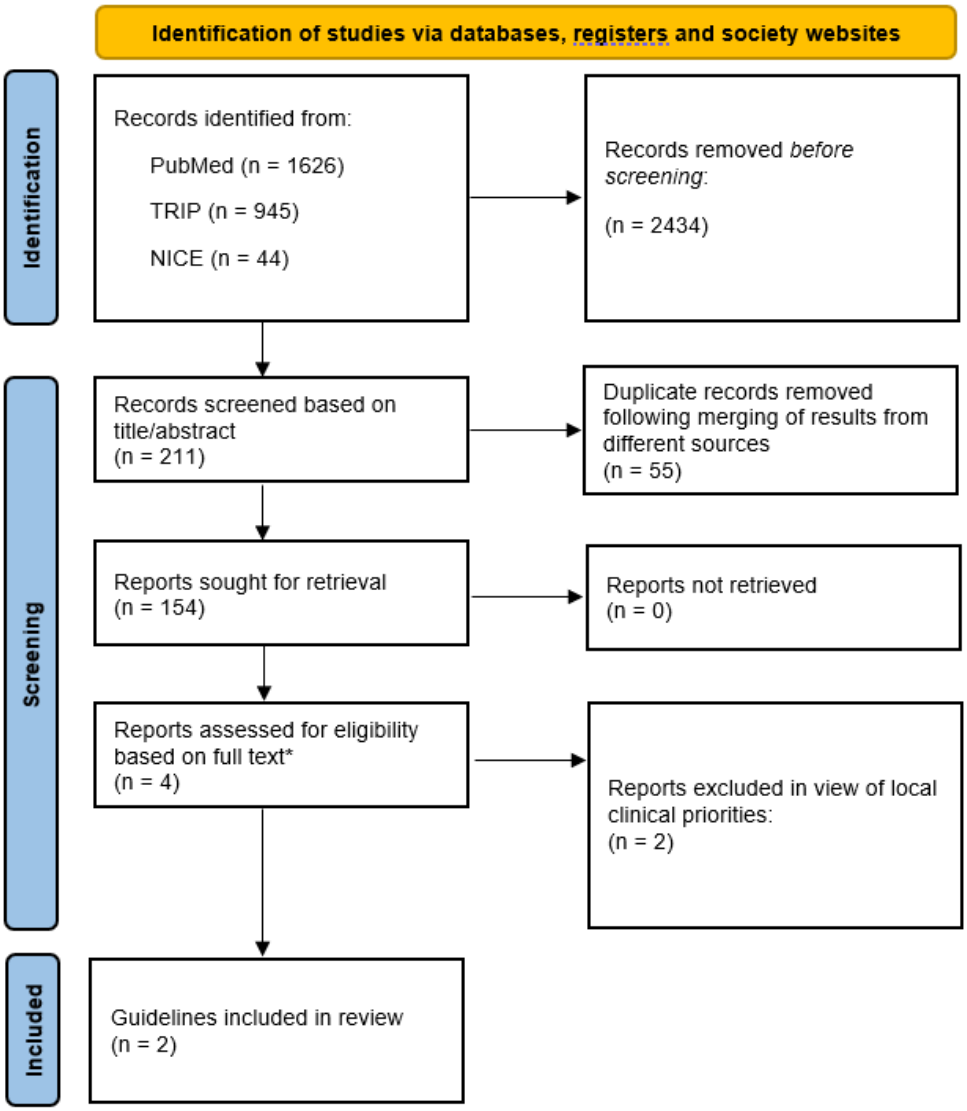
- PubMed
- NICE
- The National Guideline Clearinghouse – AHRQ
- GIN NETWORK
- Database of GRADE EtD's and Guidelines
- TRIP Database
- Epistemonikos
- CMA Infobase: Clinical Practice Guidelines Database (CPGs)
- Guidelines in practice
- BIGG. International Database for GRADE Guidelines. BIREME-OPS
- National Institute for Health and Clinical Excellence (NICE)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Scottish Clinical Guidelines
- Database of WHO guidelines
- New Zealand guidelines

Search period: 2017 to April 2021

Search strategy used for PubMed:

("Renal Insufficiency"[Mesh] OR kidney disease[tiab] OR CKD[tiab] OR renal disease*[tiab] OR renal insufficienc*[tiab] OR renal impairment*[tiab] OR renal failure[tiab] OR severe renal failure[tiab] OR End stage renal[tiab] OR end stage kidney[tiab] OR ESRD[tiab] OR ESKD[tiab] OR ESRF[tiab] OR ESKF[tiab] OR chronic kidney failure[tiab] OR chronic renal failure[tiab] OR CRF[tiab] OR CRI[tiab] OR "Renal Dialysis"[Mesh] OR Dialysis[tiab] OR renal dialysis[tiab] OR hemodialysis[tiab] OR Extracorporeal Dialysis[tiab] OR peritoneal dialysis[tiab] OR glomerular filtration rate[tiab] OR

eGFR[tiab] OR GFR[tiab] OR albuminuria[tiab] OR proteinuria[tiab] OR hematuria[tiab] OR haematuria[tiab] OR creatinine[tiab]) **AND** ((("Congress"[Publication Type] OR "Consensus"[MeSH Terms] OR "Guideline"[Publication Type] OR "Guidelines as Topic"[MeSH Terms:noexp] OR "Practice Guidelines as Topic"[MeSH Terms] OR "ACOG"[Title] OR "advisory"[Title] OR "appropriateness criteria"[Title] OR "best practice*"[Title] OR "committee opinion*"[Title] OR "committee statement*"[Title] OR "consensus"[Title] OR "expert opinion*"[Title] OR "expert panel*"[Title] OR "expert statement*"[Title] OR "guidance"[Title] OR "guideline*"[Title] OR "immunisation practice*"[ti] OR "immunization practice*"[ti] OR "policy statement*"[Title] OR "position paper*"[Title] OR "position statement*"[Title] OR "practice bulletin"[Title] OR "practice parameter*"[Title] OR "preferred practice pattern*"[Title] OR "protocol"[ti] OR "recommendation*"[Title] OR "scientific statement*"[Title] OR "task force"[Title] OR "USPSTF"[Title] OR "technology assessment*"[Title] OR "vademecum"[Title/Abstract] OR "vade mecum"[Title/Abstract] OR "white paper"[Title] OR ("standard*"[Title] AND "Care"[Title])) **NOT** ("Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Ephemera"[Publication Type] OR "Letter"[Publication Type] OR "Newspaper Article"[Publication Type] OR "News"[Publication Type])) **AND** 2015/01/01:3000/12/31[Date - Publication])



*Key inclusion criteria: Used systematic review to establish evidence base; accessible search strategy/ies; existing and accessible evidence tables/summaries. From Page et al. 2021 (Page et al., 2021). Template downloaded from http://www.prisma-statement.org/PRISMAStatement/FlowDiagram.aspx

Search strategies used for the clinical questions

Blood pressure management

- Databases searched: PubMed and Embase
- Search period: 01 April 2020 to present
- Search strategy used:

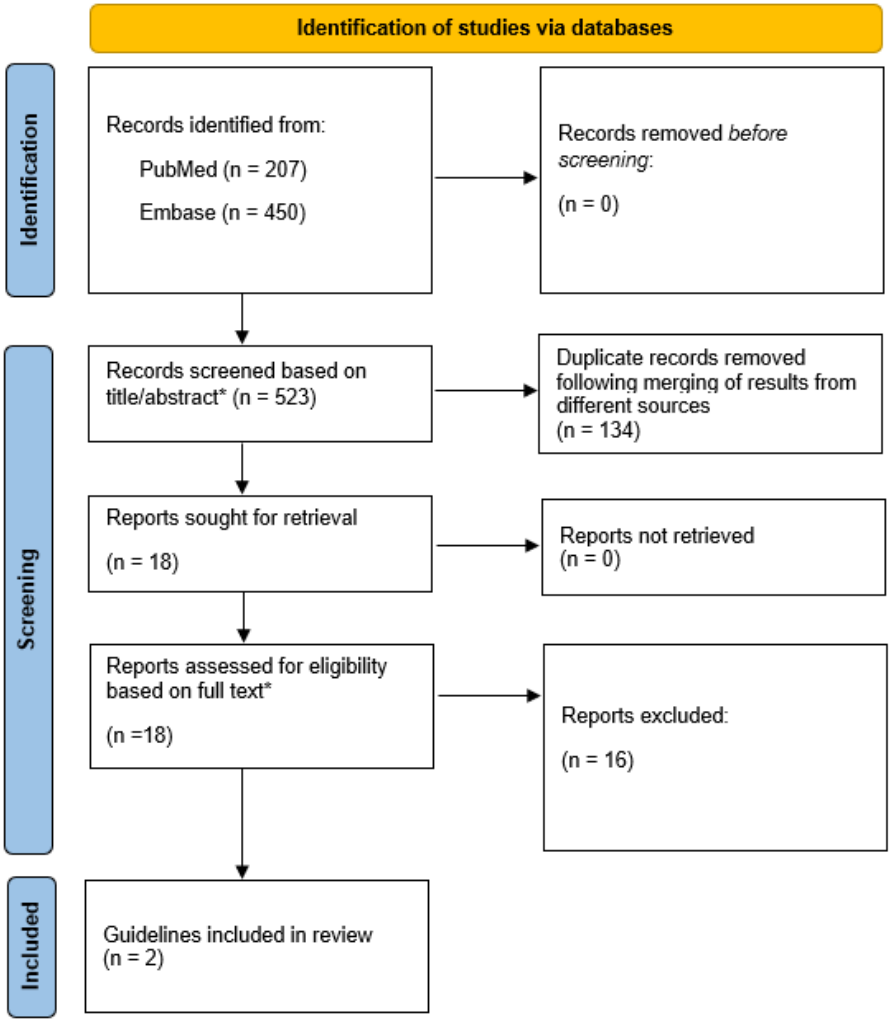
PubMed: ((((Renal Insufficiency[Mesh:NoExp] OR Renal Insufficiency, Chronic[Mesh] OR Kidney Diseases[Mesh:NoExp] OR "end-stage renal"[tiab] OR "end-stage kidney"[tiab] OR "endstage renal"[tiab] OR "endstage kidney"[tiab] OR ESRF[tiab] OR ESKF[tiab] OR ESRD[tiab] OR ESKD[tiab] OR "chronic kidney"[tiab] OR "chronic renal"[tiab] OR CKF[tiab] OR CKD[tiab] OR CRF[tiab] OR CRD[tiab])

AND ((Antihypertensive Agents[Mesh] OR antihypertensive*[tiab] OR anti-hypertensive*[tiab] OR Angiotensin-Converting Enzyme Inhibitors[Mesh] OR Angiotensin Receptor Antagonists[Mesh] OR angiotensin converting enzyme inhibitor*[tiab] OR acei[tiab] OR ace-i[tiab] OR Angiotensin II[Mesh:NoExp] OR AT receptor block*[tiab] OR AT receptor antagon*[tiab] OR ARB[tiab] OR ARBs[tiab] OR Adrenergic beta-Antagonists[Mesh] OR Adrenergic alpha-Antagonists[Mesh] OR Diuretics[Mesh] OR adrenergic beta antagonist*[tiab] OR adrenergic alpha antagonist*[tiab] OR beta block*[tiab] OR alpha block*[tiab] OR diuretic*[tiab] OR Calcium Channel Blockers[Mesh] OR calcium channel blocker*[tiab] OR CCB[tiab] OR CCBs[tiab] OR chlorothiazide[tiab] OR chlorthalidone[tiab] OR hydralazine[tiab] OR hydrochlorothiazide[tiab] OR captopril[tiab] OR enalapril[tiab] OR fosinopril[tiab] OR lisinopril[tiab] OR ramipril[tiab] OR benazepril[tiab] OR perindopril[tiab] OR trandolapril[tiab] OR losartan[tiab] OR irbesartan[tiab] OR candesartan[tiab] OR eprosartan[tiab] OR valsartan[tiab] OR olmesartan[tiab] OR telmisartan[tiab] OR amlodipine[tiab] OR diltiazem[tiab] OR felodipine[tiab] OR nicardipine[tiab] OR lacidipine[tiab] OR manidipine[tiab] OR nifedipine[tiab] OR nimodipine[tiab] OR verapamil[tiab] OR alprenolol[tiab] OR atenolol[tiab] OR metoprolol[tiab] OR nadolol[tiab] OR oxprenolol[tiab] OR pindolol[tiab] OR propranolol[tiab] OR labetalol[tiab] OR bisoprolol[tiab] OR carvedilol[tiab] OR prazosin[tiab] OR doxazosin[tiab] OR terazosin[tiab] OR eplerenone[tiab] OR spironolactone[tiab] OR triamterene[tiab] OR bumetanide[tiab] OR furosemide[tiab] OR indapamide[tiab] OR frusemide[tiab] OR diazoxide[tiab] OR eplerenone[tiab] OR amiloride[tiab] OR clonidine[tiab] OR methyldopa[tiab] OR isradipine[tiab] OR Mineralocorticoid Receptor Antagonists[Mesh] OR Canrenoate Potassium[tiab] OR Canrenone*[tiab] OR spironolactone*[tiab] OR aldosterone antagonist*[tiab] OR aldactone*[tiab] OR practon*[tiab] OR sc-9420*[tiab] OR spiractin*[tiab] OR sc-14266*[tiab] OR soldactone*[tiab] OR soludactone*[tiab] OR aldadiene*[tiab] OR phanurane*[tiab] OR sc-9376[tiab] OR eplerenone*[tiab] OR Renin-Angiotensin System[Mesh:no exp] OR renin inhibit*[tiab] OR RAS inhibit*[tiab] OR aliskiren[tiab] OR zankiren[tiab] OR terlakiren[tiab] OR remikiren[tiab] OR enalkiren[tiab] OR ditekiren[tiab]) OR ((ace[tiab] AND inhibitor*[tiab]) OR (angiotensin[tiab] AND receptor antagonist*[tiab]) OR (angiotensin[tiab] AND receptor block*[tiab])))) AND ("Controlled Clinical Trial" [Publication Type] OR "Controlled Clinical Trials as Topic"[Mesh:NoExp] OR "Randomized Controlled Trials as Topic"[Mesh] OR random*[tiab] OR "Placebos"[Mesh] OR placebo*[tiab] OR crossover[tiab] OR cross-over[tiab] OR "Cross-Over Studies"[Mesh] OR trial[ti])) NOT ("animals"[mesh] NOT "humans"[mesh])) AND ("2020/04/01"[PDAT] : "3000/12/31"[PDAT])

Embase: (((renal NEAR/1 insufficiency):ti,ab,kw) OR ((chronic NEAR/1 renal):ti,ab,kw) OR ((chronic NEAR/1 kidney):ti,ab,kw) OR ((kidney NEAR/1 insufficiency):ti,ab,kw) OR ((endstage NEAR/1 renal):ti,ab,kw) OR (('end stage' NEAR/1 renal):ti,ab,kw) OR (('end stage' NEAR/1 kidney):ti,ab,kw) OR

esrf:ti,ab,kw OR eskf:ti,ab,kw OR esrd:ti,ab,kw OR eskd:ti,ab,kw OR ckd:ti,ab,kw OR crf:ti,ab,kw OR ckf:ti,ab,kw) AND ('antihypertensive agent'/exp OR 'antihypertensive agent' OR 'dipeptidyl carboxypeptidase inhibitor'/exp OR 'dipeptidyl carboxypeptidase inhibitor' OR 'angiotensin receptor antagonist'/exp OR 'angiotensin receptor antagonist' OR 'beta adrenergic receptor blocking agent'/exp OR 'beta adrenergic receptor blocking agent' OR 'alpha adrenergic receptor blocking agent'/exp OR 'alpha adrenergic receptor blocking agent' OR 'diuretic agent'/exp OR 'diuretic agent' OR 'calcium channel blocking agent'/exp OR 'calcium channel blocking agent' OR 'mineralocorticoid receptor antagonist'/exp OR 'mineralocorticoid receptor antagonist' OR 'mineralocorticoid antagonist'/exp OR 'mineralocorticoid antagonist' OR 'renin angiotensin aldosterone system'/exp OR 'renin angiotensin aldosterone system' OR antihypertensive*:ti,ab OR 'anti hypertensive*':ti,ab OR acei:ti,ab OR arb:ti,ab OR arbs:ti,ab OR ccb:ti,ab OR ccbs:ti,ab OR chlorothiazide:ti,ab OR chlorthalidone:ti,ab OR captopril:ti,ab OR diuretic*:ti,ab OR hydralazine:ti,ab OR hydrochlorothiazide:ti,ab OR enalapril:ti,ab OR fosinopril:ti,ab OR lisinopril:ti,ab OR ramipril:ti,ab OR benazepril:ti,ab OR perindopril:ti,ab OR trandolapril:ti,ab OR losartan:ti,ab OR irbesartan:ti,ab OR candesartan:ti,ab OR eprosartan:ti,ab OR valsartan:ti,ab OR olmesartan:ti,ab OR telmisartan:ti,ab OR amlodipine:ti,ab OR diltiazem:ti,ab OR felodipine:ti,ab OR nicardipine:ti,ab OR lacidipine:ti,ab OR manidipine:ti,ab OR nifedipine:ti,ab OR nimodipine:ti,ab OR verapamil:ti,ab OR alprenolol:ti,ab OR atenolol:ti,ab OR metoprolol:ti,ab OR nadolol:ti,ab OR oxprenolol:ti,ab OR pindolol:ti,ab OR propranolol:ti,ab OR labetalol:ti,ab OR bisoprolol:ti,ab OR carvedilol:ti,ab OR prazosin:ti,ab OR doxazosin:ti,ab OR terazosin:ti,ab OR spironolactone:ti,ab OR triamterene:ti,ab OR bumetanide:ti,ab OR furosemide:ti,ab OR indapamide:ti,ab OR frusemide:ti,ab OR diazoxide:ti,ab OR eplerenone:ti,ab OR amiloride:ti,ab OR clonidine:ti,ab OR methyldopa:ti,ab OR isradipine:ti,ab OR canrenoate:ti,ab OR spironolactone*:ti,ab OR canrenone*:ti,ab OR aldactone*:ti,ab OR practon*:ti,ab OR (sc AND 9420*:ti,ab) OR spiractin*:ti,ab OR sc14266*:ti,ab OR soldactone*:ti,ab OR soludactone*:ti,ab OR aldadiene*:ti,ab OR phanurane*:ti,ab OR (sc AND 9376:ti,ab) OR aliskiren:ti,ab OR zankiren:ti,ab OR terlakiren:ti,ab OR remikiren:ti,ab OR enalkiren:ti,ab OR ditekiren:ti,ab OR ((ace NEAR/1 inhibitor*):ti,ab) OR ((adrenergic NEAR/1 alpha):ti,ab) OR ((adrenergic NEAR/1 beta):ti,ab) OR ((aldosterone NEAR/1 antagonist*):ti,ab) OR ((alpha NEAR/1 blocker*):ti,ab) OR ((angiotensin NEAR/1 ii):ti,ab) OR ((angiotensin NEAR/1 converting):ti,ab) OR ((angiotensin NEAR/1 receptor):ti,ab) OR ((beta NEAR/1 blocker*):ti,ab) OR ((ras NEAR/1 inhibit*):ti,ab) OR ((renin NEAR/1 inhibit*):ti,ab)) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it) NOT (('animals'/exp OR 'animals') NOT ('human'/exp OR 'human')) AND ('controlled clinical trial'/exp OR 'controlled clinical trial' OR 'placebo'/exp OR 'placebo' OR random*:ti,ab OR

placebo*:ti,ab OR crossover:ti,ab OR 'cross over':ti,ab OR trial:ti) AND [1-4-2020]/sd NOT [1-1-3001]/sd



*Eligibility criteria:

- Inclusion criteria: ***A) Population:*** (a) Children hospitalized or ambulatory medical patients with CKD at any stage of the disease; (b) Adults (18 years and over) hospitalized or ambulatory medical patients with CKD at any stage of the disease. ***B) Comparisons***: (a) antihypertensive agents versus standard of care in children; (b) non-RAS inhibition versus placebo or RAS inhibition; (c) lower blood pressure target versus higher blood pressure in children; (d) lower (intensive) blood pressure targets versus standard blood pressure targets in adults. ***C) Study Type:*** RCTs which could include 2 or more arms but must include at least one of the comparisons.

- Exclusion criteria: Patients having CKD with comorbidities including diabetes, heart failure, etc.

From: Page et al. 2021 (Page et al., 2021). Template downloaded from http://www.prisma-statement.org/PRISMAStatement/FlowDiagram.aspx

Kidney replacement therapy

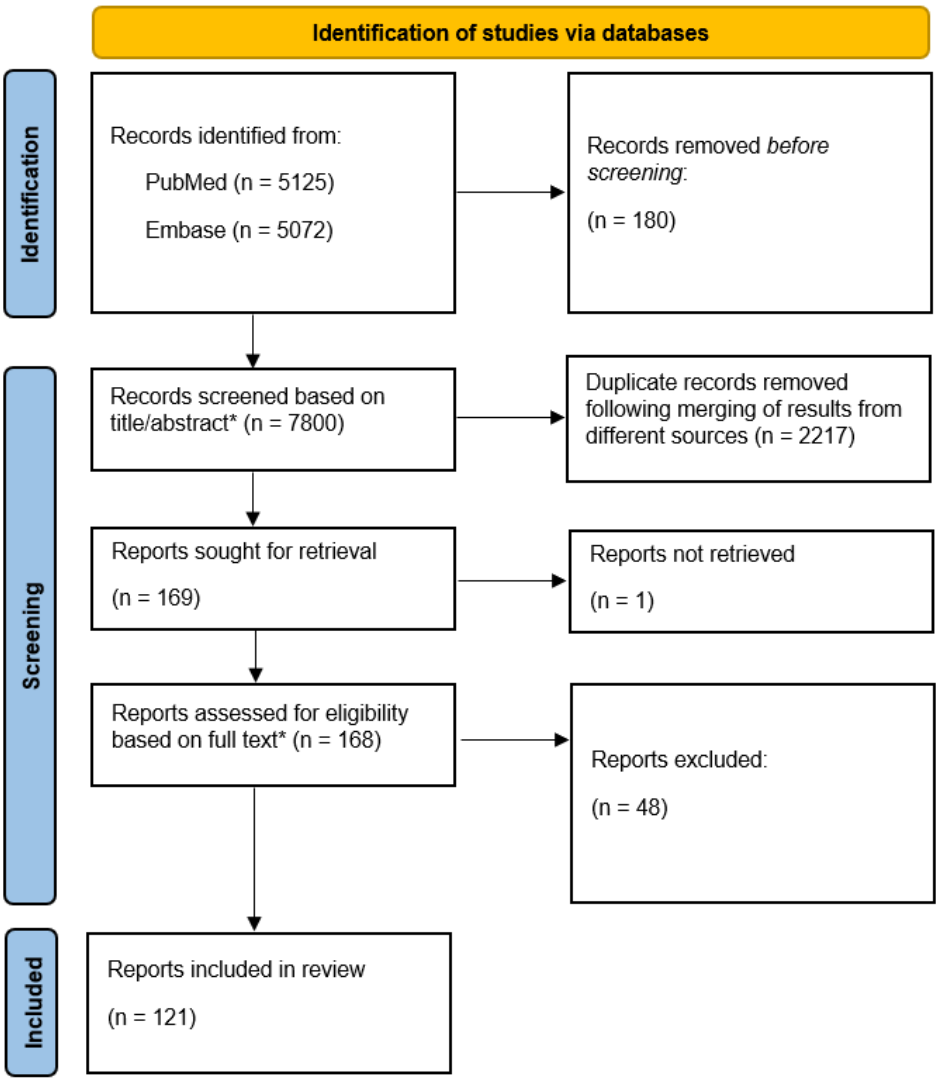
- Databases searched: PubMed and Embase
- Search period: 01 December 2017 to present
- Search strategy used:

PubMed: (((((("Renal Insufficiency, Chronic"[Mesh] OR "Chronic Kidney"[tiab] OR "Chronic Renal"[tiab] OR "End stage kidney"[tiab] OR "End stage renal"[tiab] OR "Severe renal disease*"[tiab] OR "Severe renal failure*"[tiab] OR CKD[tiab] OR CKF[tiab] OR CRF[tiab] OR ESKD[tiab] OR ESKF[tiab] OR ESRD[tiab] OR ESRF[tiab]) AND ("Renal Replacement Therapy"[Mesh] OR "Artificial kidney*"[tiab] OR "Kidney graft*"[tiab] OR "Kidney replacement*"[tiab] OR "Kidney transplant*"[tiab] OR "Renal graft*"[tiab] OR "Renal replacement*"[tiab] OR "Renal transplant*"[tiab] OR "Acetate Free Biofilt*"[tiab] OR "Extracorporeal Dialys*"[tiab] OR Haemodiafilt*[tiab] OR Haemodialys*[tiab] OR Haemoperfusion[tiab] OR Hemodiafilt*[tiab] OR Hemodialys*[tiab] OR Hemoperfusion[tiab] OR "Peritoneal Dialys*"[tiab] OR "Renal Dialys*"[tiab] OR AFB[tiab] OR CAPD[tiab] OR KRT[tiab])) AND (2017/12/1:3000/12/31[pdat]) AND (english[Filter])) NOT ("Biomarkers"[Mesh] OR "Chromatography"[Mesh] OR "Chromosomes"[Mesh] OR "Echocardiography"[Mesh] OR "Genetics"[Mesh] OR "Genome"[Mesh] OR "Genomics"[Mesh] OR "Genotype"[Mesh] OR "Incidence"[Mesh] OR "Mass Spectrometry"[Mesh] OR "Microbiota"[Mesh] OR "Mutation"[Mesh] OR "Pharmacokinetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Prevalence"[Mesh] OR "Quality of Life"[Mesh] OR "Risk Factors"[Mesh] OR "congenital" [Subheading] OR "genetics"[Subheading] OR "pharmacokinetics"[Subheading] OR assay*[tiab] OR biomarker*[tiab] OR cell[tiab] OR cells[tiab] OR chromosome*[tiab] OR genetic*[tiab] OR genome*[tiab] OR genomic*[tiab] OR "in vitro"[tiab] OR microbiom*[tiab] OR microbiota*[tiab] OR mutat*[tiab] OR pharmacokinetic*[tiab] OR polymorphism*[tiab] OR SNP[tiab] OR spectrometry[tiab] OR tissue*[tiab])) NOT (("Animals"[Mesh] OR animal*[tiab] OR ape[tiab] OR apes[tiab] OR canine*[tiab] OR cat[tiab] OR cats[tiab] OR chimpanzee*[tiab] OR dog[tiab] OR dogs[tiab] OR feline*[tiab] OR hamster*[tiab] OR lamb*[tiab] OR mice[tiab] OR monkey*[tiab] OR mouse[tiab] OR murine[tiab] OR pig[tiab] OR pigs[tiab] OR piglet*[tiab] OR porcine[tiab] OR primate*[tiab] OR rabbit*[tiab] OR rat[tiab] OR rats[tiab] OR rodent*[tiab] OR sheep*[tiab] OR swine[tiab]) NOT ("Humans"[Mesh] OR human*[tiab] OR man[tiab] OR men[tiab] OR patient*[tiab] OR woman[tiab] OR women[tiab]))) NOT ("Academic Dissertation"[Publication Type] OR "address"[Publication Type] OR "Anecdotes"[Publication Type] OR "Animation"[Publication Type] OR "autobiography"[Publication Type] OR "bibliography"[Publication Type] OR "biography"[Publication Type] OR "Book Illustrations"[Publication Type] OR "Book Review"[Publication Type] OR "Bookplate"[Publication Type] OR "Cartoon"[Publication Type] OR "Case Reports"[Publication Type] OR "Catalog"[Publication Type] OR "Chart"[Publication Type] OR

"Comment"[Publication Type] OR "congress"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "dictionary"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "Expression of Concern"[Publication Type] OR "Guideline"[Publication Type] OR "Handbook"[Publication Type] OR "interactive tutorial"[Publication Type] OR "interview"[Publication Type] OR "Juvenile Literature"[Publication Type] OR "lecture"[Publication Type] OR "legal case"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "Meeting Abstract"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "overall"[Publication Type] OR "patient education handout"[Publication Type] OR "periodical index"[Publication Type] OR "personal narrative"[Publication Type] OR "portrait"[Publication Type] OR "Review"[Publication Type] OR "Scientific Integrity Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Unpublished Work"[Publication Type] OR "hascommenton"[All Fields] OR "Cartoons as Topic"[Mesh] OR "Meta-Analysis as Topic"[Mesh] OR "Review Literature as Topic"[Mesh] OR "Systematic Reviews as Topic"[Mesh] OR "case report*"[tiab] OR "case series"[tiab] OR "integrative research review*"[tiab] OR "integrative review*"[tiab] OR "literature review"[tiab] OR meta-analys*[tiab] OR "meta analys*"[tiab] OR metaanalys*[tiab] OR "narrative review"[tiab] OR "research integration"[tiab] OR "scoping review"[tiab] OR ((methodologic*[tiab] OR quantitative*[tiab] OR systematic*[tiab]) AND (overview*[tiab] OR review*[tiab] OR synthesis*[tiab])))

Embase: (((((('chronic kidney failure'/exp OR "Chronic Kidney":ti,ab OR "Chronic Renal":ti,ab OR "End stage kidney":ti,ab OR "End stage renal":ti,ab OR "Severe renal disease*":ti,ab OR "Severe renal failure*":ti,ab OR CKD:ti,ab OR CKF:ti,ab OR CRF:ti,ab OR ESKD:ti,ab OR ESKF:ti,ab OR ESRD:ti,ab OR ESRF:ti,ab) AND ('renal replacement therapy'/exp OR "Artificial kidney*":ti,ab OR "Kidney graft*":ti,ab OR "Kidney replacement*":ti,ab OR "Kidney transplant*":ti,ab OR "Renal graft*":ti,ab OR "Renal replacement*":ti,ab OR "Renal transplant*":ti,ab OR "Acetate Free Biofilt*":ti,ab OR "Extracorporeal Dialys*":ti,ab OR Haemodiafilt*:ti,ab OR Haemodialys*:ti,ab OR Haemoperfusion:ti,ab OR Hemodiafilt*:ti,ab OR Hemodialys*:ti,ab OR Hemoperfusion:ti,ab OR "Peritoneal Dialys*":ti,ab OR "Renal Dialys*":ti,ab OR AFB:ti,ab OR CAPD:ti,ab OR KRT:ti,ab)) AND ([1-12-2017]/sd NOT [1-1-3001]/sd) AND [english]/lim) NOT ('biological marker'/exp OR 'chromatography'/exp OR 'chromosome'/exp OR 'congenital'/exp OR 'echocardiography'/exp OR 'genetic polymorphism'/exp OR 'genetics'/exp OR 'genome'/exp OR 'genomics'/exp OR 'genotype'/exp OR 'incidence'/exp OR 'mass spectrometry'/exp OR 'microbiome'/exp OR 'mutation'/exp OR 'pharmacokinetics'/exp OR 'polymorphism'/exp OR 'prevalence'/exp OR 'quality of life'/exp OR 'risk factor'/exp OR assay*:ti,ab OR biomarker*:ti,ab OR cell:ti,ab OR cells:ti,ab OR chromosome*:ti,ab OR genetic*:ti,ab OR

genome*:ti,ab OR genomic*:ti,ab OR "in vitro":ti,ab OR microbiom*:ti,ab OR microbiota*:ti,ab OR mutat*:ti,ab OR pharmacokinetic*:ti,ab OR polymorphism*:ti,ab OR SNP:ti,ab OR spectrometry:ti,ab OR tissue*:ti,ab)) NOT (('animal'/exp OR animal*:ti,ab OR ape:ti,ab OR apes:ti,ab OR canine*:ti,ab OR cat:ti,ab OR cats:ti,ab OR chimpanzee*:ti,ab OR dog:ti,ab OR dogs:ti,ab OR feline*:ti,ab OR hamster*:ti,ab OR lamb*:ti,ab OR mice:ti,ab OR monkey*:ti,ab OR mouse:ti,ab OR murine:ti,ab OR pig:ti,ab OR pigs:ti,ab OR piglet*:ti,ab OR porcine:ti,ab OR primate*:ti,ab OR rabbit*:ti,ab OR rat:ti,ab OR rats:ti,ab OR rodent*:ti,ab OR sheep*:ti,ab OR swine:ti,ab) NOT ('human'/exp OR human*:ti,ab OR man:ti,ab OR men:ti,ab OR patient*:ti,ab OR woman:ti,ab OR women:ti,ab))) NOT ('abstract report'/exp OR 'animal experiment'/exp OR 'book'/exp OR 'case finding'/exp OR 'case report'/exp OR 'case study'/exp OR 'conference paper'/exp OR 'editorial'/exp OR 'feasibility study'/exp OR 'in vitro study'/exp 'letter'/exp OR 'meta analysis'/exp OR 'meta analysis topic'/exp OR 'meta analysis (topic)'/exp OR 'note'/exp OR 'practice guideline'/exp OR 'review'/exp OR 'systematic review'/exp OR 'systematic review topic'/exp OR 'systematic review (topic)'/exp OR 'veterinary clinical trial'/exp OR 'veterinary study'/exp OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR "case report*":ti,ab OR "case series":ti,ab OR "integrative research review*":ti,ab OR "integrative review*":ti,ab OR "literature review":ti,ab OR meta-analys*:ti,ab OR "meta analys*":ti,ab OR metaanalys*:ti,ab OR meta*analys*:ti,ab OR "narrative review":ti,ab OR "research integration":ti,ab OR "scoping review":ti,ab OR (integrative NEAR/5 research NEAR/5 review*):ti,ab OR (methodologic* NEAR/5 overview*):ti,ab OR (methodologic* NEAR/5 review*):ti,ab OR (quantitativ* NEAR/5 overview*):ti,ab OR (quantitativ* NEAR/5 review*):ti,ab OR (quantitativ* NEAR/5 synthesi*):ti,ab OR (research NEAR/5 integration):ti,ab OR (systematic* NEAR/5 overview*):ti,ab OR (systematic* NEAR/5 review*):ti,ab)



*Eligibility criteria:

- Inclusion criteria: ***A) Population:*** (a) Children, young people and adults with CKD stage 3 to 5 or (b) People requiring KRT for deteriorating CKD (c) Adults and children requiring or currently receiving KRT or (d) Adults and children who are being assessed for KRT or conservative management, including for later stages of CKD, or who are undergoing KRT or conservative management, their families, caregivers, and healthcare professionals or (e) People requiring KRT for CKD or opting for conservative management, once they are established on their option of choice (no cut-off for conservative management, >1 year for transplant >3 months for hemodialysis/PD). ***B) Comparison:*** (a) initiating KRT at "early" eGFR or based on moderate symptoms compared to initiating KRT at "late" eGFR or based on severe symptoms; (b) early assessment for KRT compared to late assessment for KRT; c) conservative management compared to any KRT (hemodialysis and/or PD and/or transplant); (d) any modality of KRT (hemodialysis, PD, transplant, conservative management) compared to any other modality (hemodialysis, PD, transplant, conservative management); (e) transferring between forms of KRT or discontinuing KRT based on any suitable indicator compared to not transferring between forms of KRT or discontinuing KRT, or transferring between forms of KRT or discontinuing KRT at a later stage; (f) any early strategy (preparation by eGFR or by time from start of KRT) compared to any late strategy (preparation by eGFR, or by time from start of KRT; (g) identification of important symptoms compared to no identification of important symptoms; (h) any frequency of review for each of the forms of KRT and conservative management compared to any other review strategy; (i) information, education, and support compared to no information, education, and support. ***C) Study Type:*** Any RCTs or Non-Randomized Studies (e.g., case control, cohorts), only if adjusted for key confounders. Trials or cohorts can include 2 or more arms but must include at least one of the comparisons of interest.

- Exclusion criteria: Studies that have KRT being provided for acute kidney injury, and not for CKD, studies that have KRT being provided in a level 2 or 3 care setting, and crossover studies. Patients with diabetes, anemia, mineral bone disorders and other co-morbidities

From: Page et al. 2021 (Page et al., 2021). Template downloaded from http://www.prisma-statement.org/PRISMAStatement/FlowDiagram.aspx

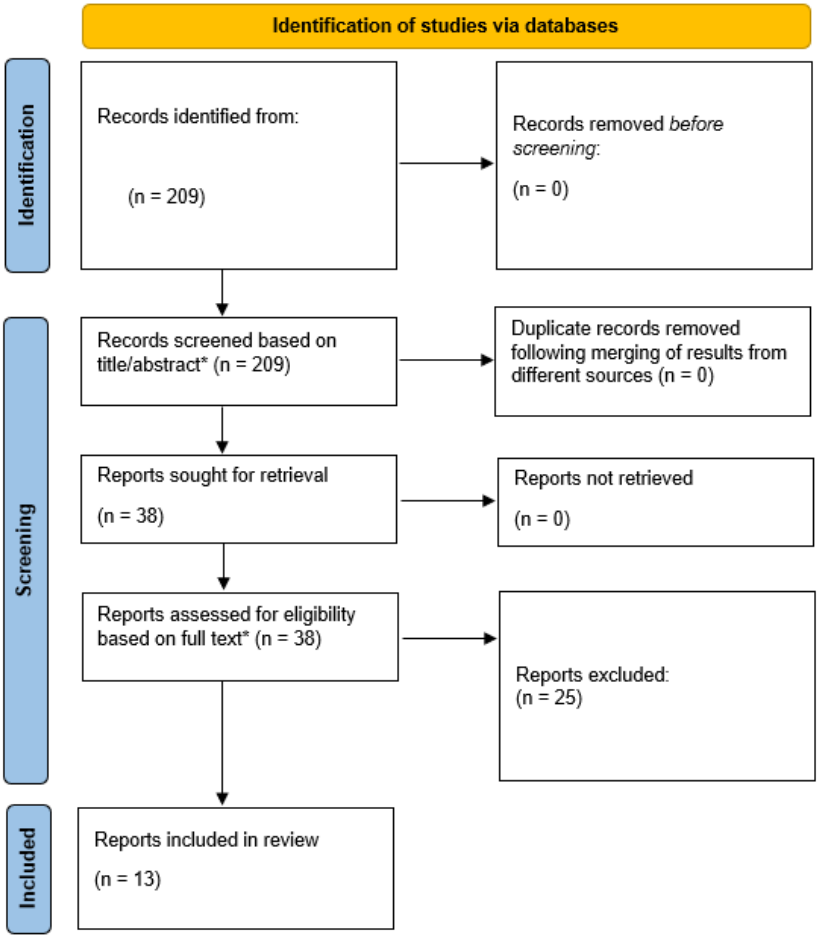
Search strategies for contextual factors

Patient values and preferences:

- Database searched: PubMed
- Search period: No filter applied
- Search strategy used:

Pubmed: ((("Decision Making"[Majr] OR "avoidance behavi*"[tiab] OR "avoidance learning"[tiab] OR decision*[tiab] OR "decision aid*"[tiab] OR "decision analy*"[tiab] OR "decision board*"[tiab] OR "decision mak*"[tiab] OR "decisions mak*"[tiab] OR decision-support[tiab] OR "decision tool*"[tiab] OR "discrete choice"[tiab] OR discrete-choice*[tiab] OR (decision*[ti] AND making[ti])) OR ("Attitude to Health"[Majr] OR "Patient Participation"[Majr] OR "Patient Satisfaction"[Majr] OR choice*[ti] OR valuat*[ti] OR value*[ti] OR acceptab*[tiab] OR attitude*[tiab] OR expectation*[tiab] OR "health perception*"[tiab] OR "health state values"[tiab] OR "health values"[tiab] OR knowledge[tiab] OR "patient choice*"[tiab] OR "patient participation"[tiab] OR "patient perce*"[tiab] OR "patient perspective*"[tiab] OR "patient valuat*"[tiab] OR "patient value*"[tiab] OR "patient view*"[tiab] OR "patients choice*"[tiab] OR "patients participation"[tiab] OR "patients perce*"[tiab] OR "patients perspective*"[tiab] OR "patients valuat*"[tiab] OR "patients value*"[tiab] OR "patients view*"[tiab] OR "patients' choice*"[tiab] OR "patients' participation"[tiab] OR "patients' perce*"[tiab] OR "patients' perspective*"[tiab] OR "patients' valuat*"[tiab] OR "patients' value*"[tiab] OR "patients' view*"[tiab] OR "patient's choice*"[tiab] OR "patient's participation"[tiab] OR "patient's perce*"[tiab] OR "patient's perspective*"[tiab] OR "patient's valuat*"[tiab] OR "patient's value*"[tiab] OR "patient's view*"[tiab] OR preference*[tiab] OR "user choice*"[tiab] OR "user participation"[tiab] OR "user perce*"[tiab] OR "user perspective*"[tiab] OR "user valuat*"[tiab] OR "user value*"[tiab] OR "user view*"[tiab] OR "users choice*"[tiab] OR "users participation"[tiab] OR "users perce*"[tiab] OR "users perspective*"[tiab] OR "users valuat*"[tiab] OR "users value*"[tiab] OR "users view*"[tiab] OR "users' choice*"[tiab] OR "users' participation"[tiab] OR "users' perce*"[tiab] OR "users' perspective*"[tiab] OR "users' valuat*"[tiab] OR "users' value*"[tiab] OR "users' view*"[tiab] OR "user's choice*"[tiab] OR "user's participation"[tiab] OR "user's perce*"[tiab] OR "user's perspective*"[tiab] OR "user's valuat*"[tiab] OR "user's value*"[tiab] OR "user's view*"[tiab]) OR ("Choice Behavior"[Mesh] OR "Decision Making"[Mesh] OR "Decision Support Systems, Clinical"[Mesh] OR "Decision Support Techniques"[Mesh] OR (health[ti] AND utilit*[ti]) OR "best worst"[tiab] OR "best-worst scaling"[tiab]

OR "feeling thermometer*"[tiab] OR gamble*[tiab] OR "health state"[tiab] OR "health utilit*"[tiab] OR "preference elicit*"[tiab] OR "preference score"[tiab] OR "probability trade-off"[tiab] OR "prospect theory"[tiab] OR "time trade-off"[tiab] OR TTO[tiab] OR "best worst scaling"[tw] OR (utility[tw] AND (value*[tw] OR score*[tw] OR estimate*[tw]))) OR ("Quality of Life"[Mesh] OR "EQ 5D"[tiab] OR "EuroQoL 5D"[tiab] OR "multi attribute"[tiab] OR "preference based"[tiab] OR "preference score"[tiab] OR "quality of life"[tiab] OR "SF 12"[tiab] OR "SF 36"[tiab] OR "SF 6D"[tiab] OR 15D[tiab] OR EQ5D[tiab] OR EuroQoL5D[tiab] OR HRQoL[tiab] OR HUI[tiab] OR multiattribute[tiab] OR QoL[tiab] OR SF12[tiab] OR SF36[tiab] OR SF6D[tiab])) AND (Kidney Diseases[Mesh:NoExp] OR Renal Insufficiency, Chronic[Mesh] OR Renal Insufficiency[Mesh:NoExp] OR "chronic kidney"[tiab] OR "chronic renal"[tiab] OR "endstage kidney"[tiab] OR "end-stage kidney"[tiab] OR "endstage renal"[tiab] OR "end-stage renal"[tiab] OR CKD[tiab] OR CKF[tiab] OR CRD[tiab] OR CRF[tiab] OR ESKD[tiab] OR ESKF[tiab] OR ESRD[tiab] OR ESRF[tiab]) AND (("Middle East"[Mesh] OR Afghanistan[All] OR Bahrain[All] OR Iran[All] OR Iraq[All] OR Israel[All] OR Jordan[All] OR Kuwait[All] OR Lebanon[All] OR Oman[All] OR Qatar[All] OR Saudi Arabia[All] OR Saudi[All] OR Syria[All] OR Turkey[All] OR United Arab Emirates[All] OR Yemen[All]) NOT (Afghanistan[AD] OR Bahrain[AD] OR Iran[AD] OR Iraq[AD] OR Israel[AD] OR Jordan[AD] OR Kuwait[AD] OR Lebanon[AD] OR Oman[AD] OR Qatar[AD] OR Saudi Arabia[AD] OR Saudi[AD] OR Syria[AD] OR Turkey[AD] OR United Arab Emirates[AD] OR Yemen[AD]))



*Eligibility criteria:

- Inclusion criteria: ***(A) Patients' values and preferences:*** defined as the relative importance that people place on health outcomes. Keywords included Discrete choice; Decision making; Decision Support Systems; Patient participation; Patient satisfaction; Patient perception; choice; value; attitude; expectation; User participation; choice; valuation; perspective; Preference score; probability trade-off; best-worst scaling; Quality of life; EQ5D; EuroQoL 5D; SF 12; SF 36; Health related Quality of Life; HRQoL ***(B) Population:*** Individuals with CKD disease with the following characteristics: patients in treatment for CKD with and without hypertension, patients with any kidney replacement therapy (hemodialysis, PD, transplant, conservative management) ***(C) Comparison:*** Antihypertensive agents (including non-RAS inhibition and RAS inhibition); Standard of care therapy; Renal replacement therapy (hemodialysis, PD, transplant, conservative management); Health Services (Management Service, Patient Care Management Managed Care Programs, Ambulatory Care Facilities, Practice Patterns Physicians, Pharmaceutical Services); Point-of-Care Systems; Self-Care; Self-administration; Drug Monitoring ***(D) Study Type:*** RCTs, Observational studies (cross-sectional, cohorts, case-controls), qualitative studies. ***(E) Geographic region:*** Middle East; Afghanistan; Bahrain; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Oman; Qatar; Saudi; Turkey; United Arab Emirates; Syria; Yemen

- Exclusion criteria: Non-primary studies (e.g., clinical practice guidelines, reviews, commentaries, communications, letters, or viewpoints), case report, and case series; as well as studies reporting health related quality of life studies not reporting utility information and health economic evaluation studies including cost- effectiveness analysis and cost utility analysis without original utility elicitation

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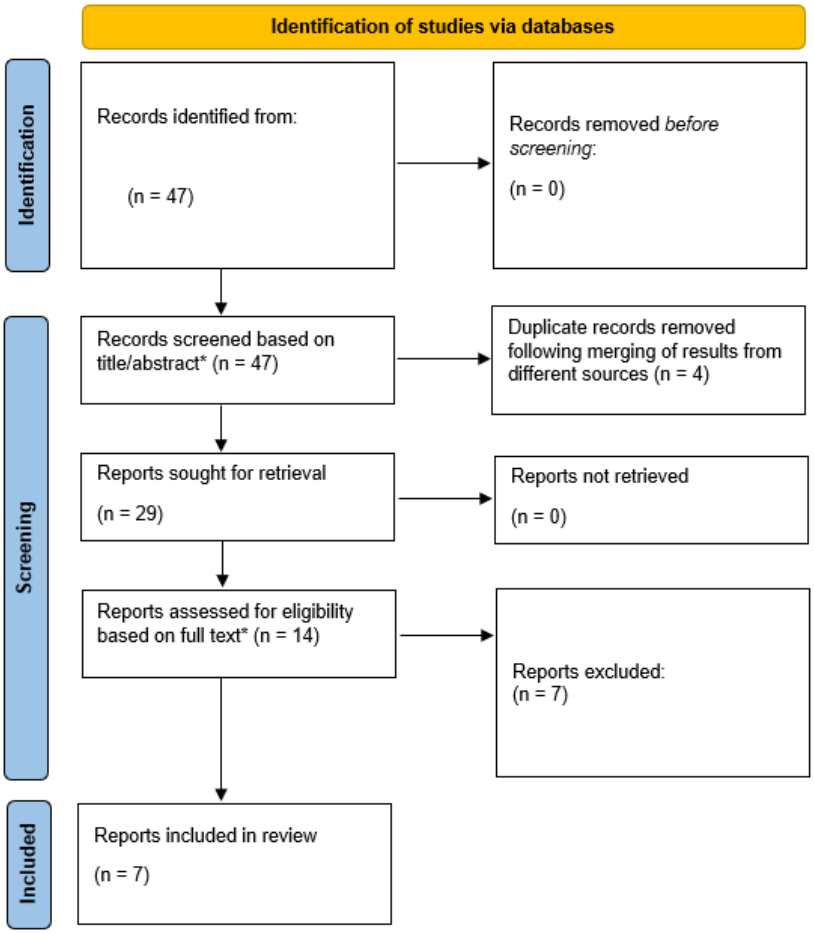
2) Equity

Database searched: PubMed

Search period: No filters applied

Search strategy used:

PubMed: ((Health Services Accessibility[Majr] OR "Access to Health Care"[tiab] OR "Access to Health Service*"[tiab] OR "Access to HealthCare"[tiab] OR "Access To Medic*"[tiab] OR "Access to Medication*"[tiab] OR "Access to Therap*"[tiab] OR "Access to Treat*"[tiab] OR "Accessibility of Health Service*"[tiab] OR "Availability of Health Service*"[tiab] OR coercion[tiab] OR coercive*[tiab] OR controvers*[tiab] OR "Health Services Accessibilit*"[tiab] OR "Health Services Availabilit*"[tiab] OR "Medication Access*"[tiab] OR "Program Accessibilit*"[tiab]) OR (Healthcare Disparities[Majr] OR equit*[tiab] OR "Health Care Disparit*"[tiab] OR "Health Care Inequalit*"[tiab] OR "Healthcare Disparit*"[tiab] OR "Healthcare Inequalit*"[tiab] OR inequit*[tiab]) OR ("Morals"[Majr] OR "ethics"[Subheading] OR ethic*[tiab] OR fairness[tiab] OR moral*[tiab] OR unethical[tiab])) AND (Kidney Diseases[Mesh:NoExp] OR Renal Insufficiency, Chronic[Mesh] OR Renal Insufficiency[Mesh:NoExp] OR "chronic kidney"[tiab] OR "chronic renal"[tiab] OR "endstage kidney"[tiab] OR "end-stage kidney"[tiab] OR "endstage renal"[tiab] OR "end-stage renal"[tiab] OR CKD[tiab] OR CKF[tiab] OR CRD[tiab] OR CRF[tiab] OR ESKD[tiab] OR ESKF[tiab] OR ESRD[tiab] OR ESRF[tiab]) AND (("Middle East"[Mesh] OR Afghanistan[All] OR Bahrain[All] OR Iran[All] OR Iraq[All] OR Israel[All] OR Jordan[All] OR Kuwait[All] OR Lebanon[All] OR Oman[All] OR Qatar[All] OR Saudi Arabia[All] OR Saudi[All] OR Syria[All] OR Turkey[All] OR United Arab Emirates[All] OR Yemen[All]) NOT (Afghanistan[AD] OR Bahrain[AD] OR Iran[AD] OR Iraq[AD] OR Israel[AD] OR Jordan[AD] OR Kuwait[AD] OR Lebanon[AD] OR Oman[AD] OR Qatar[AD] OR Saudi Arabia[AD] OR Saudi[AD] OR Syria[AD] OR Turkey[AD] OR United Arab Emirates[AD] OR Yemen[AD]))



*Eligibility criteria:

- Inclusion criteria: ***(A) Health inequity*** – was defined as systematic, socially produced (and therefore modifiable) and unfair differences in health. Populations may be considered at risk of disadvantage because of demographic and social characteristics such as a person's place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, or social capital (PROGRESS) and other characteristics such as age, disability or temporary conditions that put people at risk of health inequities, due across axes such as access, opportunity to benefit or capacity to implement changes. Keywords included: health service accessibility; access to health care; access to health service; access to medication; access to therapy; access to treat; coercion; coercive; health service availability; program accessibility; healthcare disparities; healthcare inequalities; inequities; morals; ethics; fairness; unethical. ***(B) Population:*** Individuals with CKD disease with the following characteristics: patients in treatment for CKD with and without hypertension, patients with any kidney replacement therapy (hemodialysis, PD, transplant, conservative management) ***(C) Comparison:*** Antihypertensive agents (including non-RAS inhibition and RAS inhibition); Standard of care therapy; Kidney replacement therapy (hemodialysis, PD, transplant, conservative management); Health Services (Management Service, Patient Care Management Managed Care Programs, Ambulatory Care Facilities, Practice Patterns Physicians, Pharmaceutical Services); Point-of-Care Systems; Self-Care; Self-administration; Drug Monitoring ***(D) Study Type:*** structured observational studies (surveys/structured interviews) obtaining direct input from key stakeholders. Key stakeholders could be patients, providers, or policy makers. ***(E) Geographic region:*** Middle East; Afghanistan; Bahrain; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Oman; Qatar; Saudi; Turkey; United Arab Emirates; Syria; Yemen

- Exclusion criteria: Non-primary studies (e.g., clinical practice guidelines, reviews, commentaries, communications, letters, or viewpoints), case report, and case series.

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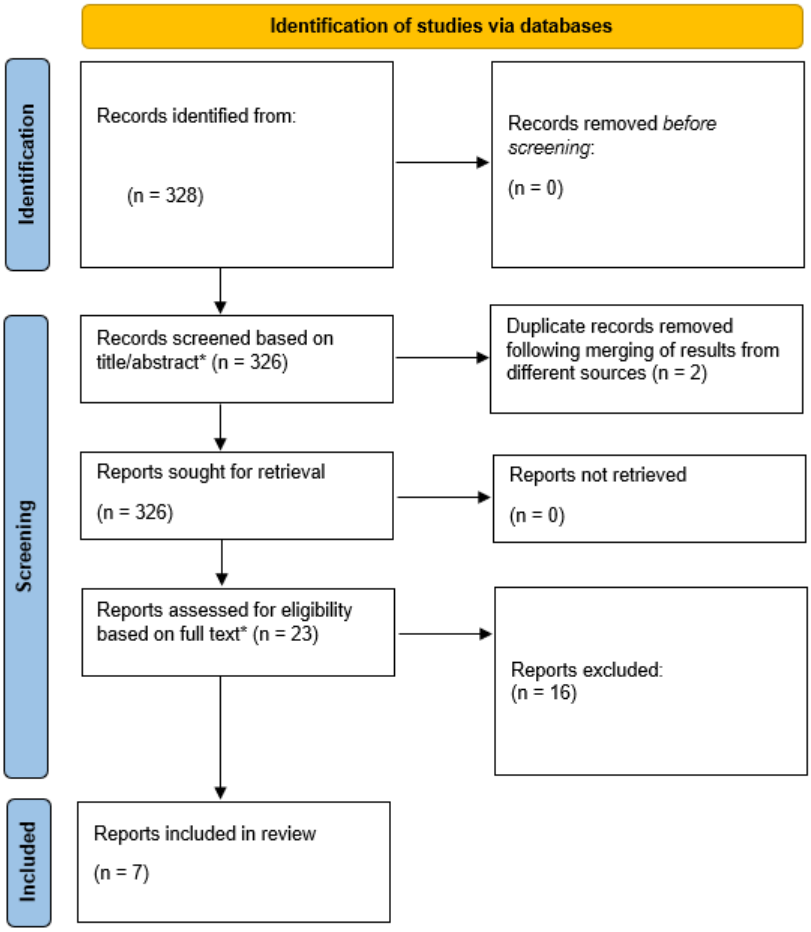
3) Feasibility

Database searched: PubMed

Search period: No filter applied

Search strategy used:

PubMed: ("Feasibility Studies"[Majr] OR feasib*[tiab] OR effective*[tiab] OR efficac*[tiab] OR facilita*[tiab] OR usabilit*[tiab] OR barrier*[tiab] OR difficult*[tiab] OR hurdle*[tiab] OR impede*[tiab] OR impediment*[tiab] OR limit*[tiab] OR obstacle*[tiab]) AND (Kidney Diseases[Mesh:NoExp] OR Renal Insufficiency, Chronic[Mesh] OR Renal Insufficiency[Mesh:NoExp] OR "chronic kidney"[tiab] OR "chronic renal"[tiab] OR "endstage kidney"[tiab] OR "end-stage kidney"[tiab] OR "endstage renal"[tiab] OR "end-stage renal"[tiab] OR CKD[tiab] OR CKF[tiab] OR CRD[tiab] OR CRF[tiab] OR ESKD[tiab] OR ESKF[tiab] OR ESRD[tiab] OR ESRF[tiab]) AND (("Middle East"[Mesh] OR Afghanistan[All] OR Bahrain[All] OR Iran[All] OR Iraq[All] OR Israel[All] OR Jordan[All] OR Kuwait[All] OR Lebanon[All] OR Oman[All] OR Qatar[All] OR Saudi Arabia[All] OR Saudi[All] OR Syria[All] OR Turkey[All] OR United Arab Emirates[All] OR Yemen[All]) NOT (Afghanistan[AD] OR Bahrain[AD] OR Iran[AD] OR Iraq[AD] OR Israel[AD] OR Jordan[AD] OR Kuwait[AD] OR Lebanon[AD] OR Oman[AD] OR Qatar[AD] OR Saudi Arabia[AD] OR Saudi[AD] OR Syria[AD] OR Turkey[AD] OR United Arab Emirates[AD] OR Yemen[AD]))



*Eligibility criteria:

- Inclusion criteria: ***(A) Feasibility*** addressed whether the procedure could be implemented, or if there were substantial barriers to overcome. Keywords included effectiveness; efficacy; facilitative; usability; barriers; difficulty; hurdles; impedes; impediment; limiting; obstacle. ***(B) Population:*** Individuals with CKD disease with the following characteristics: patients in treatment for CKD with and without hypertension, patients with any kidney replacement therapy (hemodialysis, PD, transplant, conservative management) ***(C) Comparison:*** Antihypertensive agents (including non-RAS inhibition and RAS inhibition); Standard of care therapy; Kidney replacement therapy (hemodialysis, PD, transplant, conservative management); Health Services (Management Service, Patient Care Management Managed Care Programs, Ambulatory Care Facilities, Practice Patterns Physicians, Pharmaceutical Services); Point-of-Care Systems; Self-Care; Self-administration; Drug Monitoring. ***(D) Study Type:*** structured observational studies (surveys/structured interviews) obtaining direct input from key stakeholders. Key stakeholders could be patients, providers, or policymakers. ***(E) Geographic region:*** Middle East; Afghanistan; Bahrain; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Oman; Qatar; Saudi; Turkey; United Arab Emirates; Syria; Yemen

- Exclusion criteria: Non-primary studies (e.g., clinical practice guidelines, reviews, commentaries, communications, letters, or viewpoints), case report, and case series.

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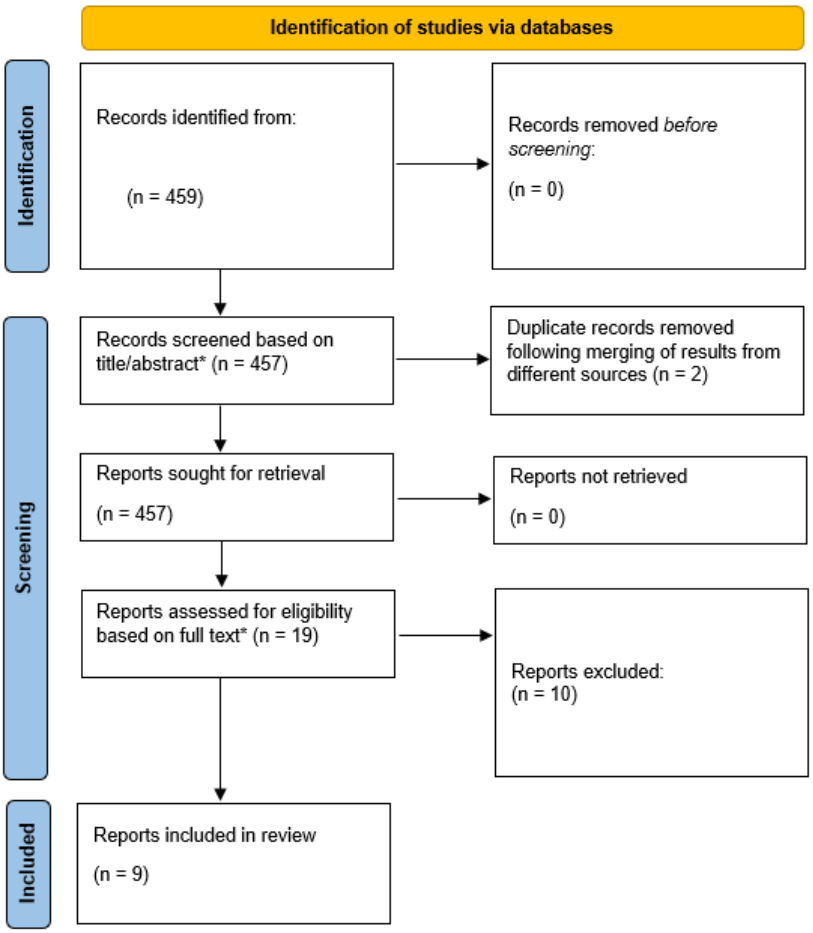
4) Acceptability

Database searched: PubMed

Search period: No filter applied

Search strategy used:

PubMed: (("Attitude to Health"[Mesh] OR accepta*[tiab] OR activat*[tiab] OR adhere*[tiab] OR agreement[tiab] OR attitude*[tiab] OR belief*[tiab] OR collaborat*[tiab] OR complianc*[tiab] OR comply[tiab] OR concordan*[tiab] OR cooperat*[tiab] OR co-operat*[tiab] OR empower*[tiab] OR experience*[tiab] OR inducement[tiab] OR intent*[tiab] OR involv*[tiab] OR motivat*[tiab] OR negotiat*[tiab] OR participat*[tiab] OR partnership[tiab] OR perception*[tiab] OR perspective*[tiab] OR reinforce*[tiab] OR view*[tiab] OR willing*[tiab]) OR ("Cooperative Behavior"[Mesh] OR "patient provider agreement*"[tiab] OR ((shared[tiab] OR joint[tiab] OR informed[tiab] OR collaborative[tiab]) AND "decision making"[tiab]) OR ((involv*[tiab] OR participat*[tiab]) AND (choice*[tiab] OR decision*[tiab])))) AND (Kidney Diseases[Mesh:NoExp] OR Renal Insufficiency, Chronic[Mesh] OR Renal Insufficiency[Mesh:NoExp] OR "chronic kidney"[tiab] OR "chronic renal"[tiab] OR "endstage kidney"[tiab] OR "end-stage kidney"[tiab] OR "endstage renal"[tiab] OR "end-stage renal"[tiab] OR CKD[tiab] OR CKF[tiab] OR CRD[tiab] OR CRF[tiab] OR ESKD[tiab] OR ESKF[tiab] OR ESRD[tiab] OR ESRF[tiab]) AND (("Middle East"[Mesh] OR Afghanistan[All] OR Bahrain[All] OR Iran[All] OR Iraq[All] OR Israel[All] OR Jordan[All] OR Kuwait[All] OR Lebanon[All] OR Oman[All] OR Qatar[All] OR Saudi Arabia[All] OR Saudi[All] OR Syria[All] OR Turkey[All] OR United Arab Emirates[All] OR Yemen[All]) NOT (Afghanistan[AD] OR Bahrain[AD] OR Iran[AD] OR Iraq[AD] OR Israel[AD] OR Jordan[AD] OR Kuwait[AD] OR Lebanon[AD] OR Oman[AD] OR Qatar[AD] OR Saudi Arabia[AD] OR Saudi[AD] OR Syria[AD] OR Turkey[AD] OR United Arab Emirates[AD] OR Yemen[AD]))



*Eligibility criteria:

- Inclusion criteria: ***(A) Acceptability***: was defined as are key stakeholders likely to find the procedure acceptable (given the relative importance they attach to the desirable and undesirable consequences of the option; the timing of the benefits, harms, and costs; and their moral values). Keywords included attitude to health; acceptability; adherence; agreement; attitude; belief; compliance; collaboration; cooperation; empower; empowerment; experience; motivation; negotiation; participation; partnership; perception; perspective; reinforcement; views; willing; cooperative behavior; patient-provider agreement; shared; joint; informed; collaborative decision making; involved or participatory choice or decision making. ***(B) Population:*** Individuals with CKD disease with the following characteristics: patients in treatment for CKD with and without hypertension, patients with any kidney replacement therapy (hemodialysis, PD, transplant, conservative management). ***(C) Comparison:*** Antihypertensive agents (including non-RAS inhibition and RAS inhibition); Standard of care therapy; Renal replacement therapy (hemodialysis, PD, transplant, conservative management); Health Services (Management Service, Patient Care Management Managed Care Programs, Ambulatory Care Facilities, Practice Patterns Physicians, Pharmaceutical Services); Point-of-Care Systems; Self-Care; Self-administration; Drug Monitoring ***(D) Study Type:*** structured observational studies (surveys/structured interviews) obtaining direct input from key stakeholders on perceived feasibility, barriers or equity related to relevant procedures will be sorted separately in case we decide to analyze them in addition to the quantitative studies. Key stakeholders could be patients, providers, or policy makers. ***(E) Geographic region:*** Middle East; Afghanistan; Bahrain; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Oman; Qatar; Saudi; Turkey; United Arab Emirates; Syria; Yemen

- Exclusion criteria: Non-primary studies (e.g., clinical practice guidelines, reviews, commentaries, communications, letters, or viewpoints), case report, and case series.

From: Page et al. 2021 (Page et al., 2021). Template downloaded from http://www.prisma-statement.org/PRISMAStatement/FlowDiagram.aspx

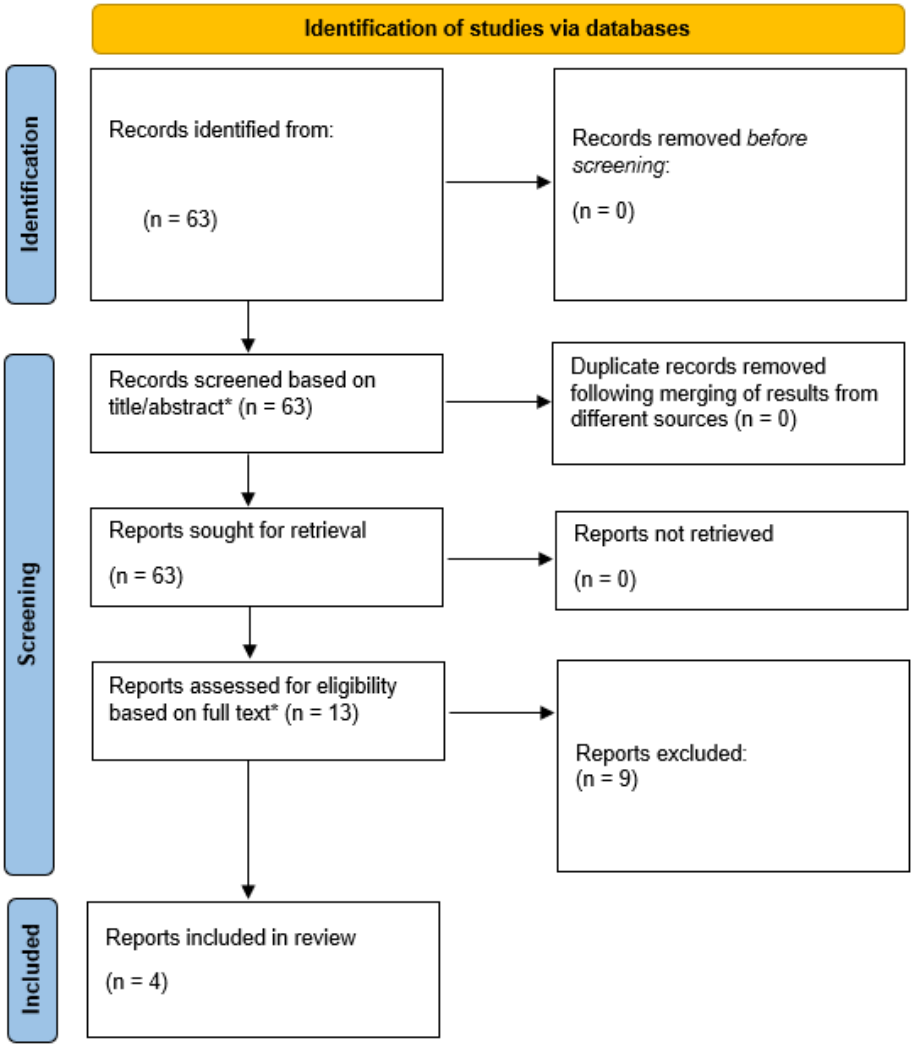
5) Implementation

Database searched: PubMed

Search period: No filter applied

Search strategy used:

PubMed: ((("Clinical Protocols"[Majr] OR "Consensus"[Majr] OR "Critical Pathways"[Majr] OR "Guideline"[Publication Type] OR "Guidelines as Topic"[Majr] OR "Health Planning Guidelines"[Majr] OR advice[tiab] OR advise*[tiab] OR consensus[tiab] OR frame-work*[tiab] OR framework*[tiab] OR guidance*[tiab] OR guideline*[tiab] OR policies[tiab] OR policy[tiab] OR protocol*[tiab] OR recommend*[tiab] OR standard*[tiab] OR statement*[tiab]) AND (accordance[tiab] OR adhere*[tiab] OR adopt*[tiab] OR aware*[tiab] OR barrier*[tiab] OR compliance*[tiab] OR complies[tiab] OR comply*[tiab] OR concordance[tiab] OR disseminat*[tiab] OR facilitat*[tiab] OR implement*[tiab] OR incorporat*[tiab] OR integrat*[tiab] OR spread*[tiab] OR sustain*[tiab] OR takeup*[tiab] OR take-up*[tiab] OR uptake*[tiab] OR up-take*[tiab])) OR ("Diffusion of Innovation"[Majr] OR "Health Plan Implementation"[Majr] OR "Information Dissemination"[Majr] OR "Guideline Adherence"[Majr] OR "Organizational Innovation"[Majr] OR "Guideline Implementation"[tiab] OR "Health Plan Implementation*"[tiab] OR "Information Dissemination"[tiab] OR "Information Distribution"[tiab] OR "Innovation Diffusion"[tiab] OR "Institutional Implementation"[tiab] OR "Policy Implementation"[tiab] OR "Protocol Implementation"[tiab])) AND (Kidney Diseases[Mesh:NoExp] OR Renal Insufficiency, Chronic[Mesh] OR Renal Insufficiency[Mesh:NoExp] OR "chronic kidney"[tiab] OR "chronic renal"[tiab] OR "endstage kidney"[tiab] OR "end-stage kidney"[tiab] OR "endstage renal"[tiab] OR "end-stage renal"[tiab] OR CKD[tiab] OR CKF[tiab] OR CRD[tiab] OR CRF[tiab] OR ESKD[tiab] OR ESKF[tiab] OR ESRD[tiab] OR ESRF[tiab]) AND (("Middle East"[Mesh] OR Afghanistan[All] OR Bahrain[All] OR Iran[All] OR Iraq[All] OR Israel[All] OR Jordan[All] OR Kuwait[All] OR Lebanon[All] OR Oman[All] OR Qatar[All] OR Saudi Arabia[All] OR Saudi[All] OR Syria[All] OR Turkey[All] OR United Arab Emirates[All] OR Yemen[All]) NOT (Afghanistan[AD] OR Bahrain[AD] OR Iran[AD] OR Iraq[AD] OR Israel[AD] OR Jordan[AD] OR Kuwait[AD] OR Lebanon[AD] OR Oman[AD] OR Qatar[AD] OR Saudi Arabia[AD] OR Saudi[AD] OR Syria[AD] OR Turkey[AD] OR United Arab Emirates[AD] OR Yemen[AD]))



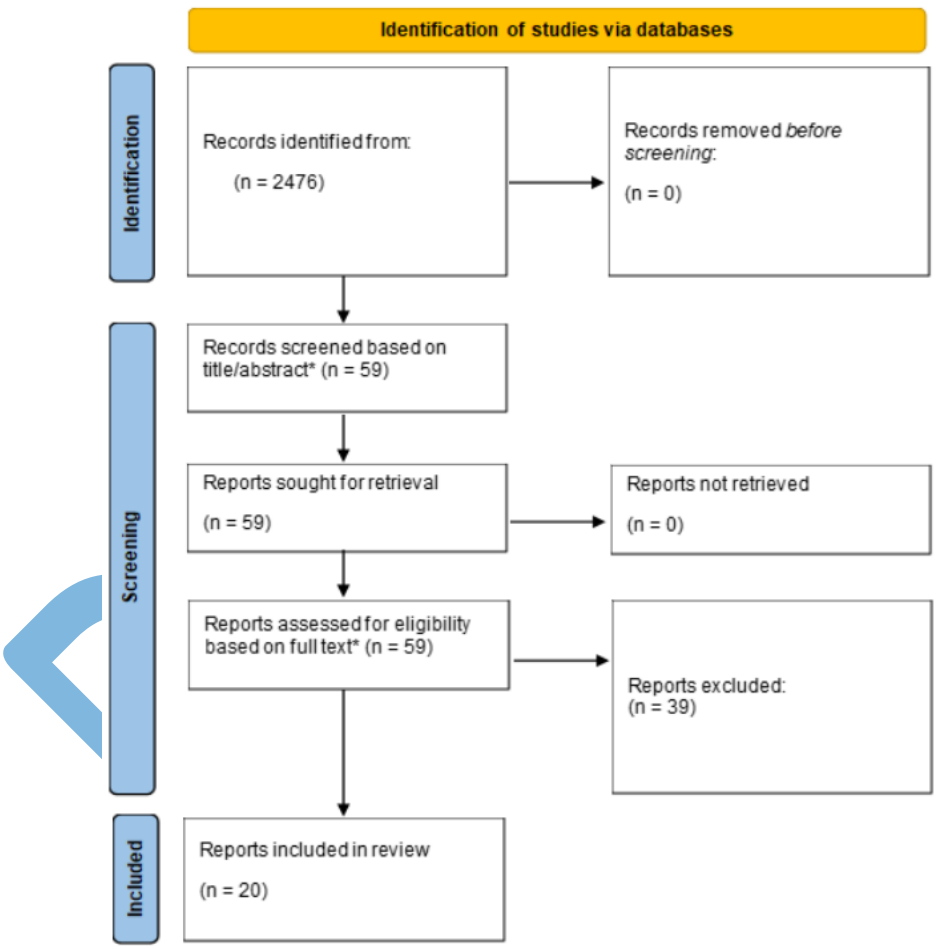
*Eligibility criteria:

- Inclusion criteria: ***(A) Implementation*** interventions was defined as any intervention aiming to improve the uptake of guideline recommendations in practice. Keywords we are looking for: accordance; adherence; adopt; aware; concordance; barrier; compliance; comply; disseminate; facilitate; implement; incorporate; integrate; spread; sustain; take-up; uptake; diffusion of innovation; health plan implementation; information dissemination; guideline adherence; organizational innovation; guideline implementation; health plan implementation; information dissemination; information distribution; innovation diffusion; institutional implementation; policy implementation; protocol implementation; clinical protocols; consensus; critical pathways; guideline; advice; framework; guidance; policies; recommendation; standard; statement. ***(B) Population:*** Individuals with CKD disease with the following characteristics: patients in treatment for CKD with and without hypertension, patients with any kidney replacement therapy (hemodialysis, PD, transplant, conservative management) ***(C) Comparison:*** Antihypertensive agents (including non-RAS inhibition and RAS inhibition); Standard of care therapy; Renal replacement therapy (hemodialysis, PD, transplant, conservative management); Health Services (Management Service, Patient Care Management Managed Care Programs, Ambulatory Care Facilities, Practice Patterns Physicians, Pharmaceutical Services); Point-of-Care Systems; Self-Care; Self-administration; Drug Monitoring ***(D) Study Type:*** structured observational studies (surveys/structured interviews) obtaining direct input from key stakeholders. Key stakeholders could be patients, providers, or policymakers. ***(E) Geographic region:*** Middle East; Afghanistan; Bahrain; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Oman; Qatar; Saudi; Turkey; United Arab Emirates; Syria; Yemen
- Exclusion criteria: Non-primary studies (e.g., clinical practice guidelines, reviews, commentaries, communications, letters, or viewpoints), case report, and case series.

From: Page et al. 2021 (Page et al., 2021). Template downloaded from http://www.prisma-statement.org/PRISMAStatement/FlowDiagram.aspx

Search strategies for cost information

- Databases searched: PubMed, Cochrane, international Health Technology Assessment (HTA) agencies' websites and a focused internet search about each intervention mentioned, using key words for every intervention
- Additional information retrieval: Cost resources such as NHS's cost information and cost information for pharmaceutical interventions (maximum and minimum prices for standard doses per indication) via the Saudi Food and Drug Authority's website (publicly listed price).



*Eligibility criteria:

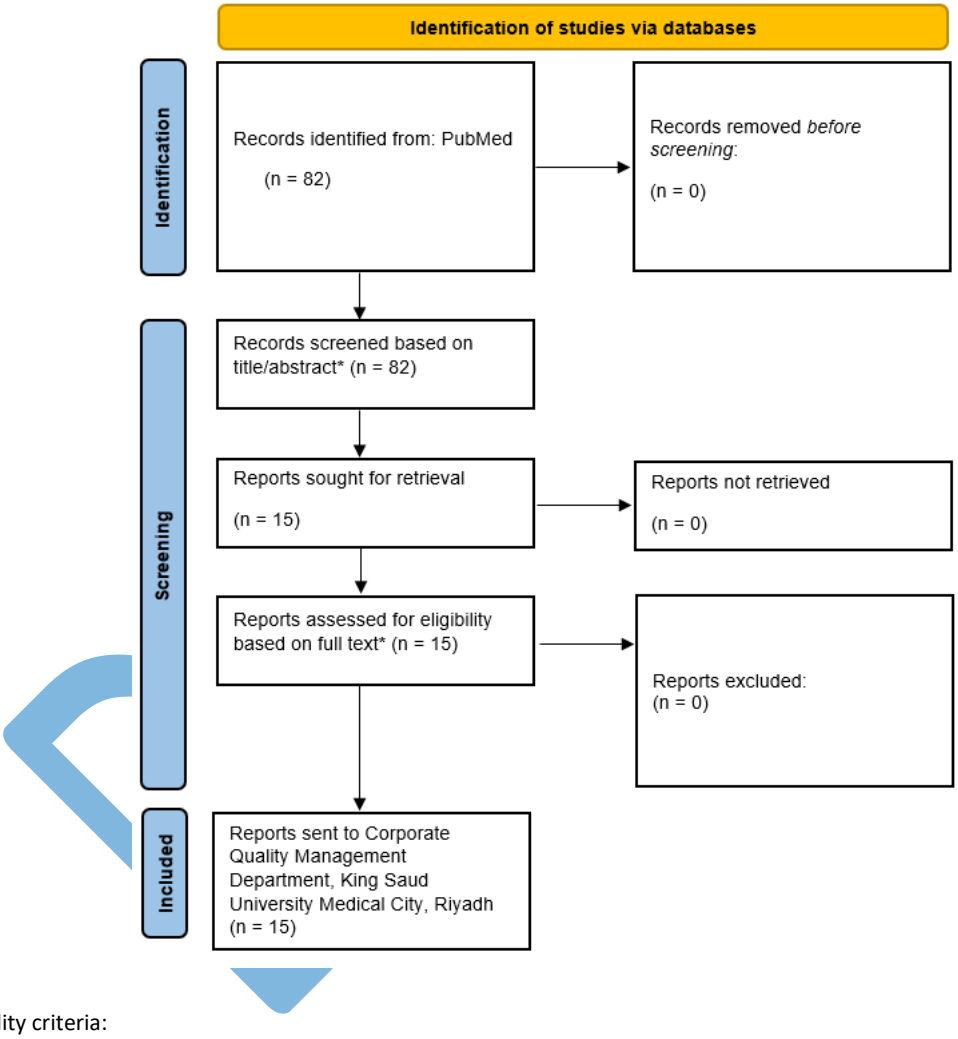
- Inclusion criteria: (a) *Concepts:* Chronic kidney disease and cost of the interventions shared. (b) *Types of studies:* health technology assessments, systematic reviews and/or meta-analyses, RCTs and economic evidence including cost-effectiveness studies
- Exclusion criteria: English-language articles only.

From: Page et al. 2021 (Page et al., 2021). Template downloaded from http://www.prisma-statement.org/PRISMAStatement/FlowDiagram.aspx

Search strategies for performance measures

- Database searched: PubMed
- Search period: No filter applied
- Search strategy used:

  ("kidney diseases"[MeSH Terms:noexp] OR "renal insufficiency, chronic"[MeSH Terms] OR "renal insufficiency"[MeSH Terms:noexp]) AND ("Quality Indicators, Health Care"[Mesh] OR "Quality Indicator*"[Title] OR "Performance Matrix"[Title] OR "Performance Matrices"[Title])



*Eligibility criteria:

- Inclusion criteria: ***(A) Population:*** Individuals with CKD disease with the following characteristics: patients in treatment for CKD with and without hypertension, patients with any kidney replacement therapy (hemodialysis, PD, transplant, conservative management). ***(B) Study Type:*** All types of studies were considered. ***(C) Comparison:*** Antihypertensive agents (including non-RAS inhibition and RAS inhibition); Standard of care therapy; Renal replacement therapy (hemodialysis, PD, transplant, conservative management); Health Services (Management Service, Patient Care Management Managed Care Programs, Ambulatory Care Facilities, Practice Patterns Physicians, Pharmaceutical Services); Point-of-Care Systems; Self-Care; Self-administration; Drug Monitoring. ***(D) Concept:*** Quality indicators or performance measures related to the comparisons.
- Exclusion criteria: Non-primary studies (e.g., clinical practice guidelines, reviews, commentaries, communications, letters, or viewpoints), case reports, and case series.

14.6. Forest plots

The Guideline Support Team created new Forest plots using the Cochrane RevMan software tool for those questions for which we had quantitative evidence synthesis.

Question 1

Figure 1 Forest plot of comparison: 1 ACEi or ARBs versus other antihypertensive agents, outcome: 1.1 ESRD.

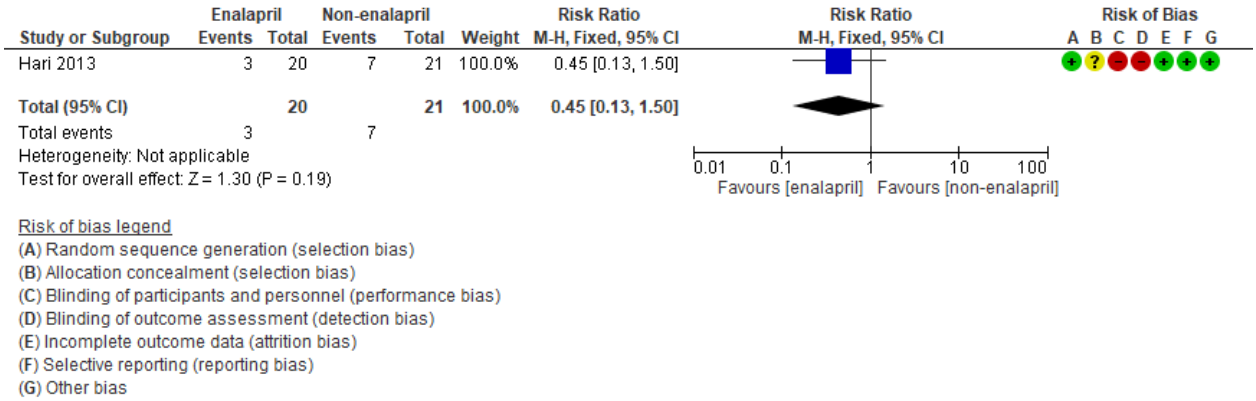


Figure 2 Forest plot of comparison: 1 ACEi or ARBs versus other antihypertensive agents, outcome: 1.2 GFR decline (mL/min/1.73 m2)).

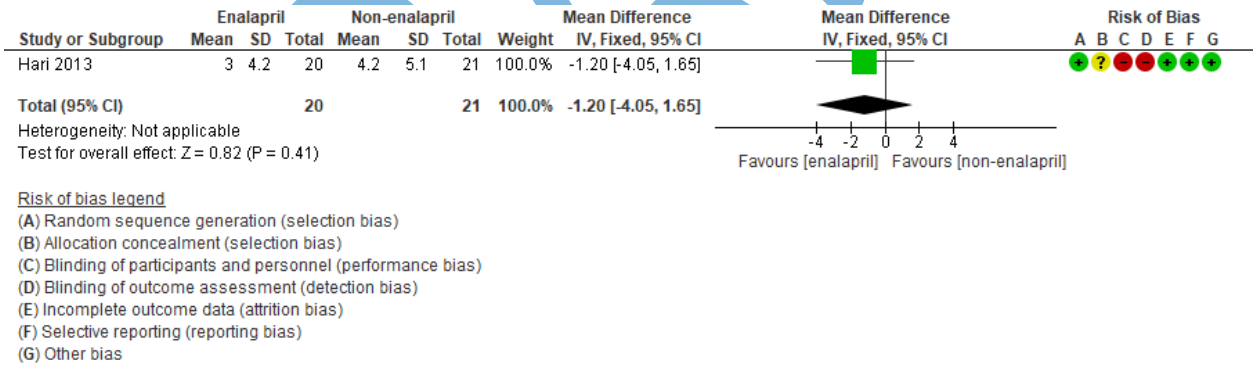


Figure 3 Forest plot of comparison: 1 ACEi or ARBs versus other antihypertensive agents, outcome: 1.3 Systolic blood pressure.

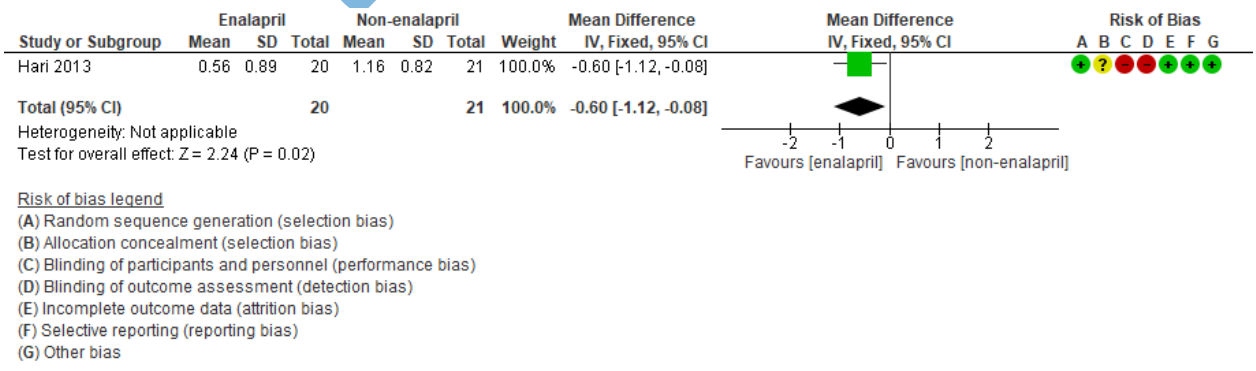
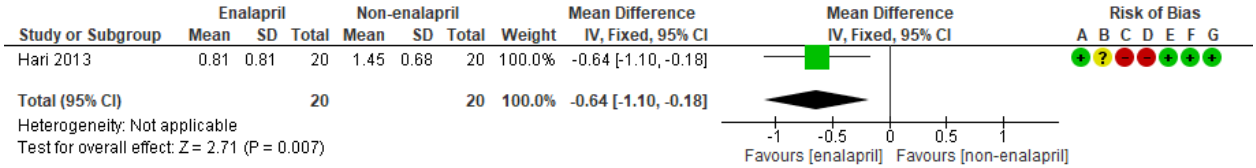
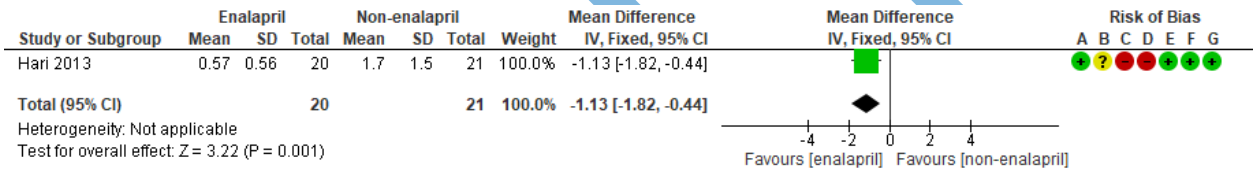


Figure 4 Forest plot of comparison: 1 ACEi or ARBs versus other antihypertensive agents, outcome: 1.4 Diastolic blood pressure.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

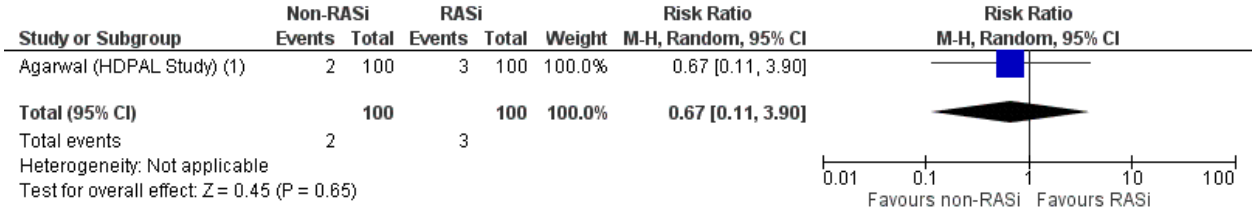
Figure 5 Forest plot of comparison: 1 ACEi or ARBs versus other antihypertensive agents, outcome: 1.5 Urine protein/creatinine (mg/mg).



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

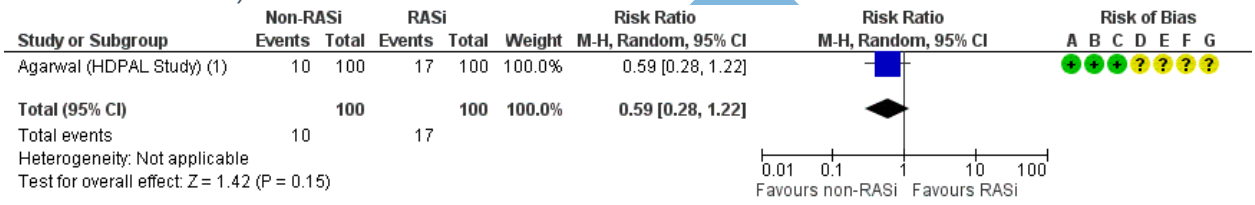
Question 2

Figure 6. Forest plot of comparison: 1 Non RASi (Beta Blockers) versus RAS inhibition in adults with CKD, outcome: 1.1 Cardiovascular mortality.



Footnotes
(1) Follow-up: 12 months

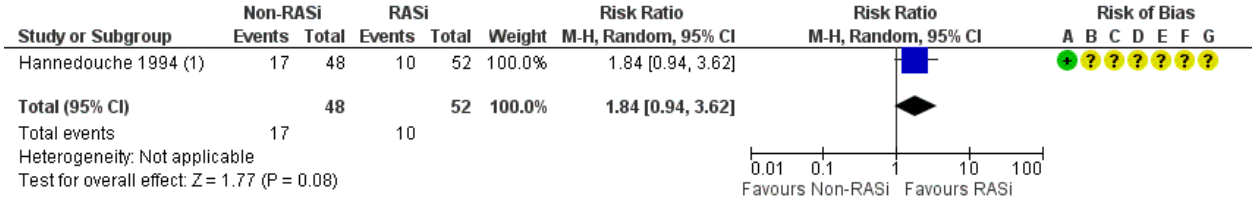
Figure 7. Forest plot of comparison: 1 Non RASi (Beta Blockers) versus RAS inhibition in adults with CKD, outcome: 1.2 Cardiovascular morbidity.



Footnotes
(1) Follow-up: 12 months

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance...
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 8. Forest plot of comparison: 1 Non RASi (Beta Blockers) versus RAS inhibition in adults with CKD, outcome: 1.3 Kidney failure.



Footnotes
(1) Follow-up: 36 months

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance...
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 9. Forest plot of comparison: 1 Non RASi (Beta Blockers) versus RAS inhibition in adults with CKD, outcome: 1.4 Diastolic blood pressure [mm Hg].

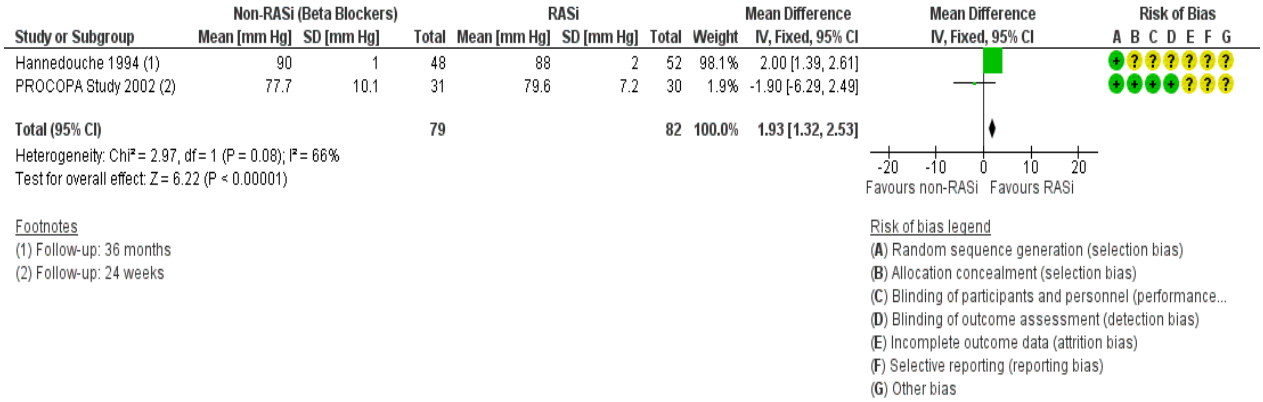


Figure 10. Forest plot of comparison: 1 Non RASi (Beta Blockers) versus RAS inhibition in adults with CKD, outcome: 1.5 Systolic blood pressure [mm Hg].

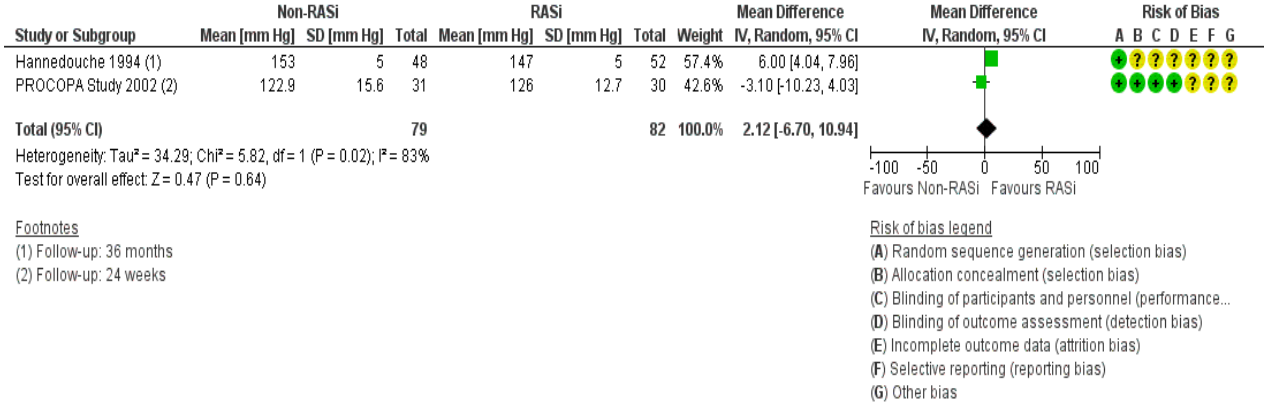


Figure 11. Forest plot of comparison: 1 Non RASi (Beta Blockers) versus RAS inhibition in adults with CKD, outcome: 1.6 Proteinuria (n/N).

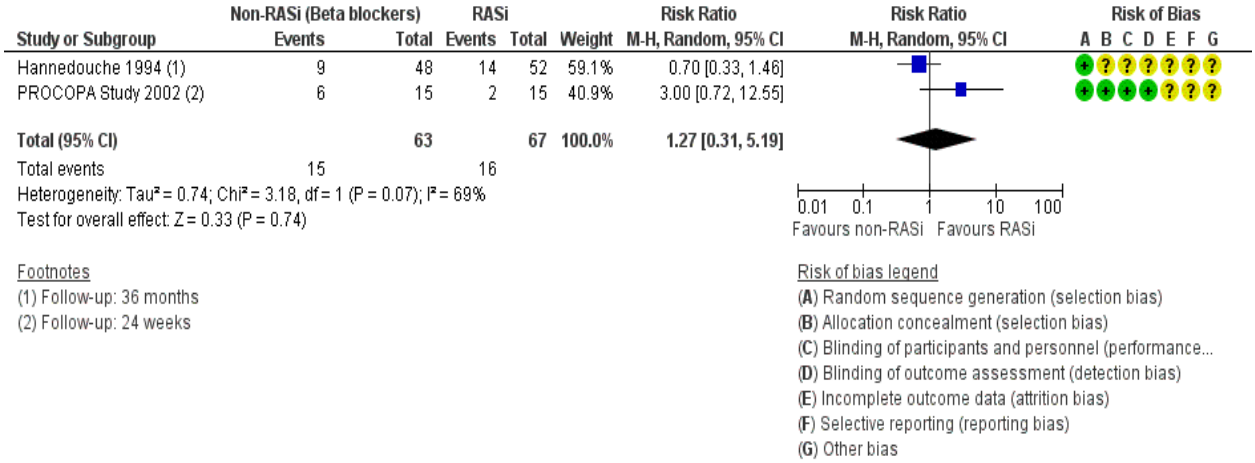


Figure 12. Forest plot of comparison: 1 Non RASi (Beta Blockers) versus RAS inhibition in adults with CKD, outcome: 1.7 Hyperkalemia/ plasma potassium concentration (mmol/L).

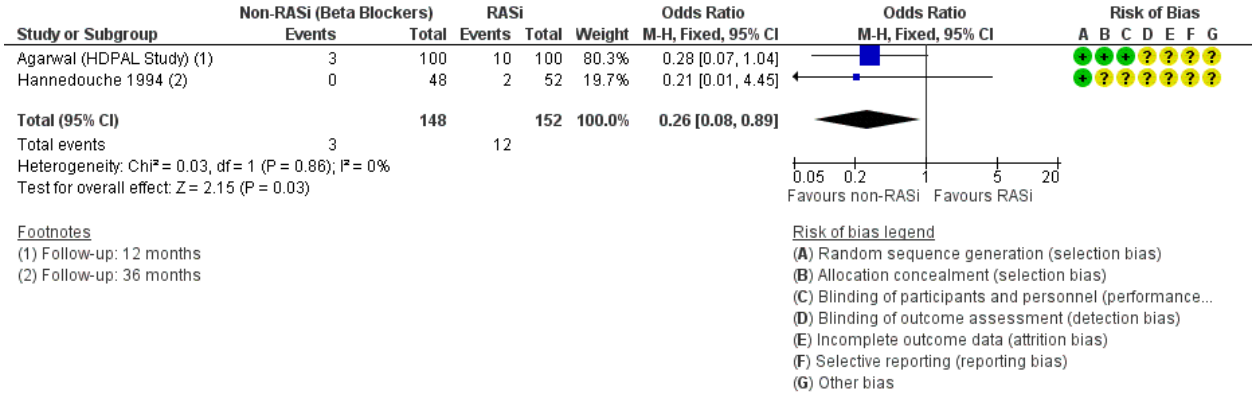


Figure 13. Forest plot of comparison: 2 Non RASi (Calcium Channel Blockers) versus Placebo in adults with CKD, outcome: 2.1 All-cause mortality.

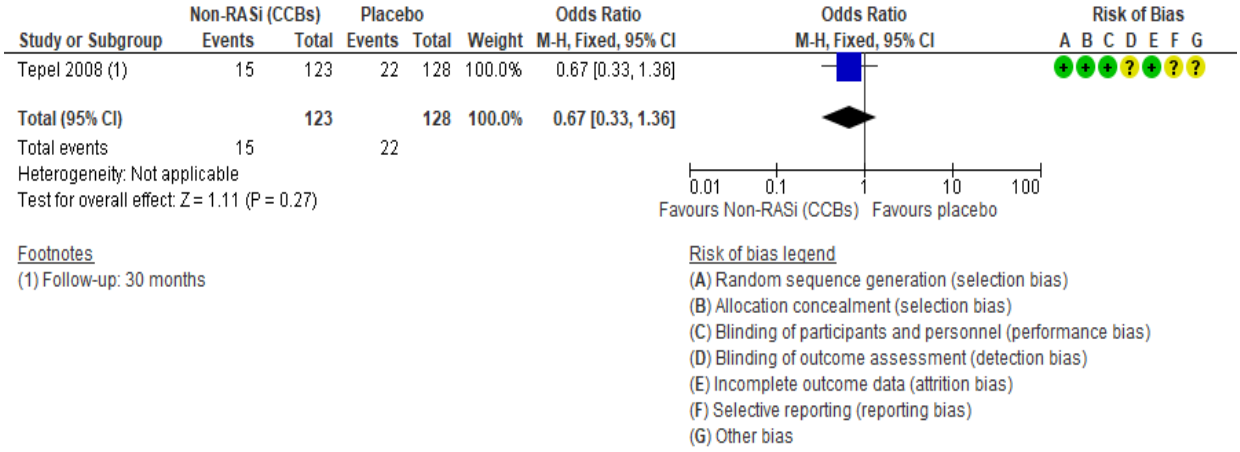


Figure 14. Forest plot of comparison: 2 Non RASi (Calcium Channel Blockers) versus Placebo in adults with CKD, outcome: 2.2 Systolic blood pressure [mm Hg].

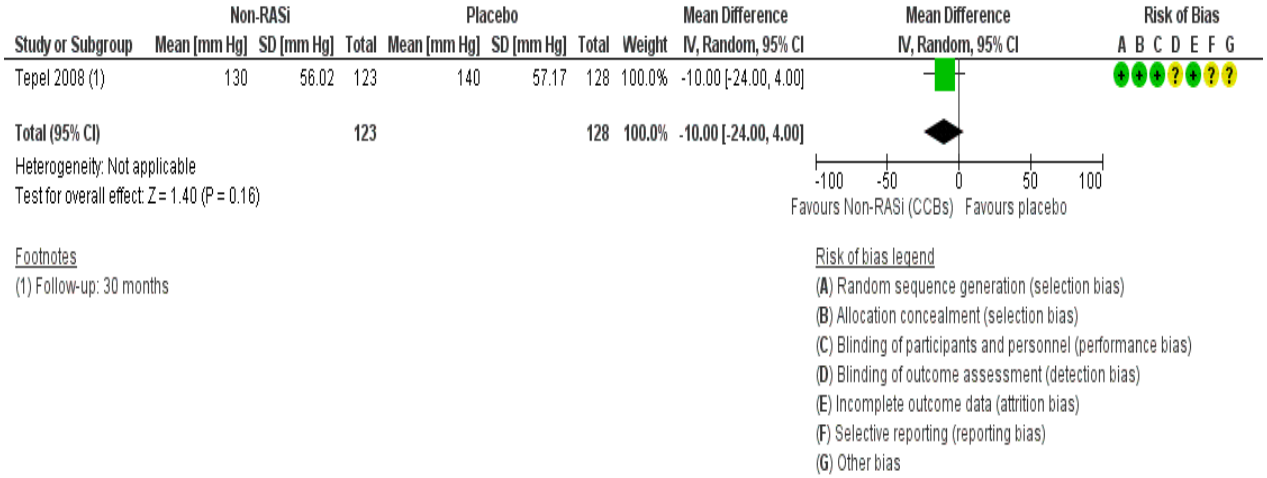


Figure 15. Forest plot of comparison: 3 Non RASi (Calcium Channel Blockers) versus RAS inhibition in adults with CKD, outcome: 3.1 Cardiovascular mortality.

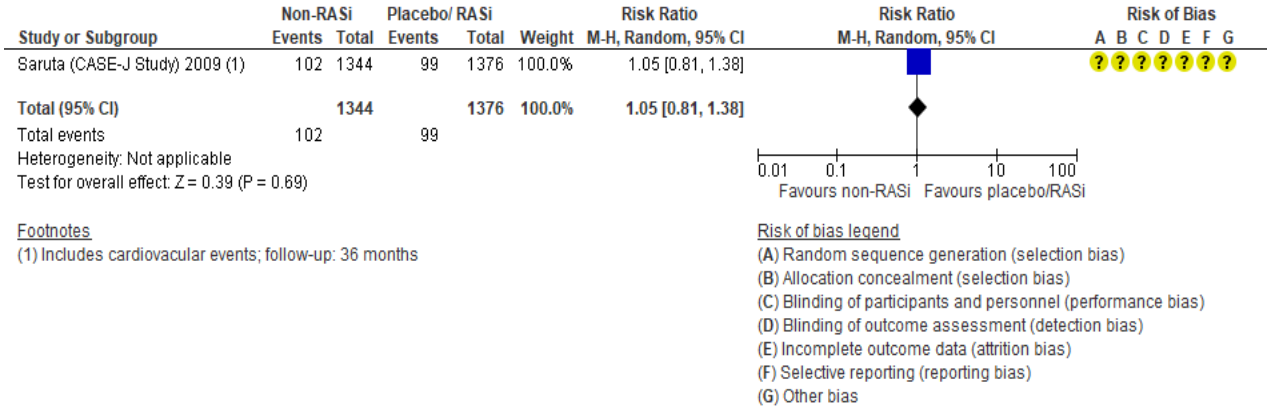


Figure 16. Forest plot of comparison: 3 Non RASi (Calcium Channel Blockers) versus RAS inhibition in adults with CKD, outcome: 3.2 Cardiovascular morbidity.

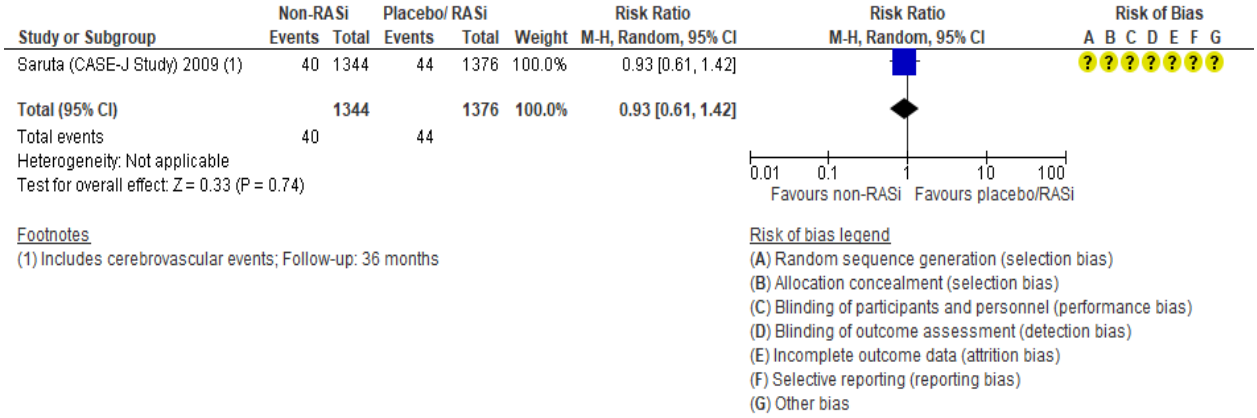


Figure 17. Forest plot of comparison: 3 Non RASi (Calcium Channel Blockers) versus RAS inhibition in adults with CKD, outcome: 3.3 Systolic blood pressure [mm Hg].

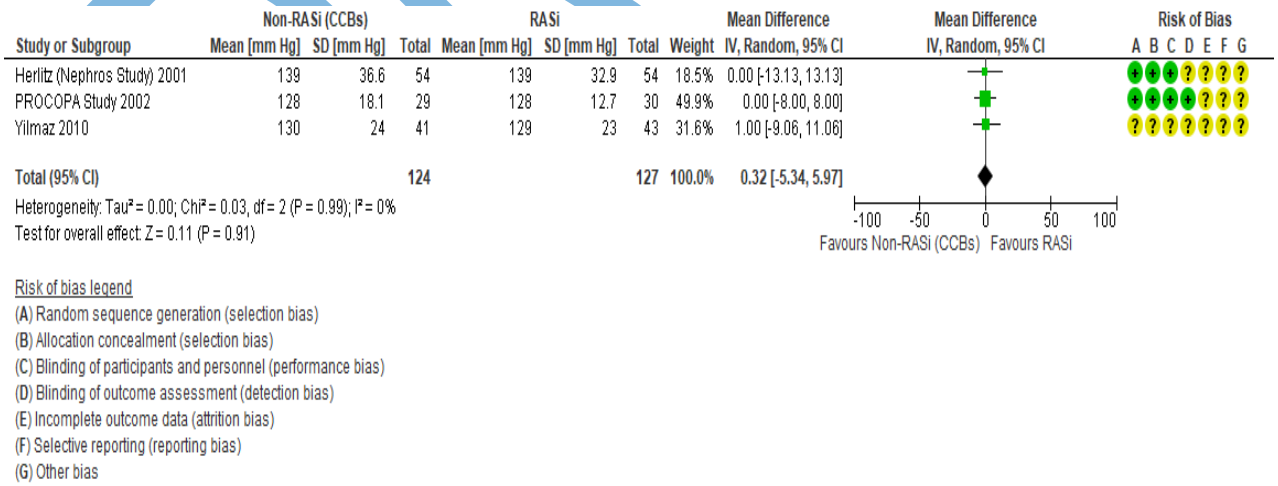
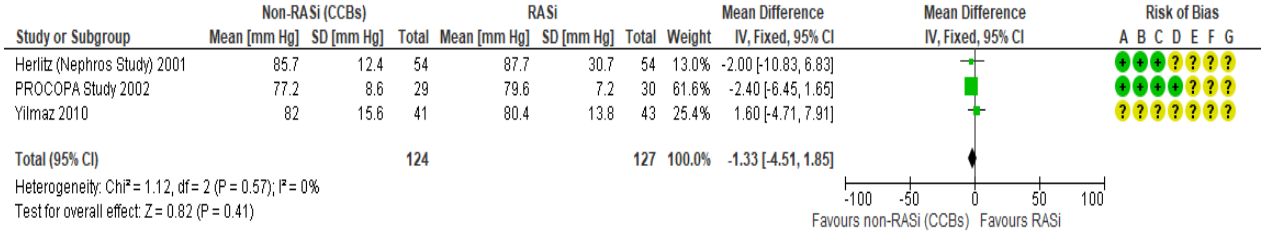
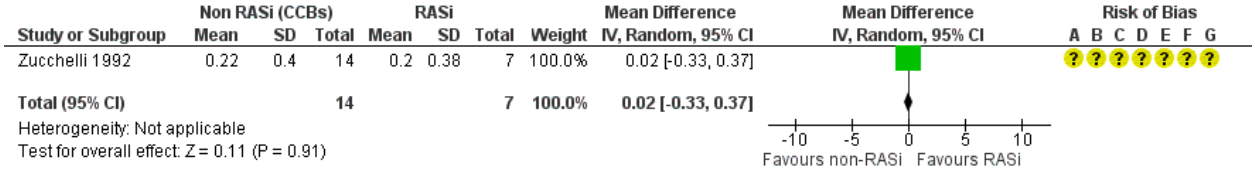


Figure 18. Forest plot of comparison: 3 Non RASi (Calcium Channel Blockers) versus RAS inhibition in adults with CKD, outcome: 3.4 Diastolic blood pressure [mm Hg].



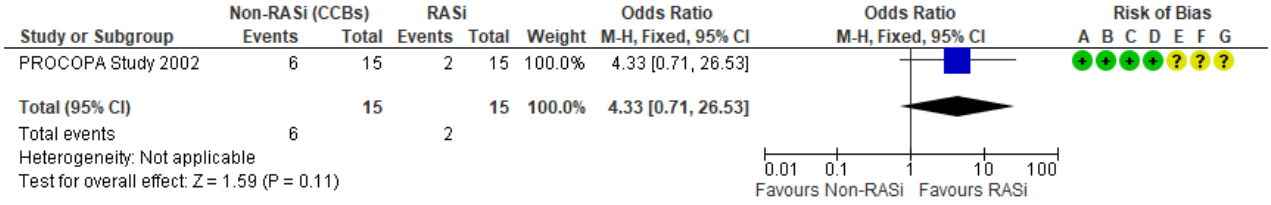
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 19. Forest plot of comparison: 3 Non RASi (Calcium Channel Blockers) versus RAS inhibition in adults with CKD, outcome: 3.5 eGFR change from baseline.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 20. Forest plot of comparison: 3 Non RASi (Calcium Channel Blockers) versus RAS inhibition in adults with CKD, outcome: 3.6 Proteinuria (g/24h).



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 21. Forest plot of comparison: 4 Non RASi versus RASi in adults with CKD, outcome: 4.1 Cardiovascular mortality.

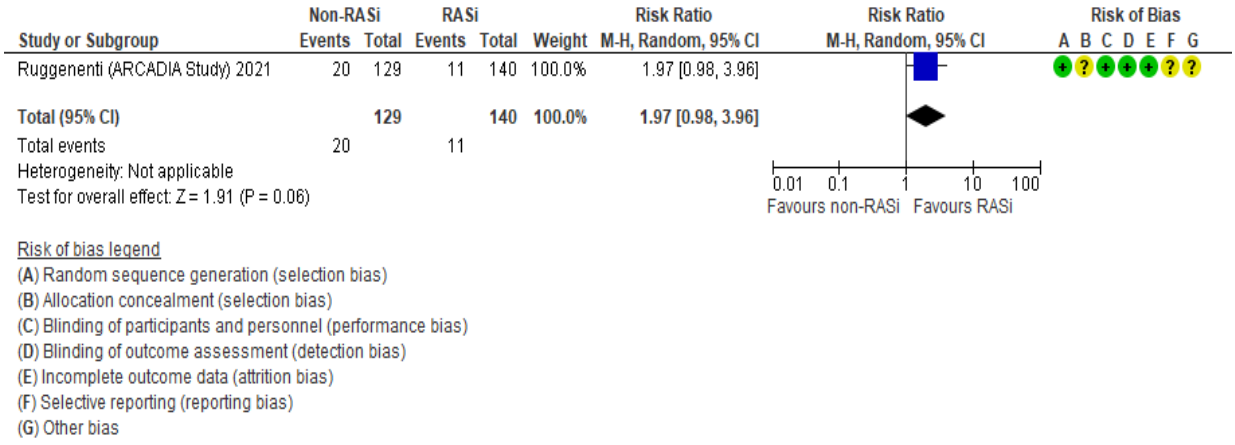


Figure 22. Forest plot of comparison: 4 Non RASi versus RASi in adults with CKD, outcome: 4.2 Cardiovascular morbidity.

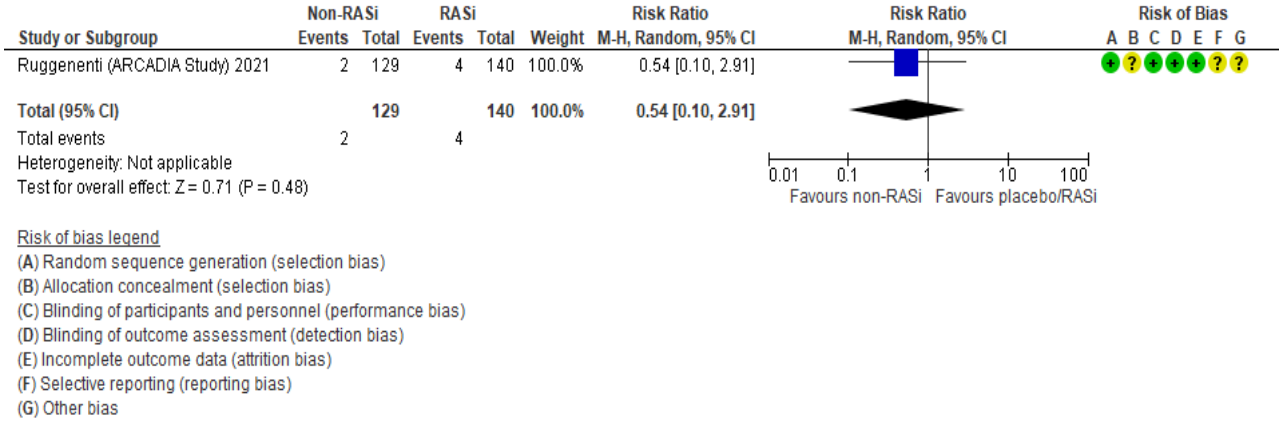
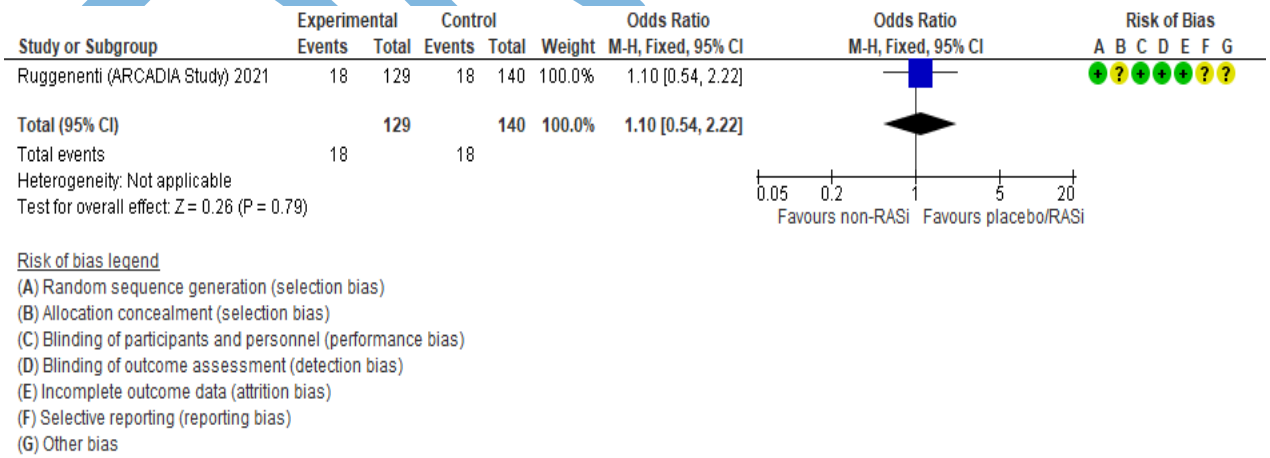


Figure 23. Forest plot of comparison: 4 Non RASi versus RASi in adults with CKD, outcome: 4.3 Hyperkalemia/ plasma potassium concentration (mmol/L).



Question 3

Figure 24 Forest plot of comparison: 1 Intensive versus standard blood pressure targets, outcome: 1.1 All cause mortality.

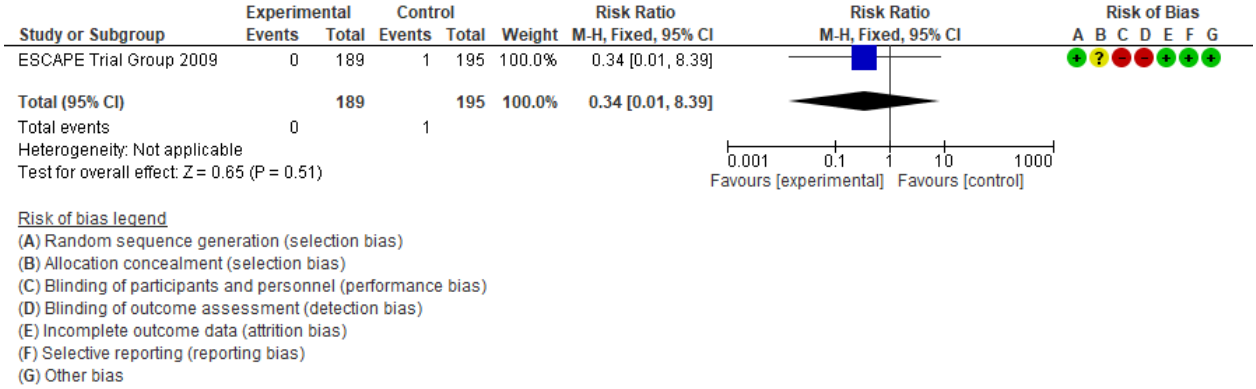


Figure 25 Forest plot of comparison: 1 Intensive versus standard blood pressure targets, outcome: 1.2 End-stage renal disease.

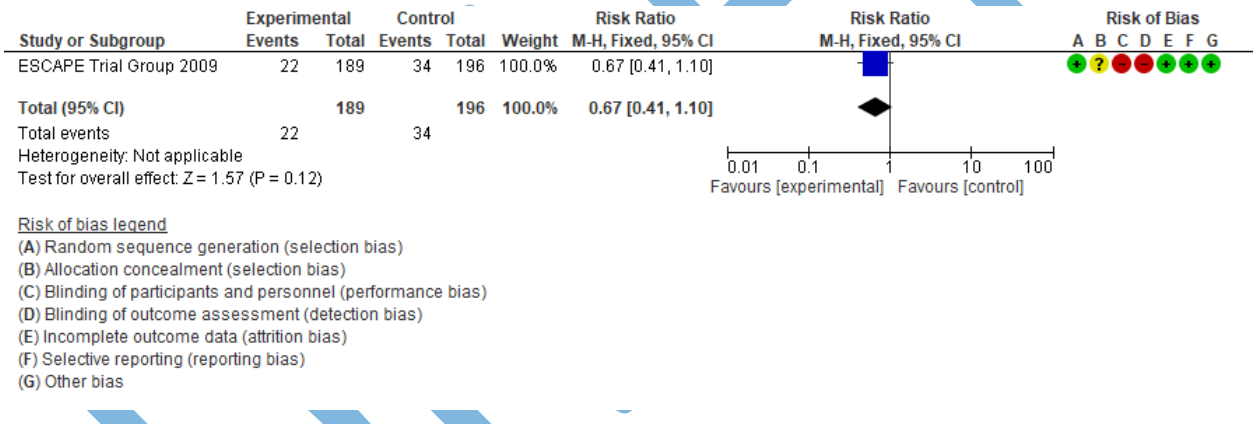


Figure 26 Forest plot of comparison: 1 Intensive versus standard blood pressure targets, outcome: 1.3 Systolic blood pressure.

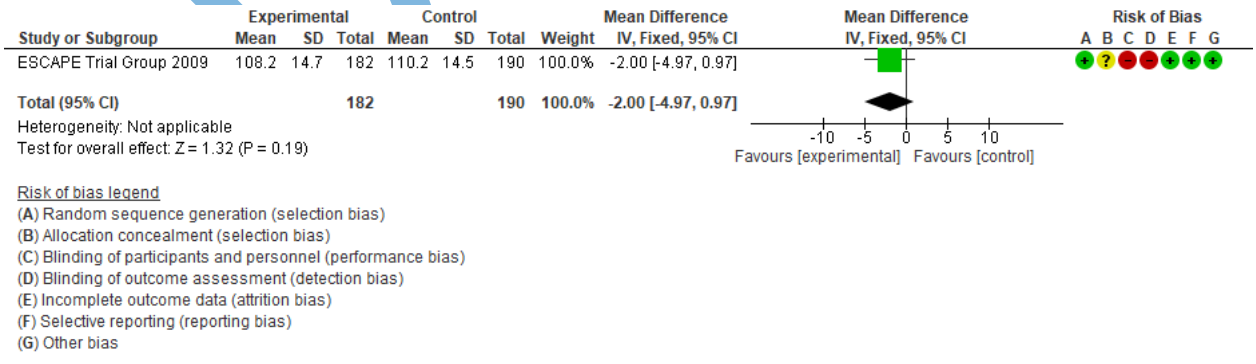


Figure 27 Forest plot of comparison: 1 Intensive versus standard blood pressure targets, outcome: 1.4 Diastolic blood pressure.

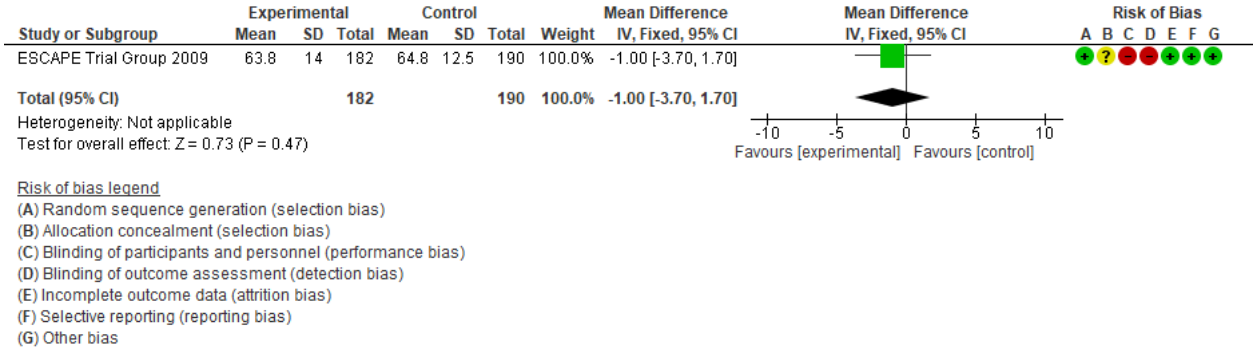
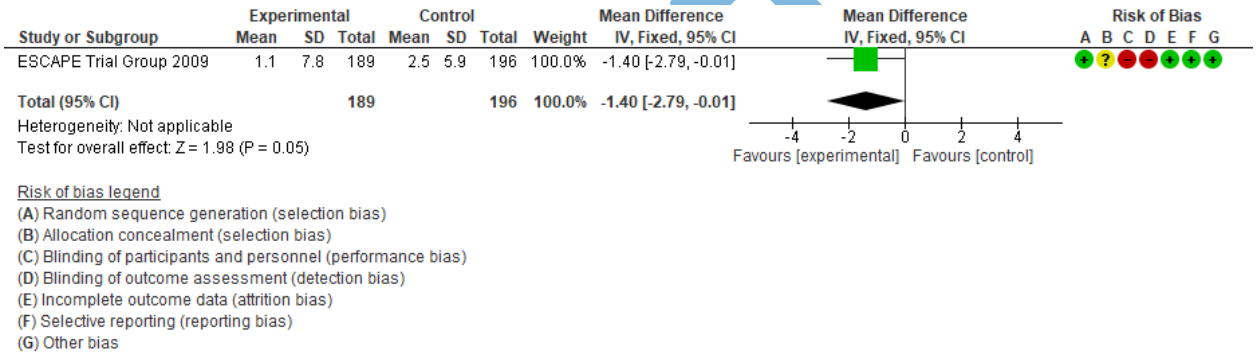


Figure 28 Forest plot of comparison: 1 Intensive versus standard blood pressure targets, outcome: 1.5 Estimated glomerular filtration rate.



Question 4

Figure 29. Forest plot of comparison: Low (Intensive) BP target versus Standard BP target, outcome: 1.1 All-cause mortality.

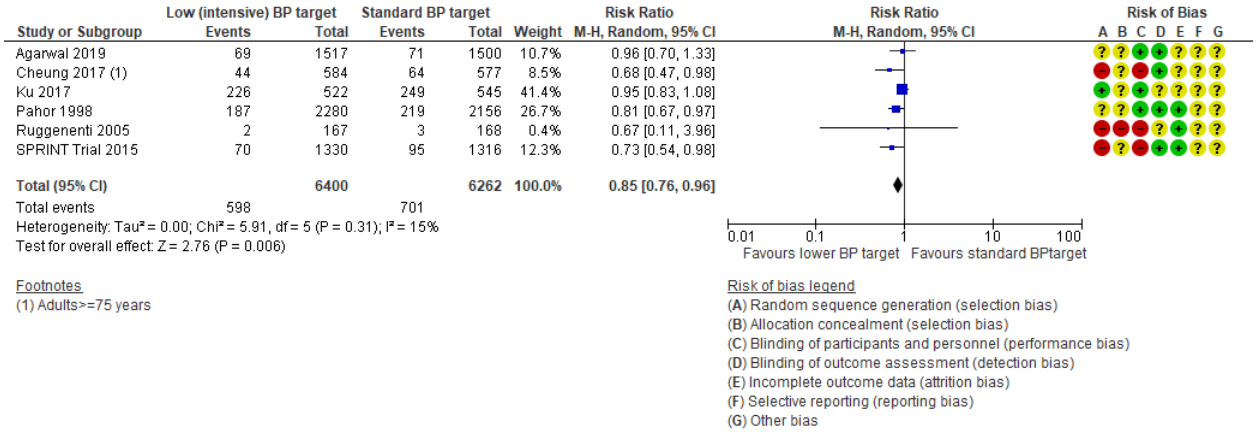


Figure 30. Forest plot of comparison: Low (Intensive) BP target versus Standard BP target, outcome: 1.2 Cardiovascular mortality.

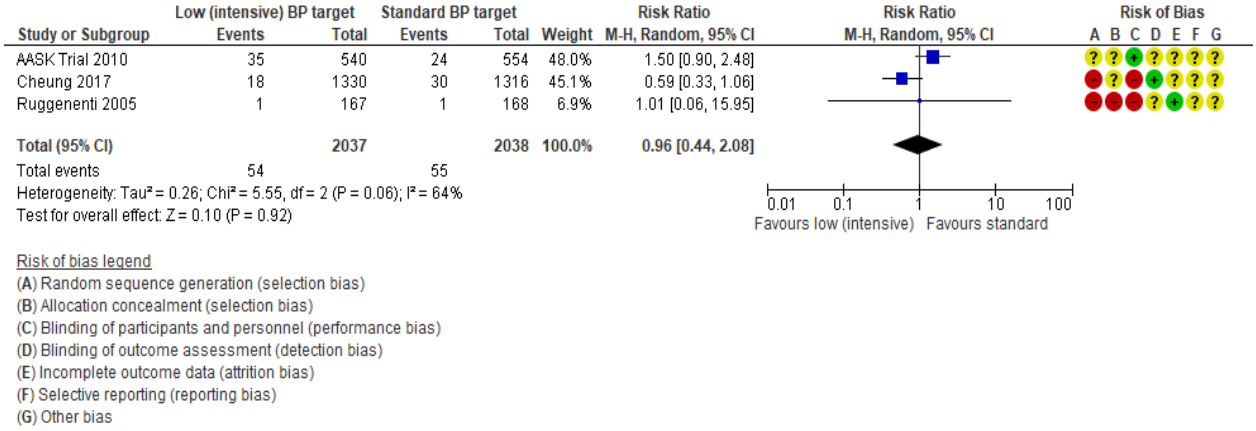


Figure 31. Forest plot of comparison: Low (Intensive) BP target versus Standard BP target, outcome: 1.3 Cardiovascular morbidity.

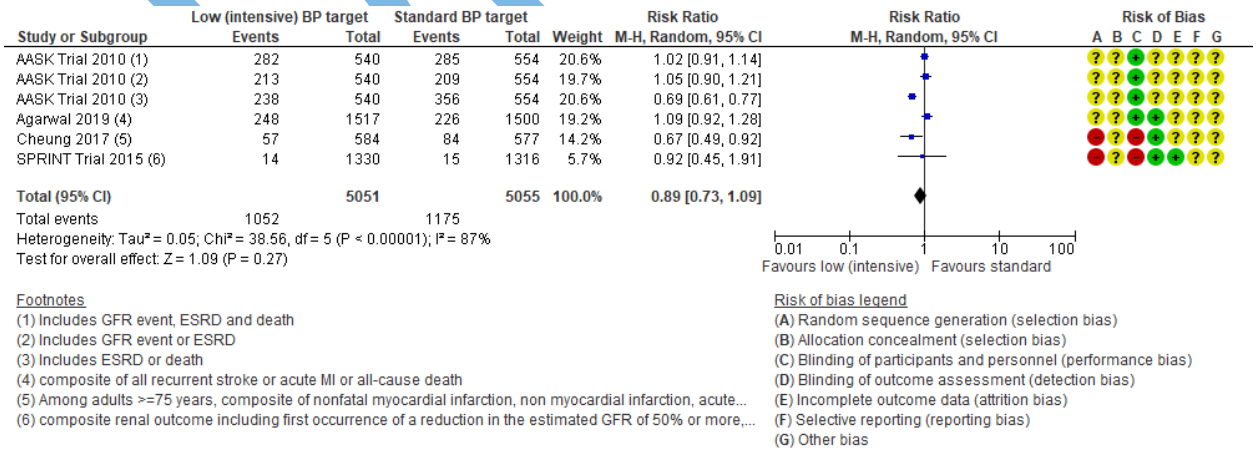
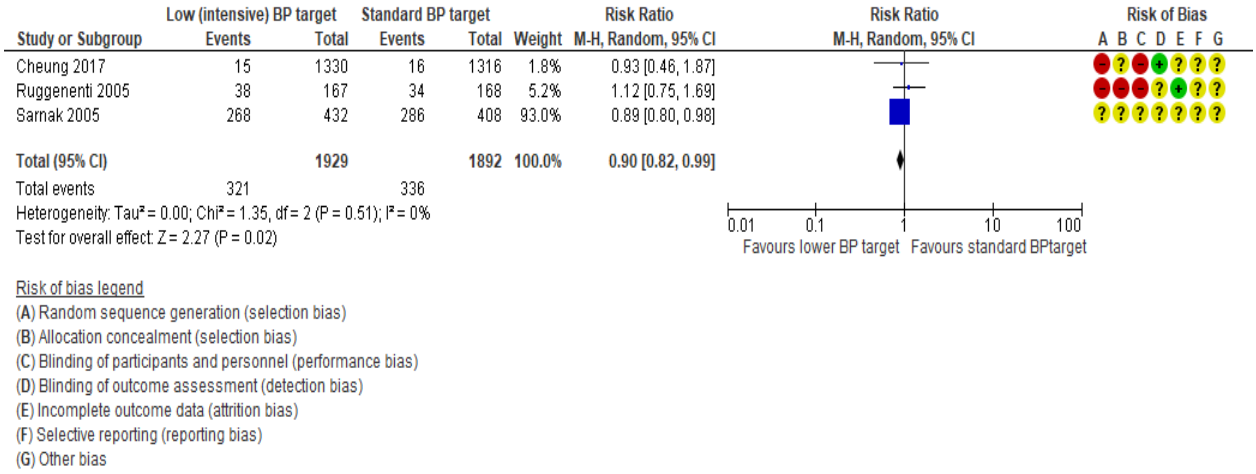
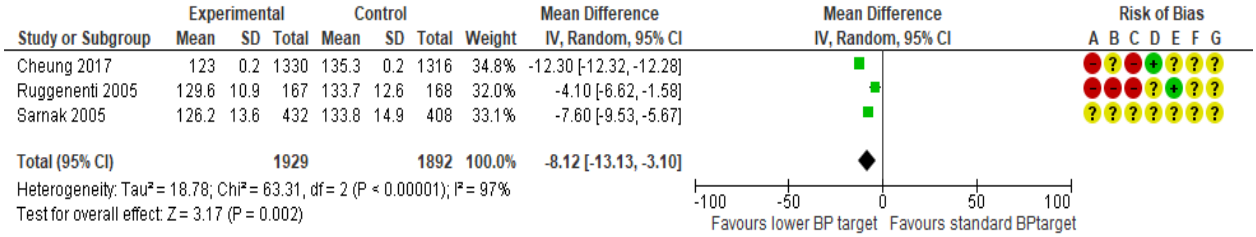


Figure 32. Forest plot of comparison: Low (Intensive) BP target versus Standard BP target, outcome: 1.4 Kidney failure (ESRD).



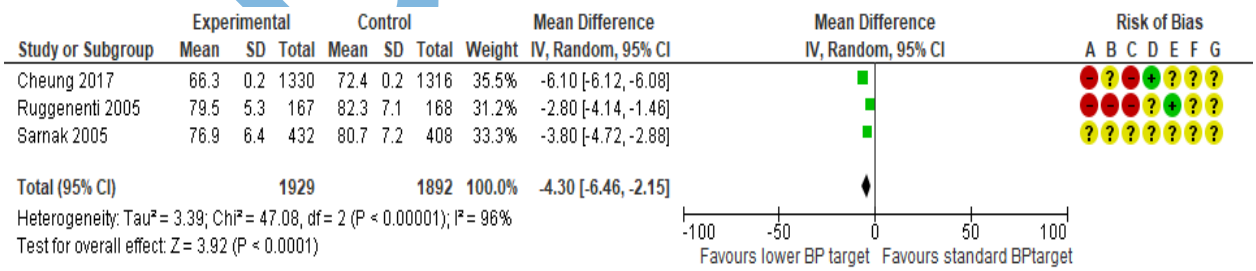
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 33. Forest plot of comparison: Low (Intensive) BP target versus Standard BP target, outcome: 1.5 Systolic blood pressure (mm Hg): Mean (SD).



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 34. Forest plot of comparison: Low (Intensive) BP target versus Standard BP target, outcome: 1.6 Diastolic blood pressure (mm Hg): Mean (SD).



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 35. Forest plot of comparison: Low (Intensive) BP target versus Standard BP target, outcome: 1.7 eGFR change from baseline.

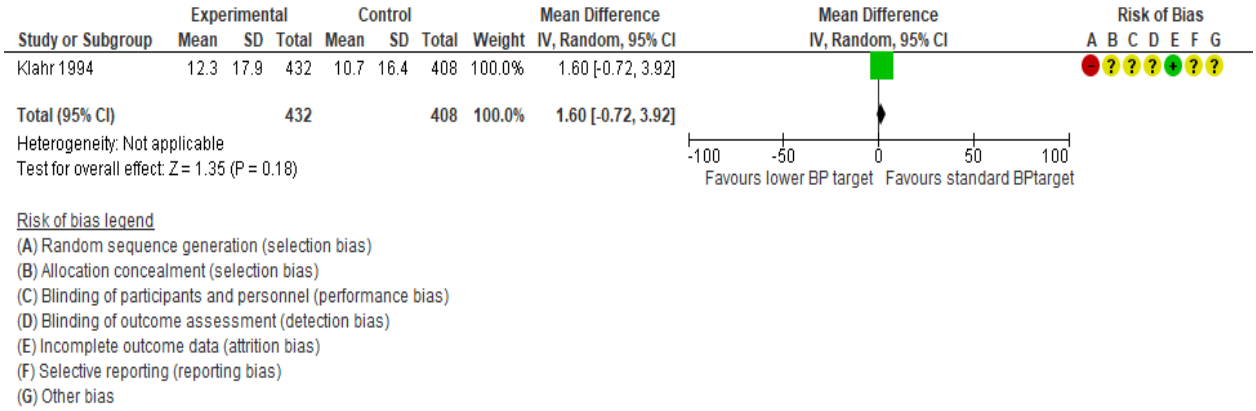
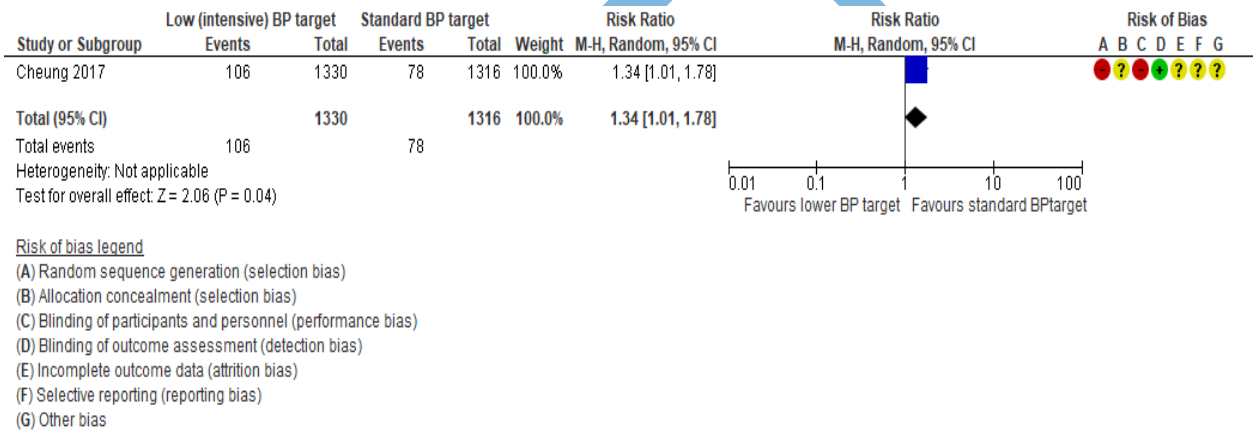


Figure 36. Forest plot of comparison: Low (Intensive) BP target versus Standard BP target, outcome: 1.8 Serum potassium >5.5 mmol/L (n/N).



Question 5

Only one observational study was included for evidence synthesis, and hence a forest plot was not derived for this question.

Question 6

No forest plots were derived for this question.

Question 7

We had only qualitative evidence for synthesis, and hence forest plots were not derived for this question.

Figure 37. Forest plot of comparison: Early vs late RRT initiation based on eGFR, outcome: 1.1 All-cause mortality (ave 3.6 years).

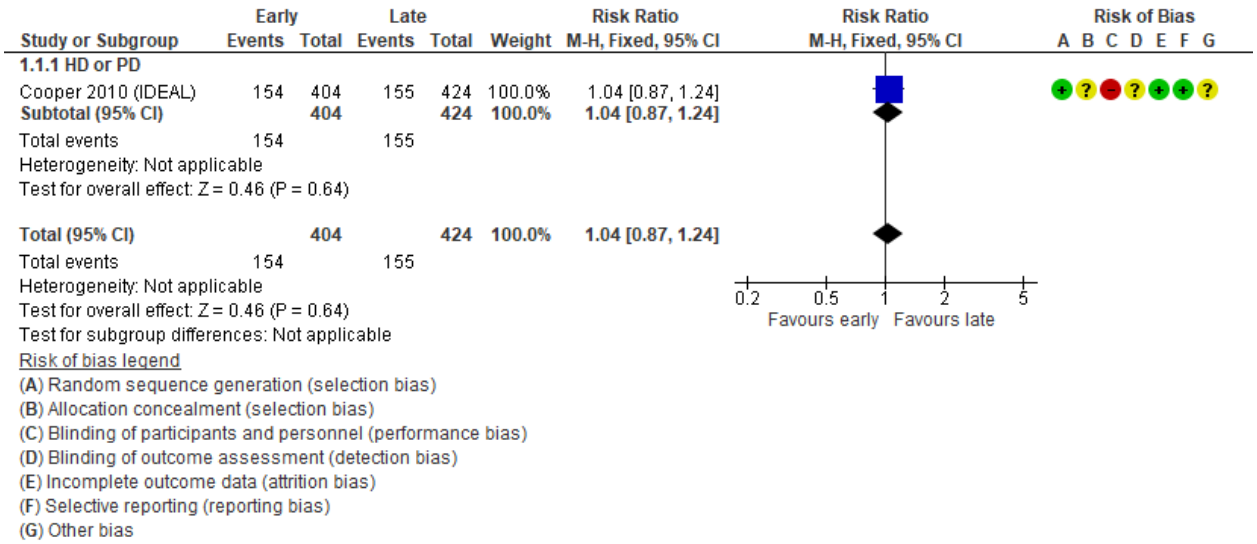


Figure 38. Forest plot of comparison: 1 Early vs late RRT initiation based on eGFR, outcome: 1.2 All-cause mortality: age<18 years.

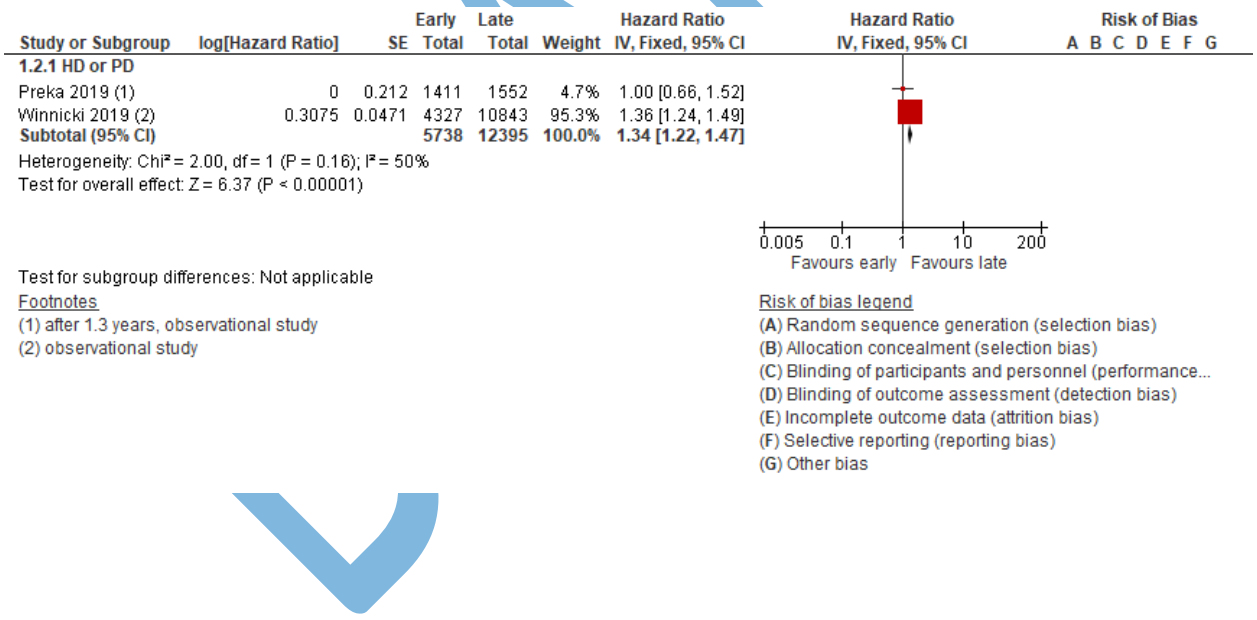


Figure 39. Forest plot of comparison: Early vs late RRT initiation based on eGFR, outcome: 1.3 Growth (height): age<18 years.

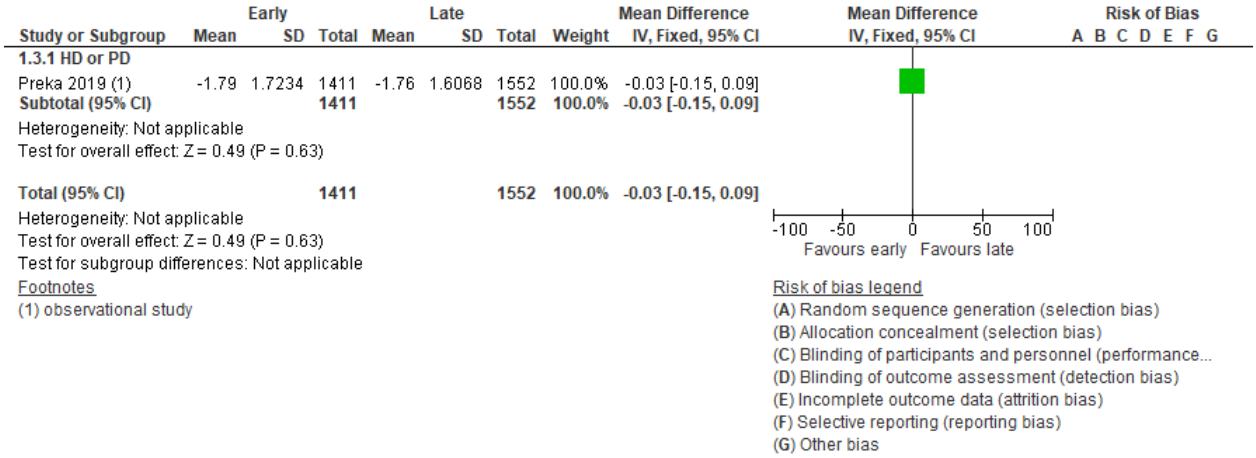


Figure 40. Forest plot of comparison: Early vs late RRT initiation based on eGFR, outcome: 1.4 Quality of Life (AQoL score, higher is better)- regression over the time of trial.

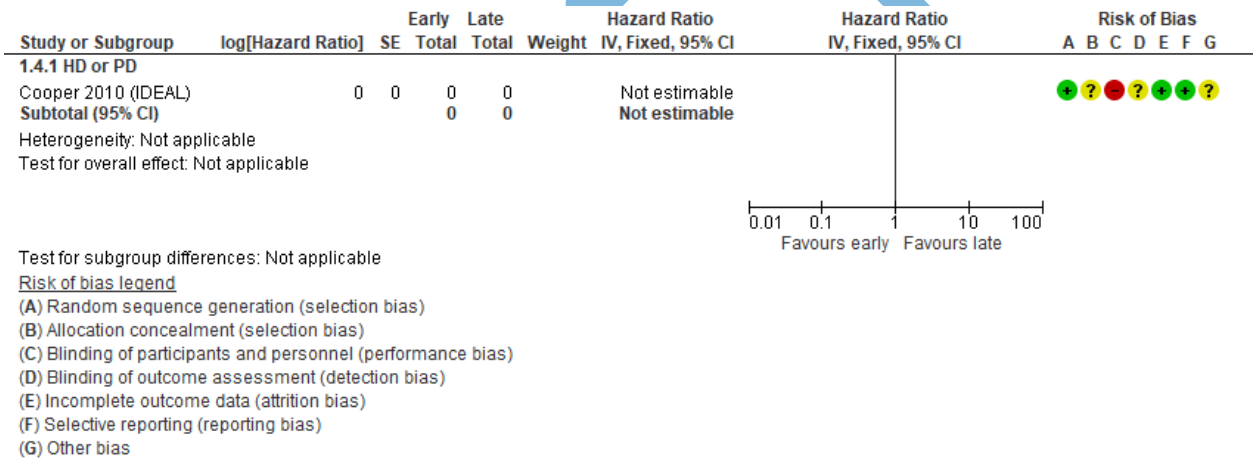


Figure 41. Forest plot of comparison: Early vs late RRT initiation based on eGFR, outcome: 1.5 Pre-emptive transplantation rates: age<18 years

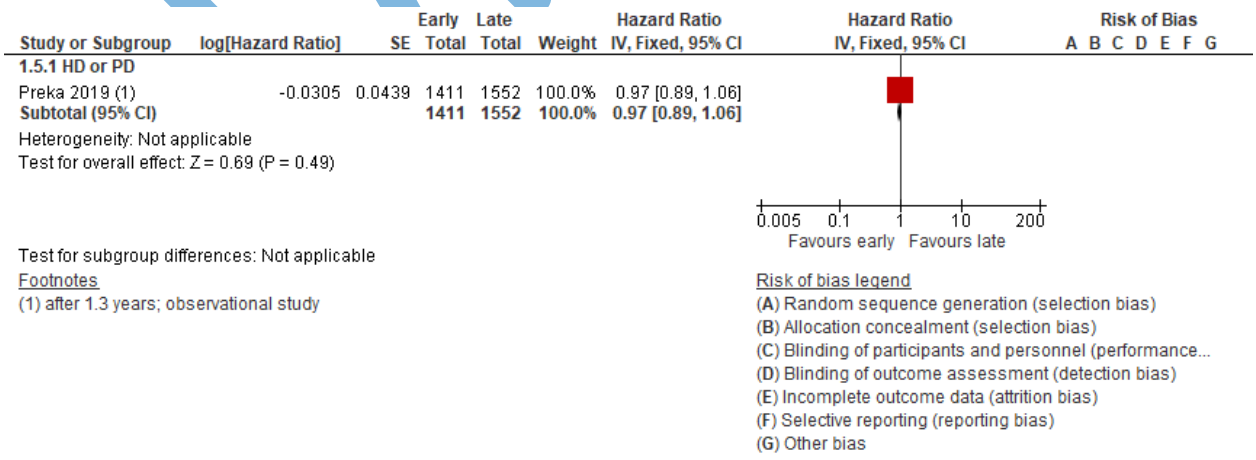


Figure 42. Forest plot of comparison: Early vs late RRT initiation based on eGFR, outcome: 1.6 Adverse events - infection events (ave 3.6 years)

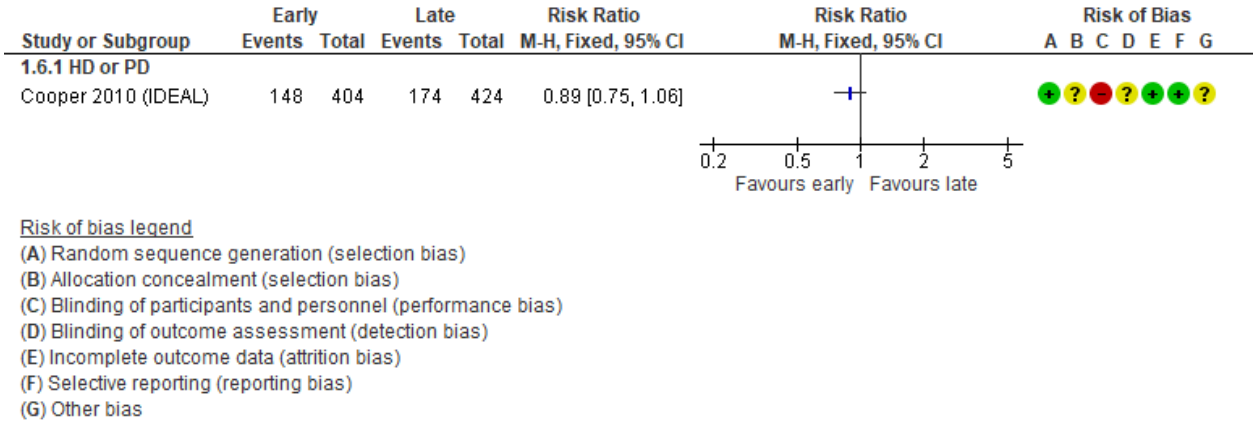


Figure 43. Forest plot of comparison: Early vs late RRT initiation based on eGFR, outcome: 1.7 Mortality: Transplant at eGFR>/=15ml/min vs <10ml/min.

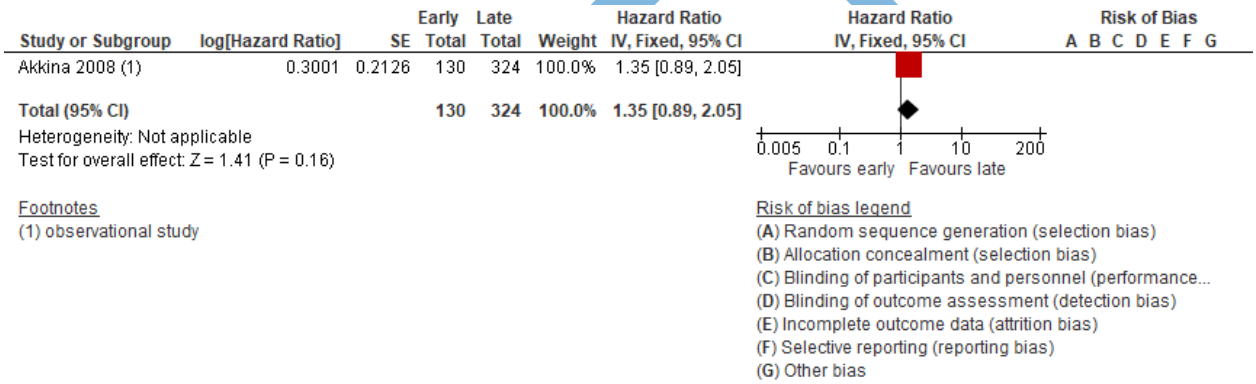
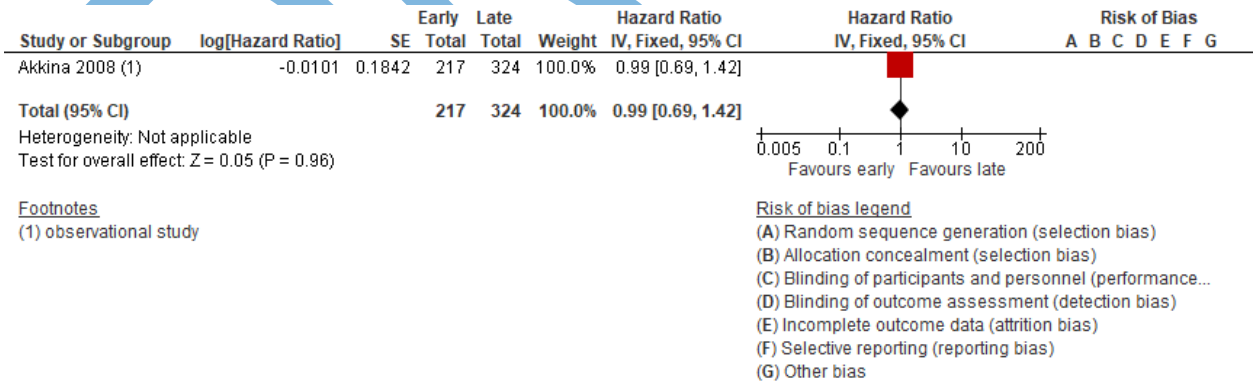


Figure 44. Forest plot of comparison: Early vs late RRT initiation based on eGFR, outcome: 1.9 Mortality: Transplant at eGFR 10 -14.9 ml/min vs <10ml/min.



Question 9

Only one observational study was included for evidence synthesis, and hence a forest plot was not derived for this question.

Question 10

No evidence was available for synthesis.

Question 11

No evidence was available for synthesis.

Question 12

We had only qualitative evidence for synthesis, and hence forest plots were not derived for this question.

14.7. Evidence profiles

This section contains the Evidence profiles for each clinical question exported from GRADEpro that the CKD Task Force used during the Recommendations Workshops inform their decisions about recommendations.

Question 1. Should ACEi or ARBs versus other antihypertensive agents be used for hypertension treatment in children with CKD?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACEi or ARBs	other antihypertensive agents	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cardiovascular mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cardiovascular morbidity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Kidney failure (or end-stage kidney disease) (follow-up: 12 months; assessed with: decline in GFR by >30% or attainment of ESRD)												
1[1]	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	3/20 (15.0%)	7/21 (33.3%) 33.4%[c]	**RR 0.45** (0.13 to 1.50)	**183 fewer per 1,000** (from 290 fewer to 167 more) **184 fewer per 1,000** (from 291 fewer to 167 more)	⊕◯◯◯ Very low	CRITICAL
Doubling serum creatinine - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acute kidney injury - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACEi or ARBs	other antihypertensive agents	Relative (95% CI)	Absolute (95% CI)		
Systolic blood pressure (follow-up: 12 months)												
1[1]	randomised trials	very serious[a]	not serious	not serious	serious[d]	none	20	21	-	MD **0.6 lower** (1.12 lower to 0.08 lower)	⊕◯◯◯ Very low	CRITICAL
Diastolic blood pressure (follow-up: 12 months)												
1[1]	randomised trials	very serious[a]	not serious	not serious	serious[d]	none	20	21	-	MD **0.64 lower** (1.1 lower to 0.18 lower)	⊕◯◯◯ Very low	CRITICAL
Estimated glomerular filtration rate (eGFR) (follow-up: 12 months; assessed with: GFR decline (mL/min/1.73 m2))												
1[1]	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	20	21	-	MD **1.2 lower** (4.05 lower to 1.65 higher)	⊕◯◯◯ Very low	CRITICAL
Proteinuria (follow-up: 12 months; assessed with: urine protein/creatinine (mg/mg))												
1[1]	randomised trials	very serious[a]	not serious	not serious	serious[d]	none	20	21	-	MD **1.13 lower** (1.82 lower to 0.44 lower)	⊕◯◯◯ Very low	CRITICAL
Left ventricular hypertrophy - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Encephalopathy - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. One study that carried the overall effect estimate rated as high risk of bias due to lack of blinding in participants and outcome assessment.

b. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference. No optimal information size was reached. We, therefore, downgraded by two levels.

c. Cross-sectional survey was performed during the period from March 2012 to October 2013 covering 13 towns around Hail city. Prevalence of concomitant hypertension in population with CKD 33.4%.

d. Serious imprecision. No optimal information size was reached in the RCT.

References

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Question 2. Should non-RASi versus RASi be used for hypertension treatment in adults with CKD?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-RAS inhibition	RASi	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cardiovascular mortality **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	2/100 (2.0%)	3/100 (3.0%)	**RR 0.67** (0.11 to 3.90)	**10 fewer per 1,000** (from 27 fewer to 87 more)	⨁⨁◯◯ Low	CRITICAL
Cardiovascular morbidity **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported												
1[1]	randomised trials	not serious	not serious	not serious	very serious[a]	none	10/100 (10.0%)	17/100 (17.0%)	**RR 0.59** (0.28 to 1.22)	**70 fewer per 1,000** (from 122 fewer to 37 more)	⨁⨁◯◯ Low	CRITICAL
Kidney failure **[Non RASi (Beta Blockers) versus RAS inhibition]												
1[2]	randomised trials	serious[b]	not serious	not serious	serious[c]	none	17/48 (35.4%)	10/52 (19.2%)	**RR 1.84** (0.94 to 3.62)	**162 more per 1,000** (from 12 fewer to 504 more)	⨁⨁◯◯ Low	CRITICAL
Doubling serum creatinine **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acute kidney injury **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Diastolic blood pressure **[Non RASi (Beta Blockers) versus RAS inhibition]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-RAS inhibition	RASi	Relative (95% CI)	Absolute (95% CI)		
2[2,3]	randomised trials	serious[d]	not serious	not serious	serious[e]	none	79	82	-	MD **1.93 higher** (1.32 higher to 2.53 higher)	⊕⊕◯◯ Low	CRITICAL
Systolic blood pressure **[Non RASi (Beta Blockers) versus RAS inhibition]												
2[2,3]	randomised trials	serious[d]	not serious	not serious	serious[c,e]	none	79	82	-	MD **2.12 higher** (6.7 lower to 10.94 higher)	⊕⊕◯◯ Low	CRITICAL
eGFR change from baseline **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Proteinuria (n/N) **[Non RASi (Beta Blockers) versus RAS inhibition]												
2[2,3]	randomised trials	serious[d]	not serious	not serious	serious[c]	none	15/63 (23.8%)	16/67 (23.9%)	**RR 1.27** (0.31 to 5.19)	**64 more per 1,000** (from 165 fewer to 1,000 more)	⊕⊕◯◯ Low	CRITICAL
Encephalopathy **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Left ventricular hypertrophy **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Hyperkalemia/ plasma potassium concentration (mmol/L) **[Non RASi (Beta Blockers) versus RAS inhibition]												
2[1,2]	randomised trials	serious[d]	not serious	not serious	serious[e]	none	3/148 (2.0%)	12/152 (7.9%)	**OR 0.26** (0.08 to 0.89)	**57 fewer per 1,000** (from 72 fewer to 8 fewer)	⊕⊕◯◯ Low	CRITICAL
All-cause mortality ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported**												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-RAS inhibition	RASi	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cardiovascular mortality ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition]**												
1[4]	randomised trials	serious[b]	not serious	not serious	serious[c]	none	102/1344 (7.6%)	99/1376 (7.2%)	**RR 1.05** (0.81 to 1.38)	**4 more per 1,000** (from 14 fewer to 27 more)	⊕⊕◯◯ Low	CRITICAL
Cardiovascular morbidity ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition] (assessed with: Stroke)**												
1[4]	randomised trials	serious[b]	not serious	not serious	serious[c]	none	40/1344 (3.0%)	44/1376 (3.2%)	**RR 0.93** (0.61 to 1.42)	**2 fewer per 1,000** (from 12 fewer to 13 more)	⊕⊕◯◯ Low	CRITICAL
Kidney failure ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition] (assessed with: Stroke - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Doubling serum creatinine ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acute kidney injury ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Systolic blood pressure ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition]**												
3[3,5,6]	randomised trials	serious[f]	not serious	not serious	serious[c]	none	124	127	-	MD **0.32 higher** (5.34 lower to 5.97 higher)	⊕⊕◯◯ Low	CRITICAL
Diastolic blood pressure ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition]**												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-RAS inhibition	RASi	Relative (95% CI)	Absolute (95% CI)		
3[3,5,6]	randomised trials	serious[f]	not serious	not serious	serious[c]	none	124	127	-	MD **1.33 lower** (4.51 lower to 1.85 higher)	⊕⊕◯◯ Low	CRITICAL
eGFR change from baseline ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition]**												
1[7]	randomised trials	serious[g]	not serious	not serious	serious[h]	none	14	7	-	MD **0.02 higher** (0.33 lower to 0.37 higher)	⊕⊕◯◯ Low	CRITICAL
Proteinuria (g/g creatinine) ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition]**												
1[7]	randomised trials	not serious[g]	not serious	not serious	very serious[h]	none	14	7	-	MD **0.08 higher** (1.42 lower to 1.58 higher)	⊕⊕◯◯ Low	CRITICAL
Proteinuria (g/24h) ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition]**												
1[3]	randomised trials	not serious	not serious	not serious	very serious[i]	none	6/15 (40.0%)	2/15 (13.3%)	**OR 4.33** (0.71 to 26.53)	**266 more per 1,000** (from 35 fewer to 670 more)	⊕⊕◯◯ Low	CRITICAL
Left ventricular hypertrophy ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Encephalopathy ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Hyperkalemia/ plasma potassium concentration (mmol/L) ***[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-RAS inhibition	RASi	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality ****(Non RASi versus RASi - Ramipril -) - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cardiovascular mortality ****(Non RASi versus RASi - Ramipril -)**												
1[8]	randomised trials	serious[b]	not serious	not serious	serious[c]	none	20/129 (15.5%)	11/140 (7.9%)	**RR 1.97** (0.98 to 3.96)	**76 more per 1,000** (from 2 fewer to 233 more)	⨁⨁◯◯ Low	CRITICAL
Cardiovascular morbidity ****(Non RASi versus RASi - Ramipril -) (assessed with: Stroke)**												
1[8]	randomised trials	serious[b]	not serious	not serious	serious[c]	none	2/129 (1.6%)	4/140 (2.9%)	**RR 0.54** (0.10 to 2.91)	**13 fewer per 1,000** (from 26 fewer to 55 more)	⨁⨁◯◯ Low	CRITICAL
Kidney failure ****(Non RASi versus RASi - Ramipril -) - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Doubling serum creatinine ****(Non RASi versus RASi - Ramipril -) - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Systolic blood pressure ****(Non RASi versus RASi - Ramipril -) - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Diastolic blood pressure ****(Non RASi versus RASi - Ramipril -) - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
eGFR change from baseline ****(Non RASi versus RASi - Ramipril -) - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Proteinuria ****(Non RASi versus RASi - Ramipril -) - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Left ventricular hypertrophy ****(Non RASi versus RASi - Ramipril -) - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-RAS inhibition	RASi	Relative (95% CI)	Absolute (95% CI)		
Encephalopathy ****(Non RASi versus RASi - Ramipril -) - not reported**												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Hyperkalemia/ plasma potassium concentration (mmol/L) ****(Non RASi versus RASi - Ramipril -)**												
1[8]	randomised trials	serious[b]	not serious	not serious	serious[c]	none	18/129 (14.0%)	18/140 (12.9%)	**OR 1.10** (0.54 to 2.22)	**11 more per 1,000** (from 55 fewer to 118 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 3 events in total. We, therefore, downgraded by two levels.
b. Study that carried all weight for the overall effect estimate rated as high risk of bias due to lack of blinding.
c. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.
d. Studies that carried a large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 1 out of 2 studies.
e. Serious imprecision. Two studies with small sample size did not meet OIS criteria.
f. Studies that carried a large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 1 out of 3 studies.
g. Study that carried all weight for the overall effect estimate did not report the randomization process nor blinding.
h. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference. We, therefore, downgraded by two levels.
i. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 8 events in total. We, therefore, downgraded by two levels.

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Question 3. Should intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets versus standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets be used for hypertension treatment in children with CKD?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets	to standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: 5 years)												
1[1]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	0/189 (0.0%)	1/195 (0.5%) 33.4%[c]	**RR 0.34** (0.01 to 8.39)	**3 fewer per 1,000** (from 5 fewer to 38 more) **220 fewer per 1,000** (from 331 fewer to 1,000 more)	⨁⨁◯◯ Low	CRITICAL
Cardiovascular mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cardiovascular morbidity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Kidney Failure (or end-stage kidney disease) (follow-up: 5 years)												
1[1]	randomised trials	serious[a]	not serious	not serious	serious[d]	none	22/189 (11.6%)	34/196 (17.3%)	**RR 0.67** (0.41 to 1.10)	**57 fewer per 1,000** (from 102 fewer to 17 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets	to standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets	Relative (95% CI)	Absolute (95% CI)		
								33.4%[c]		**110 fewer per 1,000** (from 197 fewer to 33 more)		
Doubling serum creatinine - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acute kidney injury - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Systolic blood pressure												
1[1]	randomised trials	serious[a]	not serious	not serious	serious[e]	none	182	190	-	MD **2 lower** (4.97 lower to 0.97 higher)	⨁⨁◯◯ Low	CRITICAL
Diastolic blood pressure												
1[1]	randomised trials	serious[a]	not serious	not serious	serious[e]	none	182	190	-	MD **1 lower** (3.7 lower to 1.7 higher)	⨁⨁◯◯ Low	CRITICAL
Estimated glomerular filtration rate												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets	to standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets	Relative (95% CI)	Absolute (95% CI)		
1[1]	randomised trials	serious[a]	not serious	not serious	serious[e]	none	189	196	-	MD **1.4 lower** (2.79 lower to 0.01 lower)	⨁⨁◯◯ Low	CRITICAL
Proteinuria - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Left ventricular hypertrophy - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. One study that carried the overall effect estimate rated as high risk of bias due to lack of blinding of participants and personnel, and lack of blinding of outcome assessors.

b. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 1 event in total. We, therefore, downgraded by two levels.

c. Cross-sectional survey was performed during the period from March 2012 to October 2013 covering 13 towns around Hail city. Prevalence of concomitant hypertension in general population with CKD 33.4%.

d. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including 56 event in total.

e. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm.

References

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Question 4. Should intensive (SBP <120 mm Hg) blood pressure targets compared to standard (SBP <140mm Hg) blood pressure targets be used for hypertension treatment in adults with CKD?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intensive (SBP <120 mm Hg) blood pressure targets	standard (SBP <140mm Hg) blood pressure target	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
6[1,2,3,4,5,6]	randomised trials	serious[a]	not serious	not serious	not serious	none	598/6400 (9.3%)	701/6262 (11.2%)	**RR 0.85** (0.76 to 0.96)	**17 fewer per 1,000** (from 27 fewer to 4 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
								35.8%[7,b]		**54 fewer per 1,000** (from 86 fewer to 14 fewer)		
Cardiovascular mortality												
3[3,6,8]	randomised trials	serious[c]	not serious	not serious	serious[d]	none	54/2037 (2.7%)	55/2038 (2.7%)	**RR 0.96** (0.44 to 2.08)	**1 fewer per 1,000** (from 15 fewer to 29 more)	⊕⊕◯◯ Low	CRITICAL
								35.8%[7,b]		**14 fewer per 1,000** (from 200 fewer to 387 more)		
Cardiovascular morbidity												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intensive (SBP <120 mm Hg) blood pressure targets	standard (SBP <140mm Hg) blood pressure target	Relative (95% CI)	Absolute (95% CI)		
4[3,4,5,8]	randomised trials	serious[e]	not serious	not serious	serious[f]	none	1052/5051 (20.8%)	1175/5055 (23.2%)	**RR 0.89** (0.73 to 1.09)	**26 fewer per 1,000** (from 63 fewer to 21 more)	⊕⊕◯◯ Low	CRITICAL
								35.8%[7,b]		**39 fewer per 1,000** (from 97 fewer to 32 more)		
Kidney failure (formerly known as ESKD)												
3[3,6,9]	randomised trials	serious[c]	not serious	not serious	not serious	none	321/1929 (16.6%)	336/1892 (17.8%)	**RR 0.90** (0.82 to 0.99)	**18 fewer per 1,000** (from 32 fewer to 2 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Doubling serum creatinine - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acute kidney injury - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Systolic blood pressure (mm Hg): Mean(SD)												
3[3,6,9]	randomised trials	serious[c]	not serious	not serious	not serious	none	1929	1892	-	MD **8.12 lower** (13.13 lower to 3.1 lower)	⊕⊕⊕◯ Moderate	CRITICAL
Diastolic blood pressure (mm Hg): Mean(SD)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intensive (SBP <120 mm Hg) blood pressure targets	standard (SBP <140mm Hg) blood pressure target	Relative (95% CI)	Absolute (95% CI)		
3[3,6,9]	randomised trials	serious[c]	not serious	not serious	not serious	none	1929	1892	-	MD **4.3 lower** (6.46 lower to 2.15 lower)	⨁⨁⨁◯ Moderate	CRITICAL
eGFR change from baseline												
1[10]	randomised trials	serious[g]	not serious	not serious	serious[f]	none	432	408	-	MD **1.6 higher** (0.72 lower to 3.92 higher)	⨁⨁◯◯ Low	CRITICAL
Left ventricular hypertrophy - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Encephalopathy - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Hyperkalemia (assessed with: >5.5 mmol/L (n/N))												
1[3]	randomised trials	very serious[g]	not serious	not serious	not serious	none	106/1330 (8.0%)	78/1316 (5.9%)	**RR 1.34** (1.01 to 1.78)	**20 more per 1,000** (from 1 more to 46 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 6 studies and lack of blinding in 3 out of 6 studies.

b. Based on a national survey of representative sample of noninstitutionalized adults in the USA, it is estimated that hypertension occurs in 23.3% of individuals without CKD, and 35.8% of stage 1, 48.1% of stage 2, 59.9% of stage 3, and 84.1% of stage 4-5 CKD patients. Prevalence of hypertension also varies with the cause of CKD; strong association with hypertension was reported in patients with renal artery stenosis (93%), diabetic nephropathy (87%), and polycystic kidney disease (74%).

c. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 3 studies and lack of blinding in 2 out of 3 studies.

d. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including 109 events in total.
e. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 2 out of 4 studies.
f. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.
g. One study that carried all weight for the overall effect estimate rated as high risk of bias due to lack of lack of blinding.

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Question 5. Should early assessment (i.e., eGFR 20 mL/min/1.73m2) versus late assessment (i.e., eGFR <20 mL/min/1.73m2) be used for KRT in patients with CKD?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	early assessment (i.e., eGFR 20 mL/min/1.73m2)	late assessment (i.e., eGFR <20 mL/min/1.73m2)	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 90 days)												
1[1]	observational studies	very serious[a]	not serious	not serious	serious[b]	none	465/1976 (23.5%)	363/1039 (34.9%) 10.3%[2,c]	**RR 0.67** (0.60 to 0.76)	**115 fewer per 1,000** (from 140 fewer to 84 fewer) **34 fewer per 1,000** (from 41 fewer to 25 fewer)	⨁◯◯◯ Very low	CRITICAL
Mortality (follow-up: range 90 days to 1 years)												
1[1]	observational studies	very serious[a]	not serious	not serious	serious[b]	none	411/1502 (27.4%)	190/676 (28.1%) 10.3%[2,c]	**RR 0.97** (0.84 to 1.13)	**8 fewer per 1,000** (from 45 fewer to 37 more) **3 fewer per 1,000** (from 16 fewer to 13 more)	⨁◯◯◯ Very low	CRITICAL
Patient, family/caregiver health related quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Impact late referral rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Pre-emptive transplantation rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	early assessment (i.e., eGFR 20 mL/min/1.73m2)	late assessment (i.e., eGFR <20 mL/min/1.73m2)	Relative (95% CI)	Absolute (95% CI)		
Proportion patients receiving renal replacement therapy after assessment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Symptom scores - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cognitive impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Growth - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse events - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Study that carried all weight for the overall effect estimate rated as high risk of bias due to residual confounding arising from limited characterization of the severity of comorbid conditions. We, therefore, downgraded by two levels.

b. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.

c. Mortality attributable to chronic kidney disease from a cohort study of 462 293 individuals aged older than 20 years in Taiwan.

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Question 6. Should any late preparation strategy (based on eGFR or by anticipated time to start of KRT) versus any early preparation strategy (based on eGFR or by anticipated time to start of KRT) be used in patients with CKD stage 4 to 5 to prepare the patient for the start of KRT?*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	any late preparation strategy (based on eGFR or by anticipated time to start of KRT)	any early preparation strategy (based on eGFR or by anticipated time to start of KRT)	Relative (95% CI)	Absolute (95% CI)		
Mortality (HD access, adults > 70 years) [fistula placement within 1 month before initiation vs 1-2 months before initiation] (follow-up: 4 years)												
1[1]	observational studies	very serious[a]	not serious	not serious	serious[b]	none	0/419 (0.0%)	0/0 10.3%[2,c]	**HR 1.26** (1.03 to 1.54)	**1 fewer per 1,000** (from 2 fewer to 1 fewer) **25 more per 1,000** (from 3 more to 51 more)	⨁◯◯◯ Very low	CRITICAL
Cognitive impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Growth - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Impact late referral rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Patient, family/caregiver health related QoL - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Pre-emptive transplantation rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	any late preparation strategy (based on eGFR or by anticipated time to start of KRT)	any early preparation strategy (based on eGFR or by anticipated time to start of KRT)	Relative (95% CI)	Absolute (95% CI)		
Proportion receiving RRT after assessment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Symptom scores - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse events (HD access): AVF failure [time from creation to use <30 days vs >30 days] (follow-up: 5 years)												
1[3]	observational studies	very serious[a]	not serious	not serious	not serious	none	0/184 (0.0%)	0/0	**HR 1.94** (1.34 to 2.82)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⨁◯◯◯ Very low	CRITICAL
Adverse events (PD access, 1 week vs 4 weeks from access creation use, adults 18 - 70 years): Modality failure (follow-up: 6 months)												
1[4]	randomised trials	serious[d]	not serious	not serious	serious[e]	none	1/39 (2.6%)	7/41 (17.1%)	**RR 0.15** (0.02 to 1.17)	**145 fewer per 1,000** (from 167 fewer to 29 more)	⨁⨁◯◯ Low	CRITICAL
Adverse events (PD access, 1 week vs 4 weeks from access creation use, adults 18 - 70 years): Infections (PD related/tunnel/peritonitis) (follow-up: 2 months)												
1[4]	randomised trials	serious[d]	not serious	not serious	serious[f]	none	5/39 (12.8%)	1/41 (2.4%)	**RR 5.26** (0.64 to 43.00)	**104 more per 1,000** (from 9 fewer to 1,000 more)	⨁⨁◯◯ Low	CRITICAL
Adverse events (PD access, 1 week vs 4 weeks from access creation use, adults 18 - 70 years): Leak (follow-up: 2 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	any late preparation strategy (based on eGFR or by anticipated time to start of KRT)	any early preparation strategy (based on eGFR or by anticipated time to start of KRT)	Relative (95% CI)	Absolute (95% CI)		
1[4]	randomised trials	serious[d]	not serious	not serious	serious[b]	none	11/39 (28.2%)	1/41 (2.4%)	**RR 11.56** (1.57 to 85.42)	**258 more per 1,000** (from 14 more to 1,000 more)	⨁⨁◯◯ Low	CRITICAL

Adverse events (PD access, 1 week vs 2 weeks from access creation use, adults 18 - 70 years): Modality failure (follow-up: 6 months)

1[4]	randomised trials	serious[d]	not serious	not serious	serious[g]	none	1/39 (2.6%)	1/42 (2.4%)	**RR 1.08** (0.07 to 16.63)	**2 more per 1,000** (from 22 fewer to 372 more)	⨁⨁◯◯ Low	CRITICAL

Adverse events (PD access, 1 week vs 2 weeks from access creation use, adults 18 - 70 years): Infections (PD related/tunnel/peritonitis) (follow-up: 2 months)

1[4]	randomised trials	serious[d]	not serious	not serious	serious[f]	none	5/39 (12.8%)	1/42 (2.4%)	**RR 5.38** (0.66 to 44.07)	**104 more per 1,000** (from 8 fewer to 1,000 more)	⨁⨁◯◯ Low	CRITICAL

Adverse events (PD access, 1 week vs 2 weeks from access creation use, adults 18 - 70 years): Leak (follow-up: 2 months)

1[4]	randomised trials	serious[4]	not serious	not serious	serious[h]	none	11/39 (28.2%)	4/42 (9.5%)	**RR 2.96** (1.03 to 8.53)	**187 more per 1,000** (from 3 more to 717 more)	⨁⨁◯◯ Low	CRITICAL

Adverse events (PD access, 2 weeks vs 4 weeks from access creation use, adults 18 - 70 years): Modality failure (follow-up: 6 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	any late preparation strategy (based on eGFR or by anticipated time to start of KRT)	any early preparation strategy (based on eGFR or by anticipated time to start of KRT)	Relative (95% CI)	Absolute (95% CI)		
1[4]	randomised trials	serious[d]	not serious	not serious	serious[i]	none	1/42 (2.4%)	7/41 (17.1%)	**RR 0.14** (0.02 to 1.08)	**147 fewer per 1,000** (from 167 fewer to 14 more)	⨁⨁◯◯ Low	CRITICAL
Adverse events (PD access, 2 weeks vs 4 weeks from access creation use, adults 18 - 70 years): Infections (PD related/tunnel/peritonitis) (follow-up: 2 months)												
1[4]	randomised trials	serious[d]	not serious	not serious	serious[g]	none	1/42 (2.4%)	1/41 (2.4%)	**RR 0.98** (0.06 to 15.09)	**0 fewer per 1,000** (from 23 fewer to 344 more)	⨁⨁◯◯ Low	CRITICAL
Adverse events (PD access, 2 weeks vs 4 weeks from access creation use, adults 18 - 70 years): Leak (follow-up: 2 months)												
1[4]	randomised trials	serious[d]	not serious	not serious	serious[j]	none	4/42 (9.5%)	1/41 (2.4%)	**RR 3.90** (0.46 to 33.48)	**71 more per 1,000** (from 13 fewer to 792 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; **RR:** risk ratio

Explanations

a. Study that carried all weight for the overall effect estimate rated as high risk of bias due to bias due to confounding and selection of participants into the study. We, therefore, downgraded by two levels.

b. Serious imprecision. One study with a small sample size did not meet OIS criteria.

c. Mortality attributable to chronic kidney disease for national population was calculated based on a cohort study of 462 293 individuals aged older than 20 years in Taiwan.

d. Study that carried all weight for the overall effect estimate rated as high risk of bias due to lack of blinding.

e. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.

f. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 6 events in total.

g. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 2 events in total.

h. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 15 events in total.

i. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 8 events in total.

j. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 5 events in total.

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Question 7. Should a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms that he/she is experiencing versus not using such strategy be used in patients who are undergoing or being assessed for KRT or conservative management of established kidney failure?

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Fatigue (Pre-RRT, adults aged 25 to <70)									
3	observational studies[a]						Symptom reported with no additional details. [b]	-	CRITICAL
Itching (Pre-RRT, adults aged 25 to <70)									
2	observational studies[a]						This symptom was reported relatively infrequently and as intense. [c]	-	CRITICAL
Nausea and vomiting (Pre-RRT, adults aged 25 to <70)									
2	observational studies[a]						Symptom reported with no additional details. [d]	-	CRITICAL
Weight loss (Pre-RRT, adults aged 25 to <70)									
1	observational studies[a]		very serious				Symptom reported with no additional details. [b]	-	CRITICAL
Tiredness (Aching body, conservative management, adults aged 25 to <70, 70+)									
1	observational studies[a]						Symptom reported with no additional details. [b]	-	CRITICAL
Psychological distress and mental wellbeing (Confusion, conservative management, adults aged 25 to <70, 70+)									
1	observational studies[a]						Symptom reported with no additional details. [b]	-	CRITICAL
Psychological distress and mental wellbeing (Depression, conservative management, adults aged 25 to <70, 70+)									
1	observational studies[a]						Participants reported feeling depressed as they were unable to do things they were previously able to do. [b]	-	CRITICAL
Itching (Conservative management, adults aged 25 to <70, 70+)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1	observational studies[a]						Most participants found this problematic and persistent. [b]	-	CRITICAL
Tiredness (Lack of energy, conservative management, adults aged 25 to <70, 70+)									
1	observational studies[a]						Symptom reported with no additional details. [b]	-	CRITICAL
Tiredness (Fatigue, conservative management, adults aged 25 to <70, 70+)									
1[a]	observational studies						Most participants reported feeling tired and finding it debilitating. [b]	-	CRITICAL
Nausea and vomiting (Conservative management, adults aged 25 to <70, 70+)									
1	observational studies[a]						Most participants suffered from this symptom. [b]	-	CRITICAL
Anorexia (Poor appetite, conservative management, adults aged 25 to <70, 70+)									
1	observational studies[a]						Symptom reported with no additional details. [b]	-	CRITICAL
Psychological distress and mental wellbeing (Cognitive fluctuations, conservative management, adults aged 25 to <70, 70+)									
1	observational studies[a]						Symptom reported with no additional details. [b]	-	CRITICAL
Weight loss (Conservative management, adults aged 25 to <70, 70+)									
1	observational studies[a]						Symptom reported with no additional details. [b]	-	CRITICAL
Psychological distress and mental wellbeing (Cognitive fluctuations, HD, adults aged 70+)									
1[a]	observational studies[a]						Participants reported concern about their memory and remembering to carry out day-to-day tasks. [d]	-	CRITICAL
Psychological distress and mental wellbeing (Anxiety, HD, People aged 25 to <70, 70+)									
3	observational studies[a]						Symptom reported with no additional details. [b]	-	CRITICAL
Psychological distress and mental wellbeing (Cognitive fatigue, HD, adults aged 25 to <70, 70+)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
5[a]	observational studies						Participants mentioned how weakness and fatigue affected their cognitive abilities, causing difficulty in concentrating after dialysis. [b]	-	CRITICAL
Psychological distress and mental wellbeing (Depression, HD, People aged 2 to <16, 25 to <70, 70+)									
10	observational studies[a]						Participants reported feeling depressed during and after dialysis. [c]	-	CRITICAL
Tiredness (Exhaustion, HD, People aged 16 to <25, 25 to <70, 70+)									
3	observational studies[a]						Participants reported feeling exhausted after dialysis. [b]	-	CRITICAL
Tiredness (Fatigue, HD, People aged 2 to <16, 25 to <70, 70+)									
18	observational studies[a]						This symptom was reported by most participants as both habitual and following dialysis. [c]	-	CRITICAL
Tiredness (Malaise, HD, People aged 25 to <70, 70+)									
2	observational studies[a]						A common symptom mentioned by participants associated with dialysis. [b]	-	CRITICAL
Itching (HD, People aged 25 to <70, 70+)									
5	observational studies[a]						This was a common symptom reported by participants as usually intense. [c]	-	CRITICAL
Nausea and vomiting (HD, People aged 2 to <16, 16 to <25, 25 to <70, 70+)									
4	observational studies[a]						This symptom was reported relatively infrequently. [b]	-	CRITICAL
Weight loss (HD, People aged 25 to <70)									
1	observational studies[a]						Symptom reported with no additional details. [b]	-	CRITICAL
Psychological distress and mental wellbeing (Cognitive fatigue, PD, adults aged 25 to <70, 70+)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2	observational studies[a]						Some participants reported sensations of being mentally tired more dominant than physical tiredness. [b]	-	CRITICAL
Tiredness (Fatigue, PD, People aged 25 to <70, 70+)									
5	observational studies[a]						Participants reported this symptom following dialysis. [c]	-	CRITICAL
Itching (PD, People aged 25 to <70, 70+)									
5	observational studies[a]						This was a common symptom reported by participants as usually intense. [a]	-	CRITICAL
Nausea and vomiting (PD, People aged 2 to <16, 16 to <25, 25 to <70, 70+)									
2	observational studies[a]						This symptom was reported relatively infrequently. [d]	-	CRITICAL
Weight loss (PD, People aged 25 to <70)									
1	observational studies[a]						Symptom reported with no additional details. [b]	-	CRITICAL
Psychological distress and mental wellbeing (Cognitive fatigue, Transplant, People aged 25 to <70)									
2	observational studies[a]						Symptom reported with no additional details. [c]	-	CRITICAL
Psychological distress and mental wellbeing (Depression, Transplant, People aged 25 to <70)									
1	observational studies[a]						Symptom reported with no additional details. [d]	-	CRITICAL
Tiredness (Fatigue, Transplant, People aged 16 to 25, 25 to <70, 70+)									
5	observational studies[e]						This symptom was reported by most participants as a side effect to transplant medication. [c]	-	CRITICAL
Itching (Transplant, People aged 25 to <70)									
2	observational studies[a]						This symptom was reported relatively infrequently and as intense. [c]	-	CRITICAL
Nausea and vomiting (Transplant, People aged 2 to <16, 16 to <25, 25 to <70, 70+)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2	observational studies[a]						This symptom was reported relatively infrequently. [c]	-	CRITICAL
Weight loss (Transplant, People aged 25 to <70)									
1	observational studies[a]						Symptom reported with no additional details. [b]	-	CRITICAL

CI: confidence interval

Explanations

a. Qualitative studies; individual interviews.
b. Overall assessment of certainty: LOW
c. Overall assessment of certainty: VERY LOW
d. Overall assessment of certainty: MODERATE
e. Qualitative studies; a combination of individual interviews (3) and focus groups (2).

Question 8. Should initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms versus initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms be used in previously KRT-naive adults requiring KRT for deteriorating CKD?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms	initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*	Relative (95% CI)	Absolute (95% CI)		
Mortality - HD or PD (follow-up: mean 3.6 years; assessed with: early vs late dialysis initiation based on eGFR)[b]												
1[1]	randomized trials	serious[c]	not serious	not serious	serious[d]	none	154/404 (38.1%)	155/424 (36.6%)	**RR 1.04** (0.87 to 1.24)	**15 more per 1,000** (from 48 fewer to 88 more)	⨁⨁◯◯ Low	CRITICAL
								25.6%[2,e]		**10 more per 1,000** (from 33 fewer to 62 more)		
								51.6%[2,f]		**21 more per 1,000** (from 67 fewer to 124 more)		
Mortality: age<18 years - HD or PD (follow-up: 1.3 years)												
2[3,4]	observational studies	serious[g]	not serious	not serious	serious[d]	none	0/5738 (0.0%)	0/12395 (0.0%)	**HR 1.25** (0.96 to 1.64)	**-- per 1,000** (from -- to --)	⨁◯◯◯ Very low	CRITICAL
Cognitive impairment - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[b]												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Growth age<18 years - HD or PD (assessed with: early vs late dialysis initiation based on eGFR)[b]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms	initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*	Relative (95% CI)	Absolute (95% CI)		
1[3]	observational studies	serious[c]	not serious	not serious	serious[d]	none	1411	1552	-	MD **0.03 lower** (0.15 lower to 0.09 higher)	⨁◯◯◯ Very low	CRITICAL
Impact late referral rates - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[b]												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Patient, family/caregiver health related QoL - HD or PD (assessed with: assessed with: early vs late dialysis initiation based on eGFR)[b]												
1[1]	randomised trials	very serious[c]	not serious	not serious	serious[d]	none	307	335	-	MD **0** (0.03 lower to 0.03 higher)	⨁◯◯◯ Very low	CRITICAL
Pre-emptive transplantation rates: age<18 years - HD or PD (assessed with: assessed with: early vs late dialysis initiation based on eGFR)[b]												
1[3]	observational studies	serious[c]	not serious	not serious	serious[d]	none	0/1411 (0.0%)	0/1552 (0.0%)	**HR 0.97** (0.89 to 1.06)	**-- per 1,000** (from -- to --)	⨁◯◯◯ Very low	CRITICAL
Proportion receiving KRT after assessment - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[b]												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Symptom scores - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[b]												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse events - HD or PD (follow-up: 3.6 years; assessed with: assessed with: early vs late dialysis initiation based on eGFR)[bh]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms	initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*	Relative (95% CI)	Absolute (95% CI)		
1[1]	randomised trials	serious[c]	not serious	not serious	serious[d]	none	148/404 (36.6%)	174/424 (41.0%)	**RR 0.89** (0.75 to 1.06)	**45 fewer per 1,000** (from 103 fewer to 25 more)	⊕⊕◯◯ Low	CRITICAL
Mortality: Transplant at eGFR>/=15ml/min vs <10ml/min												
1[5]	observational studies	serious[c]	not serious	not serious	serious[d]	none	0/130 (0.0%)	0/324 (0.0%) 8.7%	**HR 1.35** (0.89 to 2.05)	**-- per 1,000** (from -- to --) **29 more per 1,000** (from 9 fewer to 84 more)	⊕◯◯◯ Very low	CRITICAL
Mortality: Transplant at eGFR 10 -14.9 ml/min vs <10ml/min												
1[5]	observational studies	serious[c]	not serious	not serious	serious[d]	none	0/217 (0.0%)	0/324 (0.0%) 8.7%	**HR 0.99** (0.69 to 1.42)	**-- per 1,000** (from -- to --) **1 fewer per 1,000** (from 26 fewer to 34 more)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. * Severe uremic symptoms and/or uncontrollable fluid overload.

b. Early=10-14 ml/min, late=5-7 ml/min

c. One study that carried all weight for the overall effect estimate rated as high risk of bias.

d. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.
e. Mortality rate based on a population-based cohort study of 725 Swedish adult patients with CKD that received peritoneal dialysis.
f. Mortality rate based on a population-based cohort study of 1791 Swedish adult patients with CKD that received hemodialysis.
g. Studies that carried large weight for the overall effect estimate rated as high risk of bias.
h. Infection events

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Question 9. Should any KRT modality versus conservative management be used in certain groups of patients requiring KRT for CKD?*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	any KRT modality	conservative management	Relative (95% CI)	Absolute (95% CI)		
Mortality in over 75s (RRT = Dialysis/Transplant) (follow-up: range 1 years to 18 years)												
1[1]	observational studies	very serious[b]	not serious	not serious	serious[c]	none	0/106 (0.0%)	0/77 (0.0%) 35.8%	**HR 0.85** (0.57 to 1.27)	**-- per 1,000** (from -- to --) **44 fewer per 1,000** (from 135 fewer to 72 more)[2,d]	⨁◯◯◯ Very low	CRITICAL
Mortality in over 75s (RRT = Dialysis) (follow-up: median 2 years)												
1[1]	observational studies	very serious[b]	not serious	not serious	not serious	none	0/52 (0.0%)	0/77 (0.0%) 35.8%	**HR 2.94** (1.56 to 5.53)	**-- per 1,000** (from -- to --) **370 more per 1,000** (from 141 more to 556 more)[2,d]	⨁◯◯◯ Very low	CRITICAL
Cognitive impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Growth - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Impact late referral rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Patient, family/caregiver health related QoL - not reported												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	any KRT modality	conservative management	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	
Pre-emptive transplantation rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Proportion receiving RRT after assessment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Symptom scores - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Adverse events - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: confidence interval; **HR:** hazard Ratio

Explanations

a. * i. those that choose not to undergo dialysis, ii. those who choose to withdraw from dialysis after a period of treatment, iii. those who are coming to the end of their lives while already on long-term dialysis, iv. those who have a failing transplant and decide not to return to dialysis.

b. One study that carried all weight for the overall effect estimate rated as high risk of bias. We, therefore, downgraded by two levels.

c. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.

d. Based on a national survey of representative sample of noninstitutionalized adults in the USA, it is estimated that hypertension occurs in 23.3% of individuals without CKD, and 35.8% of stage 1, 48.1% of stage 2, 59.9% of stage 3, and 84.1% of stage 4-5 CKD patients. Prevalence of hypertension also varies with the cause of CKD; strong association with hypertension was reported in patients with renal artery stenosis (93%), diabetic nephropathy (87%), and polycystic kidney disease (74%).

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Question 10. Should transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators versus not transferring between modalities of KRT or discontinuing KRT based on suitable clinical indicators* or doing either at a later stage be used in patients with CKD currently receiving KRT?*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators*	not transferring between KRT modalities or discontinuing KRT, or doing either at a later stage (any clinical indications)	Relative (95% CI)	Absolute (95% CI)		
Mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cognitive impairment (dichotomous) and new outcome: school performance in children - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Growth - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Impact late referral rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Patient, family/caregiver health related QoL - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Pre-emptive transplantation rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Proportion receiving RRT after assessment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Symptom scores - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse events - not reported												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators*	not transferring between KRT modalities or discontinuing KRT, or doing either at a later stage (any clinical indications)	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-					-	CRITICAL

CI: confidence interval

Explanations

a. *Vascular access failures, peritoneal membrane failure or failure of kidney graft.

Question 11. Should any frequency of regular review for any KRT modality or conservative management versus any other frequency of regular review be used in patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	any frequency of regular review for any KRT modality or conservative management	any other frequency of regular review	Relative (95% CI)	Absolute (95% CI)		
Mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cognitive impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Growth - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Impact late referral rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Patient, family/caregiver health related QoL - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Pre-emptive transplantation rates - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Proportion receiving RRT after assessment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Symptom scores - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse events - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval

Question 12. Should any type of information, education, or support versus any other type of information, education, or support be used in patients requiring KRT or conservative management (and their families or caregivers as appropriate)?

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Content of information: Symptoms									
4	observational studies[a]						People mentioned information on what they may experience and how to manage them as an area they appreciated or would have appreciated. [b]	-	CRITICAL
Content of information: Prognosis									
7	observational studies[a]						People mentioned information on the likely long term consequences of their disease and life expectancy, particularly in the context of transplant as an area they appreciated or would have appreciated. [b]	-	CRITICAL
Content of information: Mode of access									
5	observational studies[a]						People mentioned information on the benefits and harms of different types of vascular access as an area they appreciated or would have appreciated. [b]	-	CRITICAL
Content of information: Services									
2	observational studies[c]						People mentioned information on the availability of support and transition from paediatric to adult as an area they appreciated or would have appreciated A study identified functional needs and home environmental barriers to social engagement through focus groups; mapped findings onto aspects of an established program, which includeshome visits with an occupational therapist, nurse,and handyman to provides ≤$1,300 worth of repairs,modifications, and devices; and piloted the program(Seniors Optimizing Community Integration toAdvance Better Living with ESRD [SOCIABLE])among 12 older adult HD patients. A home-based intervention addressing physical and social functioning of low socioeconomic status older adults on HD therapy was feasible and acceptable. [1,d]	-	CRITICAL
Content of information: Adherence									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2	observational studies[a]						People mentioned information on the importance of adherence and consequences of non-adherence as an area they appreciated or would have appreciated. [d]	-	CRITICAL
Content of information: Transplant listing									
2	observational studies[e]						People mentioned information on the actual practicalities of listing an area they appreciated or would have appreciated [d]	-	CRITICAL
Content of information: How to approach potential living donors									
1	observational studies[f]						People mentioned information on how to approach potential living donors in an area they appreciated or would have appreciated. [d]	-	CRITICAL
Content of information: Acute situations									
3	observational studies[e]						People mentioned information on what to expect with acute situations and how to handle them as areas they appreciated or would have appreciated A mixed method study demonstrated content gaps that included prognosis, decisionsupport, mental health and cognition, advance care planning, cost, and diet. Slide presentations used did not consistently reflect best practices related to health literacy. [2,d]	-	CRITICAL
Content of information: Kidney function and CKD									
2	observational studies[c]						People mentioned information to gain a basic understanding of their disease as an area they appreciated or would have appreciated. In a study, mean scores of the emotional and instrumental social support were 3.92 (± 0.78) and 3.81 (± 0.69) respectively, an indication of good support received. The most frequent sources of instrumental and emotional social support mentioned by participants were partners, spouse, companion or boyfriend and friends. [3,d]	-	CRITICAL
Content of information: End of life care									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1	observational studies[g]						People mentioned information on end of life care as an area they appreciated or would have appreciated. [d]	-	CRITICAL
Preferred format of information provision: Depth and timing of information									
17	observational studies[h]						People appreciate more complete information, provided in stages from an earlier starting point to avoid being overwhelmed. Patients with CKD stages 3 to 4 wanted information on slowing diseaseprogression and avoiding transplant Increasing access to culturally responsive transplant education in multiple languages, pairing appropriate content to the disease stage, and increasing system-wide follow-up as the disease progresses might help patients make more informed choices about transplant (Waterman, 2020).A study highlights the importance of improving pre-hemodialysis education to ensure that patients' expectations are realistic, as well as identifying individualized coping strategies by patients (Balogun, 2019). All participants were reluctant to initiate HD, but made the decision on advice from their physicians for varying reasons.Even though the majority of participants identified several difficulties with being on HD, they also had positive coping strategies, and the majority indicated that they would make the same decision to initiate HD. [b]	-	CRITICAL
Preferred format of information provision: Personalisation									
6	observational studies[i]						People appreciated when information provided to them was individualised and tailored to their circumstances.Multidisciplinary education (MDE) enhanced participants' disease-specific knowledge and ability for coping. It also improved sympathy, helpfulness, and the mutual responsibilities of family members (Polner 2021) [b]	-	CRITICAL
Preferred format of information provision: Classes and tours									
5	observational studies[j]						People appreciated formal education methods like pre-dialysis classes and tours of facilities before beginning RRT. [b]	-	CRITICAL
Preferred format of information provision: Multiple formats									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
7	observational studies[a]						People noted that they found it useful when information/education was provided in multiple formats, for example, oral and written Educational videos were well utilized with nearly half of the participants (42.5%) reporting that they watched at least one of the videos, and the majority reporting that the videos seen had an overall positive impact on health (Magnus, 2017)[b]	-	CRITICAL

Preferred format of information provision: Target of education/information

1	observational studies[c]						People and their family/carers both noted that it was useful to have information and education with aspects tailored to each individual. In a semi-structured interview, self-care requirements, self-care deficit, and education and information management for self-care emerged as three categories. People were aware of the importance of carrying out their self-care. They also stated not to carry out the care actions rigorously enough showing some limitations. Finally, people's knowledge about their condition was usually acquired from the Internet and from their own experience rather than through consultations with a health team (Santana, 2020) Preliminary findings emphasized thar strengthening patient education strategies in the clinics,hospitals, and community settings should be given due attention by relevant healthcare professionals (Sowtali, 2020)[d]	-	CRITICAL

Decision making: Availability of choice

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
10	observational studies[a]						People reported that they did not always feel like all options that should have been available to them, were available . Evidence suggests that various personal, family-related, psychological, social, and economic factors could affect the decision on the type of dialysis in patients. Therefore, basic infrastructures such as social support, education, and even the specialist and positive perspective of the Ministry of Health are required to choose this therapeutic method. (Ahmadi, 2018) According to an evidence (Cassidy , 2018), three themes influenced dialysis modality decision making: (i) Patient Factors: individualization, autonomy, and emotions; (ii) Educational Factors: tailored education, time and preparation, and available resources; and (iii) Support Systems: partnership with health care team, and family and friends. When providing decisional support to pre-dialysis stage patients, practitioners need to increase patients' decision self-efficacy, provide both haemodialysis and peritoneal dialysis pre-dialysis education, increase dialysis knowledge and provide professional support (Chen, 2018). Comparing patients who chose peritoneal dialysis (PD) and hemodialysis (HD), there were no differences on anxiety (p= 0.55), and depressionscores (p= 0.467), and stress (p= 0.854). Anxious (p= 0.007) and depressive (p= 0.030) patients presented lower levels ofphosphate than those not affected. There was a significant correlation between anxiety and depressionscores, anxiety and stress scores, depression and stress scores (Bezerra, 2018) Patients from low-GDP countries reported later in-formation provision, less information about other modalitiesthan CHD and lower satisfaction with information. The major-ity of modality decisions were made involving both patient andnephrologist. Patients reported subjective (e.g. quality of life andfears) and objective reasons (e.g. costs and availability of treat-ments) for modality choice (Jong, 2021) [d]	-	CRITICAL
Decision making: Reversibility									
1	observational studies[g]						People felt it was particularly important that the reversibility of any decisions they made was made clear [d]	-	CRITICAL
Impact of transport on care									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
3	observational studies[k]						People noted that the availability of transport affected their ability to engage with RRT and was a significant psychological stressor during RRT [b]	-	CRITICAL
Psychological support									
7	observational studies[l]						People reported that they felt healthcare professionals were not always aware of the emotional and social distress associated with their RRT. People reported that having someone to talk to was important. Caregivers were found to be moderately burdened and their lives hadchanged for the worst as a result of caregiving. There were significant differences incaregiving outcome scores before and after the intervention (Alnazly , 2018)A study identified main themes like “immersion in an ocean of psychological tension,” which suggests that the mothers of the children undergoing hemodialysis are overwhelmed by the numerouspsychological pressures that they encounter during their children’s treatment. This theme was constituted by the subthemes “bewilderment between hope and despair,” “endless concerns,” “agony and sorrow,” and “a sense of being ignored (Pourghaznein, 2021) The findings from the dyadic perspective (Sousa, 2021) were conceptualized into twomajor themes: negative impacts (emotional distress, constraints on leisure and dailyactivities, impacts on couples’dynamics, and difficulties in meal planning) andunmet needs (educational, relational, financial, instrumental, and supportive needs). [b]	-	CRITICAL
Barriers to good care									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
6	observational studies						The most commonly cited barriers to home dialysis were lack of a care partner, lack of home space, and patient preference (Shamy 2021). Many participants felt that dialysis center technicians treated them poorly (Salter, 2015). Financial barrier: Some of the participants encountered periods of limited funds. Some of the participants experienced the effects of the hidden costs of dialysis, such as specific dietary requirements including specific, more costly food groups (Small, 2010). Many felt disempowered by the system, and worn down by the need to continually justify their requirement for assistance. For some, the time and expense that was required to gather all the documentation to apply for assistance resulted in them not completing this process and not receiving the assistance to which they were entitled (Walker, 2016). Some felt healthcare professionals underestimated their ability to accept and cope with their illness (Wells, 2013). Lack of information and dissatisfaction with their healthcare providers regarding perceptions of their care. Lack of explanation of results, not being completely honest, kept in the dark about the seriousness of the problem and not being clear about when dialysis would occur were problems patients described (Harwood, 2005) [d]	-	CRITICAL
Facilitators of good care									
4	observational studies						Patients thought 1:1 time with transplant team members was helpful. Patients wanted additional information sources as well, without losing 1:1 time(Korus, 2011). Hospital staff also played a key role, including teachers, youth workers and nurses. Being able to trust healthcare staff was valued highly (Wells, 2013). Patients identified needing time to absorb information and adjust to the approaching dialysis. Some reported how it was hard difficult to grasp and absorb the information (Harwood, 2005). The importance/effect of a good nurse/patient relationship. Most patients wanted to discuss the importance of good care received by nurses and how it affected their condition. It is valuable for the nurse to listen to the dialysis patients and hear their views, and incorporate these views in care planning (KABA, 2007) [d]	-	CRITICAL
Impact of treatment on lifestyle									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
4	observational studies						People mentioned information on of any modality choice, including limitations on travel, and sexual activity as areas they appreciated or would have appreciated. [d]	-	CRITICAL
Information sources other than healthcare professionals (e.g. support groups, online resources)									
14	observational studies						People valued peer support as a useful format of providing information or education when presented in an open, unbiased and supportive manner [d]	-	CRITICAL
Information around transitions between forms of RRT - not reported									
-	-	-	-	-	-	-		-	CRITICAL
Modality of RRT									
7	observational studies						People mentioned information on the benefits and harms of different modalities of RRT and conservative management as an area they appreciated or would have appreciated. There was a significant impact of PDEP on reducing HD choice. Most of the PD patients (81.8%) did not have an infection as compared to 42.3% of the HD patients. HD was also associated with increased admission days.(Alghamdi, 2020). Five themes related to continuation or discontinuation of HHD emerged: (1) degree of independence (increasedflexibility, burden of therapy), (2) availability of support (emotional andphysical support and caregiver burden), (3) technical aspects (familiarity with machine), (4) home environment (ability to organize supplies, space in home), and (5) attitude and expectations (positive or negative outlook about performing HHD). For each theme, positive aspects facilitated continuation of HHD and negative aspects contributed to discontinuation of HHD (Seshasai, 2019) [d]	-	CRITICAL

CI: confidence interval

Explanations

a. Qualitative studies; combination of interviews and focus groups, all 25 to <70, all during RRT.

b. Overall assessment of certainty: HIGH

c. Qualitative studies; focus groups, 25 to <70, during RRT.

d. Overall assessment of certainty: MODERATE

e. Qualitative studies; interviews, all 25 to <70, all during RRT.
f. Qualitative study; focus groups, 25 to <70, during RRT.
g. Qualitative study, Interviews groups, 25 to <70, during RRT.
h. Qualitative studies; combination of interviews and focus groups, mix of 25 to <70 (n=14) and over 70 (n=1), all during RRT
i. Qualitative studies; combination of interviews and focus groups, a mix of 2 to 16 years old (n=1) 25 to <70 years old (n=5), all during RRT.
j. Qualitative studies; combination of interviews and focus groups, a mix of 25 to <70 (n=4) and over 70 (n=1), all during RRT.
k. Qualitative studies; interviews, mix of 25 to <70 (n=2) and over 70 (n=1), both pre-RRT (n=1) and during RRT (n=2).
l. Qualitative studies; combination of interviews and focus groups, mix of 25 to <70 (n=6) and over 70 (n=1), all during RRT.

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14.8. Evidence-to-Decision frameworks and Summary of Findings tables

This section contains the EtD frameworks (and associated SoF tables) for each clinical question exported from GRADEpro that the CKD Task Force used during the Recommendations Workshops (together with the respective Evidence profiles, see Appendix 14.7) to make and document their recommendations.

Question 1. Should ACEi or ARBs versus other antihypertensive agents be used for hypertension treatment in children with CKD?

Population:	Children with CKD
Intervention:	ACEi or ARBs
Comparison:	other antihypertensive agents
Main outcomes:	All-cause mortality; Cardiovascular mortality; Cardiovascular morbidity; Kidney failure (or end-stage kidney disease); Doubling serum creatinine; Acute kidney injury; Systolic blood pressure; Diastolic blood pressure; Estimated glomerular filtration rate (eGFR); Proteinuria; Left ventricular hypertrophy; Encephalopathy.
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (1).
Conflict of interests:	**KSA conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dhalbi Muneera Rashid Al-Jelaify Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari Ahmed Mitwalli **Panel members recused as a result of risk of conflicts of interest:**

	None

Assessment

Problem **Is the problem a priority?**		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	• The prevalence of CKD in Saudi Arabia is not known. • Reports indicate that mortality among children who progress to ESRD is 30 to 50 times higher compared to that in the general population (2, 3). • The main causes of CKD in this population of patients were congenital abnormalities of the renal system, in 50% of patients, followed by neurogenic bladder in almost 20% of the children, acquired causes (14%), and hereditary conditions (12%) (4). • There is a considerable delay in referring children with CKD to a pediatric nephrologist as well as in the management of preventable causes such as neurogenic bladder associated with spina bifida (4).	
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	**Research evidence**	**Additional considerations**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1*	The panel noted that it is difficult to perform large RCTs in the pediatric population.
Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	**Research evidence**	**Additional considerations**

○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	*See Appendix 1*	During discussion of final recommendations, the panel noted that hyperkalemia and progression of CKD (decrease in GFR) are known complications of treatment.
Certainty of evidence What is the overall certainty of the evidence of effects?		
Judgement	**Research evidence**	**Additional considerations**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty in the evidence is reduced as a result of imprecision and risk of bias for the assessment of outcomes of one study.	Based on the lowest certainty of the critical outcomes.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not identify primary studies addressing the relative importance of the outcomes for this specific question. **A guideline described the following regarding the relative importance of outcomes and patients' preferences for antihypertensive agents in children with CKD** (5)The Work Group judged that preventing kidney failure and progressive kidney function loss would be of high value to nearly all well-informed patients or caregivers. Published patient-reported outcome data from the SONG–Kids study reported that children with kidney disease and caregivers rated kidney function as an important outcome, whereas blood pressure (BP) control was also rated as an important outcome by caregivers (6).In the judgment of the Work Group, most patients would value these clinical benefits despite the inconvenience and potential risk of harms associated with aggressive BP management (e.g., multiple medications, more frequent dosing, possible adverse events if dehydrated, and the burden of monitoring with 24-hour ambulatory BP monitoring (ABPM). Patients for whom medication burden or the burden of ABPM monitoring are particularly important concerns may be more inclined not to follow this recommendation.	The panel debated a judgment of possibly important vs. probably no important uncertainty or variability and ultimately agreed on a judgment of possibly important due to insufficient evidence. They agreed that patient representative input may be helpful.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel judged the balance as probably favoring the intervention because of uncertainty about the effects.
Resources required How large are the resource requirements (costs)?		
Judgement	**Research evidence**	**Additional considerations**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost per package size of antihypertensive treatment drugs (angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers) is from 2.20 USD to 44 USD in patients with CKD. **A guideline described the following regarding the resource use and costs of blood pressure treatment in children** (5)In the judgement of the guideline Work Group, the potential benefits associated with ambulatory blood pressure monitoring (ABPM) outweigh the costs and inconvenience associated with its implementation. Patients and families in areas where ABPM is unavailable or less affordable will be less inclined to follow this recommendation and may choose to use clinic-based auscultatory BP monitoring instead.	The panel discussed the issue of immediate costs (cost of medication) in light of possible long-term savings such as prevention of future renal transplant or dialysis, as well as possible improvement in future quality of life. It was clarified that the judgement related to costs for the healthcare system as a whole rather than for individuals. However, the implications of how the intervention might prevent future complications of CKD still applied for healthcare systems. Ultimately the judgement was moderate savings because of this.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
Judgement	**Research evidence**	**Additional considerations**

○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify direct evidence to address the certainty of the evidence of resource requirements.	

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Following the assessment of the existing evidence base for the cost-effectiveness of antihypertensive agents vs. standard of care be used in children with CKD, no existing studies were identified comparing antihypertensive agents vs. standard of care. No firm conclusions can be drawn on the cost-effectiveness of antihypertensive agents for the control of blood pressure. However, we identified indirect evidence that suggests for other populations that an intensive blood pressure target compared with a conventional blood pressure target is cost-effective (7).	

Equity
What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased	We did not identify evidence to address equity for this specific question.	The panel noted that equity depends on availability and access, including limited access in geographical areas or healthcare resources, primarily related to supplying these medications.

○ Increased ○ Varies ○ Don't know		The judgment was based on panel experience in the absence of research evidence. The judgment of probably no impact was related to a system of full healthcare coverage in Saudi Arabia.
Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not identify direct evidence to address acceptability for this specific question. However, a treatment study suggests that lower and higher pressure targets are usually acceptable to patients and to healthcare providers (8).A randomized controlled trial that included 385 children with chronic kidney disease (CKD) showed that intensified blood-pressure control delays the progression of renal disease in children with CKD who receive a fixed high dose of an angiotensin-converting enzyme (ACE) inhibitor.Despite the relatively modest additional reduction in blood pressure achieved with intensified antihypertensive treatment, the progression of renal disease was significantly delayed with the intensified-intervention protocol.	
Feasibility Is the intervention feasible to implement?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question. Research and clinical practice showed that implementing ambulatory blood pressure monitoring (ABPM) for monitoring the treatment of hypertension is challenging (9). For instance, blood pressure (BP) monitors are not always available when needed; they require time from a parent or other adult to return the monitor to the clinic and are expensive. With this in mind, there are certain situations where there is a low probability of finding elevated BP by ABPM.	The panel noted that antihypertensive therapy, in Saudi Arabia, is inexpensive, available, and easy to carry out.

Summary of judgments

	JUDGMENT						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	**Moderate**	Small	Trivial		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

In children with CKD, the CKD Task Force suggests using ACEi or ARBs rather than other antihypertensive agents for hypertension treatment (conditional recommendation, very low certainty in the evidence of effects). This recommendation applies to all children with CKD stages 1-3 and to those with advanced CKD (stages 4-5) who are not receiving KRT.

Justification

The panel judged that the balance of desirable and undesirable consequences favors the use of ACEi or ARBs over other antihypertensive agent in this population. Specifically, the panel felt that most patients will get benefit due to a balance that proabaly favors ACEi or ARBs in the context of very low certainty evidence, resources required with moderate savings, and cost-effectiveness that probably favors ACEi or ARBs.

Subgroup considerations

Based on expert experience the panel identified children with advanced CKD who are not on KRT as a subpopulation of people who might be affected differently than most by this recommendation. The panel judged that for this population this recommendation does not apply.

Implementation considerations

No implementation considerations were made for this recommendation because there was no research evidence identified.

Monitoring and evaluation

Based on guidance in current literature and collective experience, the guideline panel judged that monitoring serum potassium levels is required in children with CKD.

Research priorities

No research priorities were identified by the panel.

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Appendix 1 - Summary of findings

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	**Anticipated absolute effects* (95% CI)**	
				Risk with other antihypertensive agents	**Risk difference with ACEi or ARBs**
All-cause mortality - not reported	-	-	-	-	-
Cardiovascular mortality - not reported	-	-	-	-	-
Cardiovascular morbidity - not reported	-	-	-	-	-
Kidney failure (or end-stage kidney disease) assessed with: decline in GFR by >30% or attainment of ESRD follow-up: 12 months	41 (1 RCT)[1]	⨁◯◯◯ Very low[a,b]	**RR 0.45** (0.13 to 1.50)	Study population	
				333 per 1,000	**183 fewer per 1,000** (290 fewer to 167 more)
				Moderate	
				334 per 1,000[c]	**184 fewer per 1,000** (291 fewer to 167 more)
Doubling serum creatinine - not reported	-	-	-	-	-
Acute kidney injury - not reported	-	-	-	-	-
Systolic blood pressure follow-up: 12 months	41 (1 RCT)[1]	⨁◯◯◯ Very low[b,d]	-	The mean systolic blood pressure was **0**	MD **0.6 lower** (1.12 lower to 0.08 lower)
Diastolic blood pressure follow-up: 12 months	41 (1 RCT)[1]	⨁◯◯◯ Very low[b,d]	-	The mean diastolic blood pressure was **0**	MD **0.64 lower** (1.1 lower to 0.18 lower)
Estimated glomerular filtration rate (eGFR) assessed with: GFR decline (mL/min/1.73 m2) follow-up: 12 months	41 (1 RCT)[1]	⨁◯◯◯ Very low[a,b]	-	The mean estimated glomerular filtration rate (eGFR) was **0**	MD **1.2 lower** (4.05 lower to 1.65 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with other antihypertensive agents	**Risk difference with ACEi or ARBs**
Proteinuria assessed with: urine protein/creatinine (mg/mg) follow-up: 12 months	41 (1 RCT)[1]	⨁◯◯◯ Very low[b,d]	-	The mean proteinuria was **0**	MD **1.13 lower** (1.82 lower to 0.44 lower)
Left ventricular hypertrophy - not reported	-	-	-	-	-
Encephalopathy - not reported	-	-	-	-	-

References

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Explanations

a. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference. No optimal information size was reached. We, therefore, downgraded by two levels.
b. One study that carried the overall effect estimate rated as high risk of bias due to lack of blinding in participants and outcome assessment.
c. Cross-sectional survey was performed during the period from March 2012 to October 2013 covering 13 towns around Hail city. Prevalence of concomitant hypertension in population with CKD 33.4%.
d. Serious imprecision. No optimal information size was reached in the RCT.

Question 2. Should non-RASi versus RASi be used for hypertension treatment in adults with CKD?

Population:	hypertension treatment in adults with CKD
Intervention:	non-RAS inhibition
Comparison:	RASi
Main outcomes:	All-cause mortality; Cardiovascular mortality; Cardiovascular morbidity; Kidney failure; Doubling serum creatinine; Acute kidney injury; Systolic blood pressure; Diastolic blood pressure; eGFR change from baseline; Proteinuria (g/g creatinine); Left ventricular hypertrophy; Encephalopathy; Hyperkalemia
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (Gadelkarim AH, 2019).
Conflict of interests:	**KSA conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dhalbi Muneera Rashid Al-Jelaify Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari Ahmed Mitwalli **Panel members recused as a result of risk of conflicts of interest:** None

Assessment

Problem Is the problem a priority?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	• The incidence and prevalence of CKD reportedly increased in Saudi Arabia over the last several decades, especially in the Western region. Diabetes, hypertension, and obesity are important factors (1). • Most community-based prevalence studies concerning these three issues in relation to CKD have taken place in Northern Saudi Arabia (2). • Hypertension is a known risk factor for and complication of CKD. In surveys in Saudi Arabia, the overall prevalence of hypertension was about 30% of adults (2).	
Desirable Effects How substantial are the desirable anticipated effects?		
Judgment	**Research evidence**	**Additional considerations**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1*	
Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgment	**Research evidence**	**Additional considerations**
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	*See Appendix 1*	
Certainty of evidence		

What is the overall certainty of the evidence of effects?		
Judgment	**Research evidence**	**Additional considerations**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty in the evidence is reduced as a result of imprecision and risk of bias for the assessment of surrogate outcomes in studies.	Based on the lowest certainty of the critical outcomes.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgment	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not identify primary studies addressing the relative importance of the outcomes for this specific question. **A guideline described the following regarding the relative importance of outcomes and patients' preferences for antihypertensive agents in adults with chronic kidney disease (CKD):** The presence of severely increased albuminuria and CKD is associated with a higher prevalence of cardiovascular disease, progressive CKD, and attendant loss of quality of life. In the opinion of the Work Group, most well-informed patients with CKD and severely increased albuminuria would place emphasis on preventing cardiovascular outcomes in addition to preventing CKD progression. They also think that many well-informed patients would place more emphasis on the potential for preventing CKD progression (3).	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgment	**Research evidence**	**Additional considerations**

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Evidence from the REIN (Ramipril Efficacy in Nephropathy) study suggests that RAS inhibitors medications offer kidney benefits in individuals with CKD and severe proteinuria without diabetes. RAS inhibitors (such as ramipril) slow down CKD progression by gradually lowering the eGFR decline. Other evidence from the AIPRI trial (The Angiotensin-Converting Enzyme Inhibitors and Kidney Protection trial) also indicates that RAS inhibitors lower doubling of serum creatinine or ESKD. Meta-analysis studies suggest the ACE inhibitors and ARBs improve kidney outcomes (Cheung et al., 2021) There is insufficient evidence for the comparison between non-RAS inhibition vs RASi. Evidence presented includes only non-RAS inhibition (aldosterone antagonist) vs placebo.
Resources required How large are the resource requirements (costs)?		
Judgment	**Research evidence**	**Additional considerations**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost per package size of antihypertensive treatment drugs (angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers) is from 12 SAR to 165 SAR (3.20 USD to 44 USD) in patients with CKD (4)	

Class	Drug	Strength	Cost per pckage size	
			Lowest price	Highest price
Angiotensin Converting Enzyme Inhibitors (ACEI)	Lisinopril	5 mg	12 sr	26 sr
		10mg	40 sr	20 sr
		20 mg	15 sr	65 sr
	Captopril	mg/ml	140 sr	165 sr
		25 mg	15 sr	20 sr
		50 mg	25 sr	35 sr
	Enalapril	5mg	12 sr	26 sr
		10 mg	20 sr	44 sr
		20mg	14 sr	60 sr
	Fosinopril	10 mg	42 sr	52 sr
		20 mg	78 sr	
	Perindopril	5 mg	34 sr	
		10 mg	45 sr	
Angiotensin Receptor Blocker (ARB)	Azilsartan	40 mg	65 sr	
		80 mg	100 sr	
	Candesartan	8 mg	23 sr	50 sr
		16 mg	55 sr	
		32 mg	77 sr	
	Losartan	50 mg	42 sr	55 sr
		100 mg	80 sr	98 sr
	Olmesartan	20 mg	37 sr	71 sr
		40 mg	50 sr	70 sr
	Valsartan	80, 160, 320 mg	35 sr	
	Telmisartan	40, 80 mg	50 sr	
	Irbesartan	150, 300 mg	45 sr	60 sr
	Eprosartan	600 mg	100 sr	

A guideline described the following regarding the resource use and costs of blood pressure treatment in patients with CKD:

When treating patients with CKD (G1–G4, A2) where the indication for ACEi or ARB therapy is not strong, consideration should be given to the clinical impact on the patient and the costs of starting RASi, including additional clinic visits and the need for additional lab testing (3).

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

Judgment	Research evidence	Additional considerations

○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify direct evidence to address the certainty of the evidence of resource requirements.	

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgment	Research evidence	Additional considerations
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Following the assessment of the existing evidence base for the cost-effectiveness of antihypertensive agents used in adults with CKD, the use of RASi medications is associated with lower costs. However, in advanced stages of CKD (G1-G4 with A3), the use of RASi warrants: adequate patient education and training especially on temporarily discontinuing and subsequently restarting RASi medications, awareness to avoid and lower hyperkalemia and AKI, regular lab investigations, and repeated visits and check-ups. The evidence suggests that the costs incurred for regular check-ups and visits to monitor patients counterbalance the benefits of RASi medications in retarding renal decline (5).	

Equity
What would be the impact on health equity?

Judgment	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify evidence to address equity for this specific question.	The judgment of probably no impact was related to a system of full healthcare coverage in Saudi Arabia.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgment	Research evidence	Additional considerations

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address acceptability for this specific question.	

Feasibility Is the intervention feasible to implement?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question.	

Summary of judgments

	JUDGMENT						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know

	JUDGMENT						
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

Conclusions

Recommendation

In adults with CKD, the CKD Task Force suggests using RASi over non-RASi for hypertension treatment (conditional recommendation, low certainty in the evidence of effects). This recommendation applies to all adults with CKD stages 1-3 and to those with advanced CKD (stages 4-5) who are not receiving KRT.

Justification

The panel judged that the balance of desirable and undesirable consequences does not favor the use of non-RAS inhibition over RASi in this population. Specifically, the panel felt that most patients will get benefit due to a balance that probably favors RASi in the context of low certainty evidence, and cost-effectiveness that probably favors RASi.

Subgroup considerations

The panel suggests that potassium levels should be assessed regularly (initially 4-7 days after initiation, then at each CKD clinic visit) in adult patients with CKD who receive RASi agents. Based on expert experience the panel identified adults with advanced CKD who are not on KRT as a subpopulation of people who might be affected differently than most by this recommendation. The panel judged that for this population this recommendation does not apply.

Implementation considerations

No implementation considerations were made for this recommendation because there was no research evidence identified.

Monitoring and evaluation

The guideline panel suggested including non-randomized studies as part of the body of evidence for future guideline updates.

Research priorities

The guideline panel identified research needs in conducting randomized controlled trials that compare calcium channel blockers vs RASi agents. Also, since there is insufficient evidence on the role of diuretics as first line therapy for the treatment of high blood pressure in patients with CKD, the panel proposes that researchers perform more studies to clarify the role of diuretics as initial therapy in this population.

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Appendix 1 - Summary of findings

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	**Anticipated absolute effects* (95% CI)**	
				Risk with RASi	**Risk difference with non-RAS inhibition**
All-cause mortality **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported	-	-	-	-	-
Cardiovascular mortality **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported	200 (1 RCT)[1]	⨁⨁◯◯ Low[a]	**RR 0.67** (0.11 to 3.90)	Study population	
				30 per 1,000	**10 fewer per 1,000** (27 fewer to 87 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with RASi	**Risk difference with non-RAS inhibition**
Cardiovascular morbidity **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported	200 (1 RCT)[1]	⨁⨁◯◯ Low[a]	**RR 0.59** (0.28 to 1.22)	Study population	
				170 per 1,000	**70 fewer per 1,000** (122 fewer to 37 more)
Kidney failure **[Non RASi (Beta Blockers) versus RAS inhibition]	100 (1 RCT)[2]	⨁⨁◯◯ Low[b,c]	**RR 1.84** (0.94 to 3.62)	Study population	
				192 per 1,000	**162 more per 1,000** (12 fewer to 504 more)
Doubling serum creatinine **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported	-	-	-	-	-
Acute kidney injury **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported	-	-	-	-	-
Diastolic blood pressure **[Non RASi (Beta Blockers) versus RAS inhibition]	161 (2 RCTs)[2,3]	⨁⨁◯◯ Low[d,e]	-	The mean diastolic blood pressure **[Non RASi (Beta Blockers) versus RAS inhibition] was **0**	MD **1.93 higher** (1.32 higher to 2.53 higher)
Systolic blood pressure **[Non RASi (Beta Blockers) versus RAS inhibition]	161 (2 RCTs)[2,3]	⨁⨁◯◯ Low[b,d,e]	-	The mean systolic blood pressure **[Non RASi (Beta Blockers) versus RAS inhibition] was **0**	MD **2.12 higher** (6.7 lower to 10.94 higher)
eGFR change from baseline **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported	-	-	-	-	-
Proteinuria (n/N) **[Non RASi (Beta Blockers) versus RAS inhibition]	130 (2 RCTs)[2,3]	⨁⨁◯◯ Low[b,d]	**RR 1.27** (0.31 to 5.19)	Study population	
				239 per 1,000	**64 more per 1,000** (165 fewer to 1,001 more)
Encephalopathy **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported	-	-	-	-	-
Left ventricular hypertrophy **[Non RASi (Beta Blockers) versus RAS inhibition] - not reported	-	-	-	-	-

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with RASi	**Risk difference with non-RAS inhibition**
Hyperkalemia/ plasma potassium concentration (mmol/L) **[Non RASi (Beta Blockers) versus RAS inhibition]	300 (2 RCTs)[1,2]	⨁⨁◯◯ Low[d,e]	**OR 0.26** (0.08 to 0.89)	Study population	
				79 per 1,000	**57 fewer per 1,000** (72 fewer to 8 fewer)
All-cause mortality *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported	-	-	-	-	-
Cardiovascular mortality *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition]	2720 (1 RCT)[4]	⨁⨁◯◯ Low[b,c]	**RR 1.05** (0.81 to 1.38)	Study population	
				72 per 1,000	**4 more per 1,000** (14 fewer to 27 more)
Cardiovascular morbidity *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] assessed with: Stroke	2720 (1 RCT)[4]	⨁⨁◯◯ Low[b,c]	**RR 0.93** (0.61 to 1.42)	Study population	
				32 per 1,000	**2 fewer per 1,000** (12 fewer to 13 more)
Kidney failure *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] (assessed with: Stroke - not reported	-	-	-	-	-
Doubling serum creatinine *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported	-	-	-	-	-
Acute kidney injury *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported	-	-	-	-	-
Systolic blood pressure *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition]	251 (3 RCTs)[3,5,6]	⨁⨁◯◯ Low[b,f]	-	The mean systolic blood pressure *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] was **0**	MD **0.32 higher** (5.34 lower to 5.97 higher)
Diastolic blood pressure *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition]	251 (3 RCTs)[3,5,6]	⨁⨁◯◯ Low[b,f]	-	The mean diastolic blood pressure *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] was **0**	MD **1.33 lower** (4.51 lower to 1.85 higher)
eGFR change from baseline *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition]	21 (1 RCT)[7]	⨁⨁◯◯ Low[g,h]	-	The mean eGFR change from baseline *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] was **0**	MD **0.02 higher** (0.33 lower to 0.37 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with RASi	**Risk difference with non-RAS inhibition**
Proteinuria (g/g creatinine) *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition]	21 (1 RCT)[7]	⨁⨁◯◯ Low[g,h]	-	The mean proteinuria (g/g creatinine) *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] was **0**	MD **0.08 higher** (1.42 lower to 1.58 higher)
Proteinuria (g/24h) *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition]	30 (1 RCT)[3]	⨁⨁◯◯ Low[i]	**OR 4.33** (0.71 to 26.53)	Study population	
				133 per 1,000	**266 more per 1,000** (35 fewer to 670 more)
Left ventricular hypertrophy *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported	-	-	-	-	-
Encephalopathy *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported	-	-	-	-	-
Hyperkalemia/ plasma potassium concentration (mmol/L) *****[Non RASi (Calcium Channel Blockers) versus RAS inhibition] - not reported	-	-	-	-	-
All-cause mortality ******(Non RASi versus RASi - Ramipril -) - not reported	-	-	-	-	-
Cardiovascular mortality ******(Non RASi versus RASi - Ramipril -)	269 (1 RCT)[8]	⨁⨁◯◯ Low[b,c]	**RR 1.97** (0.98 to 3.96)	Study population	
				79 per 1,000	**76 more per 1,000** (2 fewer to 233 more)
Cardiovascular morbidity ******(Non RASi versus RASi - Ramipril -) assessed with: Stroke	269 (1 RCT)[8]	⨁⨁◯◯ Low[b,c]	**RR 0.54** (0.10 to 2.91)	Study population	
				29 per 1,000	**13 fewer per 1,000** (26 fewer to 55 more)
Kidney failure ******(Non RASi versus RASi - Ramipril -) - not reported	-	-	-	-	-
Doubling serum creatinine ******(Non RASi versus RASi - Ramipril -) - not reported	-	-	-	-	-

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with RASi	**Risk difference with non-RAS inhibition**
Systolic blood pressure ******(Non RASi versus RASi - Ramipril -) - not reported	-	-	-	-	-
Diastolic blood pressure ******(Non RASi versus RASi - Ramipril -) - not reported	-	-	-	-	-
eGFR change from baseline ******(Non RASi versus RASi - Ramipril -) - not reported	-	-	-	-	-
Proteinuria ******(Non RASi versus RASi - Ramipril -) - not reported	-	-	-	-	-
Left ventricular hypertrophy ******(Non RASi versus RASi - Ramipril -) - not reported	-	-	-	-	-
Encephalopathy ******(Non RASi versus RASi - Ramipril -) - not reported	-	-	-	-	-
Hyperkalemia/ plasma potassium concentration (mmol/L) ******(Non RASi versus RASi - Ramipril -)	269 (1 RCT)[8]	⨁⨁◯◯ Low[b,c]	**OR 1.10** (0.54 to 2.22)	Study population	
				129 per 1,000	**11 more per 1,000** (55 fewer to 118 more)

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Explanations

a. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 3 events in total. We, therefore, downgraded by two levels.
b. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.
c. Study that carried all weight for the overall effect estimate rated as high risk of bias due to lack of blinding.
d. Studies that carried a large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 1 out of 2 studies.
e. Serious imprecision. Two studies with small sample size did not meet OIS criteria.
f. Studies that carried a large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 1 out of 3 studies.
g. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference. We, therefore, downgraded by two levels.
h. Study that carried all weight for the overall effect estimate did not report the randomization process nor blinding.
i. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 8 events in total. We, therefore, downgraded by two levels.

Question 3. Should intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets versus standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets be used for hypertension treatment in children with CKD?

Population:	hypertension treatment in children with CKD
Intervention:	intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets
Comparison:	to standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets
Main outcomes:	All-cause mortality; Cardiovascular mortality; Cardiovascular morbidity ; Kidney Failure (or end-stage kidney disease); Doubling serum creatinine; Acute kidney injury; Systolic blood pressure; Diastolic blood pressure; Estimated glomerular filtration rate; Proteinuria; Left ventricular hypertrophy;
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (1)
Conflict of interests:	**KSA conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dhalbi Muneera Rashid Al-Jelaify Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari Ahmed Mitwalli Sumayah Askandarani **Panel members recused as a result of risk of conflicts of interest:**

	None

Assessment

Problem Is the problem a priority?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	• The prevalence of CKD in Saudi Arabia is not known. Reports indicate that mortality among children who progress to end-stage renal disease (ESRD) is 30 to 50 times higher compared to that in the general population (2, 3). • The main causes of CKD in this population of patients were congenital abnormalities of the renal system, in 50% of patients, followed by neurogenic bladder in almost 20% of the children, acquired causes (14%), and hereditary conditions (12%) (4). • There is a considerable delay in referring children CKD to a pediatric nephrologist as well as in the management of preventable causes such as neurogenic bladder associated with spina bifida (4).	
Desirable Effects **How substantial are the desirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1*	The panel noted that there is insufficient evidence about the effects of intensive lowering blood target compared to higher blood pressure target in children with CKD. The study identified included a small sample size so may not have been adequately powered at certain outcomes. Therefore, when making the judgments, the panel considered small desirable effects.
Undesirable Effects **How substantial are the undesirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	*See Appendix 1*	

Certainty of evidence
What is the overall certainty of the evidence of effects?

Judgment	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty in the evidence is reduced as a result of imprecision and risk of bias for the assessment of outcomes of one study.	Based on the lowest certainty of the critical outcomes.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgment	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not identify primary studies addressing the relative importance of the outcomes for this specific question. **A guideline described the following regarding the relative importance of outcomes and patients' preferences for lower and higher pressure targets** (5) The Work Group judged that the prevention of kidney failure and progressive kidney function loss would be of high value to nearly all well-informed patients or caregivers. Published patient-reported outcome data from the SONG–Kids study reported that children with kidney disease and caregivers rated kidney function as an important outcome, whereas blood pressure (BP) control was also rated as an important outcome by caregivers (6). In the judgment of the Work Group, most patients would value these clinical benefits despite the inconvenience and potential risk of harms associated with aggressive BP management (e.g., multiple medications, more frequent dosing, possible adverse events if dehydrated, and the burden of monitoring with 24-hour ambulatory BP monitoring (ABPM). Patients for whom medication burden or the burden of ABPM monitoring are particularly important concerns may be more inclined not to follow this recommendation.	In the absence of direct evidence, the panel discussed the relative importance of the outcomes from the patient perspective, based on their clinical expertise.

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel judged the balance as probably favoring the intervention because of uncertainty about the effects.

Resources required How large are the resource requirements (costs)?		
Judgment	**Research evidence**	**Additional considerations**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost per package size of antihypertensive treatment drugs (angiotensin-converting enzyme inhibitors [ACEi] and angiotensin receptor blockers) is from 2.20 USD to 44 USD in patients with CKD. **A guideline described the following regarding the resource use and costs of blood pressure treatment in children** (5) In the judgment of the Work Group, the potential benefits associated with ambulatory blood pressure monitoring (ABPM) outweigh the costs and inconvenience associated with its implementation. Patients and families in areas where ABPM is unavailable or less affordable will be less inclined to follow this recommendation and may choose to use clinic-based auscultatory blood pressure monitoring instead.	The panel noted that CKD treatment decreases the progression of CKD.

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
Judgment	**Research evidence**	**Additional considerations**

○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify direct evidence to address the certainty of the evidence of resource requirements.	

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgment	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Following the assessment of the existing evidence base for the cost-effectiveness of a higher blood pressure target for the progression of renal disease in children with chronic kidney disease who receive a fixed high dose of an angiotensin-converting enzyme (ACE) inhibitor, no existing studies were identified comparing lower blood pressure target versus higher blood pressure target. No firm conclusions can be drawn on the cost-effectiveness of a higher blood pressure target for the progression of renal disease in children. However, we identified indirect evidence that suggests for other populations that an intensive blood pressure target compared with a conventional blood pressure target is cost-effective (7)	The panel noted that there was uncertainty in the evidence due to insufficient evidence for outcome measurements and assessments. The judgment was therefore made on the basis of the panel's clinical experience and expertise to probably favor the intervention.

Equity
What would be the impact on health equity?

Judgment	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify evidence to address equity for this specific question.	The judgment of probably no impact was related to a system of full healthcare coverage in Saudi Arabia.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgment	Research evidence	Additional considerations

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address acceptability for this specific question. However, a treatment study suggests that lower and higher pressure targets are usually acceptable to patients and health care providers (8). A randomized controlled trial that included 385 children with chronic kidney disease showed that intensified blood-pressure control delays the progression of renal disease in children with chronic kidney disease who receive a fixed high dose of an angiotensin-converting enzyme (ACE) inhibitor. Despite the relatively modest additional reduction in blood pressure achieved with intensified antihypertensive treatment, the progression of renal disease was significantly delayed with the intensified-intervention protocol.	The panel agreed that a lower blood pressure target in children with CKD is acceptable to implement in Saudi Arabia's healthcare system.

Feasibility Is the intervention feasible to implement?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question. Research and clinical practice showed that the implementation of ambulatory blood pressure monitoring (ABPM) for monitoring the treatment of hypertension is challenging (9). For instance, blood pressure (BP) monitors are not always available when needed; they require time from a parent or other adult to return the monitor to the clinic and are expensive. With this in mind, there are certain situations in which there is a low probability of finding elevated BP by ABPM.	

Summary of judgments

	JUDGMENT						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies

	JUDGMENT						
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

In children with CKD, the CKD Task Force suggests using intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets rather than standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets for hypertension treatment (conditional recommendation, low certainty in the evidence of effects).

Justification

The panel judged that the balance of desirable and undesirable consequences favors the use of intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets over standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets in this population. Specifically, the panel felt that most patients will get benefit due to a balance that proabaly favors intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets in the context of low certainty evidence, moderate savings, and cost-effectiveness that probably favours intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets.

Subgroup considerations

No subgroup considerations were made for this recommendation.

Implementation considerations

No implementation considerations were made for this recommendation because there was no research evidence identified.

Monitoring and evaluation

No monitoring and evaluation considerations were made for this recommendation.

Research priorities

- The guideline panel considers there is a need for developing and conducting new RCTs to justify blood pressure targets, and that also includes assessment of outcomes that do not yet provide evidence and to make the data available to other countries.
- To set up a National Research Center that collects all the research done in Saudi Arabia and to encourage independent research centers of each university to exchange information and prevent wastage of research and duplication of efforts.

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Appendix 1 - Summary of findings

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	**Anticipated absolute effects* (95% CI)**	
				Risk with to standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets	**Risk difference with intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets**
All-cause mortality follow-up: 5 years	384 (1 RCT)[1]	⨁⨁◯◯ Low[a,b]	**RR 0.34** (0.01 to 8.39)	Study population	
				5 per 1,000	**3 fewer per 1,000** (5 fewer to 38 more)
				High	
				334 per 1,000[c]	**220 fewer per 1,000** (331 fewer to 2,468 more)
Cardiovascular mortality - not reported	-	-	-	-	-
Cardiovascular morbidity - not reported	-	-	-	-	-
Kidney Failure (or end-stage kidney disease) follow-up: 5 years	385 (1 RCT)[1]	⨁⨁◯◯ Low[b,d]	**RR 0.67** (0.41 to 1.10)	Study population	
				173 per 1,000	**57 fewer per 1,000** (102 fewer to 17 more)
				High	
				334 per 1,000[c]	**110 fewer per 1,000** (197 fewer to 33 more)
Doubling serum creatinine - not reported	-	-	-	-	-

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with to standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets	**Risk difference with intensive (targeting 24-hour MAP <50th percentile of normal children) blood pressure targets**
Acute kidney injury - not reported	-	-	-	-	-
Systolic blood pressure	372 (1 RCT)[1]	⨁⨁◯◯ Low[b,e]	-	The mean systolic blood pressure was **0**	MD **2 lower** (4.97 lower to 0.97 higher)
Diastolic blood pressure	372 (1 RCT)[1]	⨁⨁◯◯ Low[b,e]	-	The mean diastolic blood pressure was **0**	MD **1 lower** (3.7 lower to 1.7 higher)
Estimated glomerular filtration rate	385 (1 RCT)[1]	⨁⨁◯◯ Low[b,e]	-	The mean estimated glomerular filtration rate was **0**	MD **1.4 lower** (2.79 lower to 0.01 lower)
Proteinuria - not reported	-	-	-	-	-
Left ventricular hypertrophy - not reported	-	-	-	-	-

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Explanations

a. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 1 event in total. We, therefore, downgraded by two levels.

b. One study that carried the overall effect estimate rated as high risk of bias due to lack of blinding of participants and personnel, and lack of blinding of outcome assessors.

c. Cross-sectional survey was performed during the period from March 2012 to October 2013 covering 13 towns around Hail city. Prevalence of concomitant hypertension in general population with CKD 33.4%.

d. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including 56 event in total.

e. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm.

Question 4. Should intensive (SBP <120 mm Hg) blood pressure targets compared to standard (SBP <140mm Hg) blood pressure targets be used for hypertension treatment in adults with CKD?

Population:	Patients with CKD
Intervention:	intensive (SBP <120 mm Hg) blood pressure targets
Comparison:	standard (SBP <140mm Hg) blood pressure target
Main outcomes:	All-cause mortality; Composite Outcome; Cardiovascular mortality; Cardiovascular events; Stroke; Acute MI; Kidney failure (ESRD); Systolic blood pressure (mm Hg): Mean(SD); Diastolic blood pressure (mm Hg): Mean(SD); eGFR change from baseline; eGFR <=50% (n/N); Serum potassium >5.5 mmol/L (n/N)
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (Gadelkarim AH, 2019).
Conflict of interests:	**ASH conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dhalbi Muneera Rashid Al-Jelaify Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari Ahmed Mitwalli **Panel members recused as a result of risk of conflicts of interest:** None

Assessment

Problem Is the problem a priority?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	• In a community-based screening program in commercial centers in Riyadh, including a sample of 491 volunteers, the overall CKD all-stage prevalence was 5.7%. The prevalence of CKD stages 1, 2 and 3 was 3.5%, 1.6% and 0.6%, respectively (1). • Results from a cross-sectional, community-based study involving 13 cities and 2800 volunteers from around the city of Hail, the estimated overall prevalence of CKD was 7.8% (2). • Hypertension is a known risk factor for and complication of CKD. In surveys in Saudi Arabia, the overall prevalence of hypertension was about 33.4% of adults (2).	
Desirable Effects How substantial are the desirable anticipated effects?		
Judgment	**Research evidence**	**Additional considerations**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1*	The panel noted that it may be difficult to carry out RCTs to find further evidence because of the ethical consideration of antihypertensive therapy vs. placebo.
Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgment	**Research evidence**	**Additional considerations**
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	*See Appendix 1*	
Certainty of evidence What is the overall certainty of the evidence of effects?		

Judgment	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty in the evidence is reduced as a result of imprecision and risk of bias for the assessment of outcomes.	Based on the lowest certainty of the critical outcomes.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgment	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not identify primary studies addressing the relative importance of the outcomes for this specific question. **A guideline described the following regarding the relative importance of outcomes and patients' preferences for antihypertensive agents in adults with CKD:** The presence of severely increased albuminuria and CKD is associated with a higher prevalence of cardiovascular (CV) disease, progressive CKD, and attendant loss of quality of life. In the opinion of the Work Group, most well-informed patients with CKD and severely increased albuminuria would place emphasis on preventing CV outcomes in addition to preventing CKD progression. They also think that many well-informed patients would place more emphasis on the potential for preventing CKD progression (3).	The panel considered that patients with CKD place a high value on the mortality outcome.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel judged the balance as probably favoring the intervention because of uncertainty about the effects.
Resources required How large are the resource requirements (costs)?		

Judgment	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost per package size of antihypertensive treatment drugs (angiotensin-converting enzyme inhibitors [ACEi] and angiotensin receptor blockers) is from 12 SAR to 165 SAR (3.20 USD to 44 USD) in patients with CKD (4). **A guideline described the following regarding the resource use and costs of blood pressure treatment in patients with CKD:** When treating patients with CKD (G1–G4, A2) where the indication for ACEi or ARB therapy is not strong, consideration should be given to the clinical impact on the patient and the costs of starting renin-angiotensin system inhibitors (RASi), including additional clinic visits and the need for additional lab testing (3).	

Class	Drug	Strength	Cost per pckage size	
			Lowest price	Highest price
Angiotensin Converting Enzyme Inhibitors (ACEI)	Lisinopril	5 mg	12 sr	26 sr
		10mg	40 sr	20 sr
		20 mg	15 sr	65 sr
	Captopril	mg/ml	140 sr	165 sr
		25 mg	15 sr	20 sr
		50 mg	25 sr	35 sr
	Enalapril	5mg	12 sr	26 sr
		10 mg	20 sr	44 sr
		20mg	14 sr	60 sr
	Fosinopril	10 mg	42 sr	52 sr
		20 mg	78 sr	
	Perindopril	5 mg	34 sr	
		10 mg	45 sr	
Angiotensin Receptor Blocker (ARB)	Azilsartan	40 mg	65 sr	
		80 mg	100 sr	
	Candesartan	8 mg	23 sr	50 sr
		16 mg	55 sr	
		32 mg	77 sr	
	Losartan	50 mg	42 sr	55 sr
		100 mg	80 sr	98 sr
	Olmesartan	20 mg	37 sr	71 sr
		40 mg	50 sr	70 sr
	Valsartan	80, 160, 320 mg	35 sr	
	Telmisartan	40, 80 mg	50 sr	
	Irbesartan	150, 300 mg	45 sr	60 sr
	Eprosartan	600 mg	100 sr	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?		
Judgment	**Research evidence**	**Additional considerations**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify direct evidence to address the certainty of the evidence of resource requirements.	
Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Following the assessment of the existing evidence base for the cost-effectiveness of antihypertensive agents used in adults with CKD, the use of renin-angiotensin system inhibitor (RASi) medications is associated with lower costs. However, in advanced stages of CKD (G1-G4 with A3), the use of RASi warrants: adequate patient education and training especially on temporarily discontinuing and subsequently restarting RASi medications, awareness to avoid and lower hyperkalemia and acute kidney injury (AKI), regular lab investigations, and repeated visits and check-ups. The evidence suggests that the costs incurred for regular check-ups and visits to monitor patients counterbalance the benefits of RASi medications in retarding renal decline (5).	
Equity **What would be the impact on health equity?**		
Judgment	**Research evidence**	**Additional considerations**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify evidence to address equity for this specific question.	The judgment of probably no impact was related to a system of full healthcare coverage in Saudi Arabia.
Acceptability **Is the intervention acceptable to key stakeholders?**		
Judgment	**Research evidence**	**Additional considerations**

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address acceptability for this specific question.	The panel agreed that there was acceptability in the healthcare system in Saudi Arabia to implement the intervention in patients with CKD.

Feasibility Is the intervention feasible to implement?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question.	

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know

	Judgment						
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

In adults with CKD, the CKD Task Force suggests using intensive (SBP <120 mm Hg) blood pressure targets rather than standard (SBP <140mm Hg) blood pressure targets for hypertension treatment (conditional recommendation, low certainty in the evidence of effects).

Justification

The panel judged that the balance of desirable and undesirable consequences favors the use of intensive (SBP <120 mm Hg) blood pressure targets over standard (targeting 24-hour MAP 50th-99th percentile of normal children) blood pressure targets in this population. Specifically, the panel felt that most patients will get benefit due to a balance that proabaly favors intensive (SBP <120 mm Hg) blood pressure targets in the context of low certainty evidence, moderate savings, and cost-effectiveness that probably favours intensive (SBP <120 mm Hg) blood pressure targets.

Subgroup considerations

No subgroup considerations were made for this recommendation.

Implementation considerations

No implementation considerations were made for this recommendation because there was no research evidence identified.

Monitoring and evaluation

No monitoring and evaluation considerations were made for this recommendation.

Research priorities

There were no future research needs prioritized by the panel.

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Appendix 1 – Summary of findings

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard (SBP <140mm Hg) blood pressure target	**Risk difference with intensive (SBP <120 mm Hg) blood pressure targets**
All-cause mortality	12662 (6 RCTs)[1,2,3,4,5,6]	⨁⨁⨁◯ Moderate[a]	**RR 0.85** (0.76 to 0.96)	Study population	
				112 per 1,000	**17 fewer per 1,000** (27 fewer to 4 fewer)
				High	
				358 per 1,000[7,b]	**54 fewer per 1,000** (86 fewer to 14 fewer)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard (SBP <140mm Hg) blood pressure target	Risk difference with intensive (SBP <120 mm Hg) blood pressure targets
Cardiovascular mortality	4075 (3 RCTs)[3,6,8]	⨁⨁◯◯ Low[c,d]	**RR 0.96** (0.44 to 2.08)	Study population	
				27 per 1,000	**1 fewer per 1,000** (15 fewer to 29 more)
				High	
				358 per 1,000[7,b]	**14 fewer per 1,000** (200 fewer to 387 more)
Cardiovascular morbidity	10106 (4 RCTs)[3,4,5,8]	⨁⨁◯◯ Low[e,f]	**RR 0.89** (0.73 to 1.09)	Study population	
				232 per 1,000	**26 fewer per 1,000** (63 fewer to 21 more)
				High	
				358 per 1,000[7,b]	**39 fewer per 1,000** (97 fewer to 32 more)
Kidney failure (formerly known as ESKD)	3821 (3 RCTs)[3,6,9]	⨁⨁⨁◯ Moderate[d]	**RR 0.90** (0.82 to 0.99)	Study population	
				178 per 1,000	**18 fewer per 1,000** (32 fewer to 2 fewer)
Doubling serum creatinine - not reported	-	-	-	-	-
Acute kidney injury - not reported	-	-	-	-	-
Systolic blood pressure (mm Hg): Mean(SD)	3821 (3 RCTs)[3,6,9]	⨁⨁⨁◯ Moderate[d]	-	The mean systolic blood pressure (mm Hg): Mean(SD) was **0**	MD **8.12 lower** (13.13 lower to 3.1 lower)
Diastolic blood pressure (mm Hg): Mean(SD)	3821 (3 RCTs)[3,6,9]	⨁⨁⨁◯ Moderate[d]	-	The mean diastolic blood pressure (mm Hg): Mean(SD) was **0**	MD **4.3 lower** (6.46 lower to 2.15 lower)
eGFR change from baseline	840 (1 RCT)[10]	⨁⨁◯◯ Low[e,g]	-	The mean eGFR change from baseline was **0**	MD **1.6 higher** (0.72 lower to 3.92 higher)
Left ventricular hypertrophy - not reported	-	-	-	-	-

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard (SBP <140mm Hg) blood pressure target	Risk difference with intensive (SBP <120 mm Hg) blood pressure targets
Encephalopathy - not reported	-	-	-	-	-
Hyperkalemia assessed with: >5.5 mmol/L (n/N)	2646 (1 RCT)[3]	⨁⨁◯◯ Low[g]	**RR 1.34** (1.01 to 1.78)	Study population	
				59 per 1,000	**20 more per 1,000** (1 more to 46 more)

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Explanations

a. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 6 studies and lack of blinding in 3 out of 6 studies.
b. Based on a national survey of representative sample of noninstitutionalized adults in the USA, it is estimated that hypertension occurs in 23.3% of individuals without CKD, and 35.8% of stage 1, 48.1% of stage 2, 59.9% of stage 3, and 84.1% of stage 4-5 CKD patients. Prevalence of hypertension also varies with the cause of CKD; strong association with hypertension was reported in patients with renal artery stenosis (93%), diabetic nephropathy (87%), and polycystic kidney disease (74%).
c. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including 109 events in total.
d. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 3 studies and lack of blinding in 2 out of 3 studies.
e. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.

f. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 2 out of 4 studies.
g. One study that carried all weight for the overall effect estimate rated as high risk of bias due to lack of lack of blinding.

Question 5. Should early assessment (i.e., eGFR 20 mL/min/1.73m2) versus late assessment (i.e., eGFR <20 mL/min/1.73m2) be used for KRT in patients with CKD?

Population:	patients requiring RRT for deteriorating CKD
Intervention:	early assessment (i.e., eGFR 20 mL/min/1.73m2)
Comparison:	late assessment (i.e., eGFR <20 mL/min/1.73m2)
Main outcomes:	All cause mortality; All cause mortality; Patient, family/caregiver health related quality of life; Impact late referral rates; Pre-emptive transplantation rates; Proportion patients receiving renal replacement therapy after assessment; Symptom scores ; Cognitive impairment; Growth ; Malignancy; Adverse events.
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (1).
Conflict of interests:	**KSA conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dhalbi Muneera Rashid Al-Jelaify Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari Ahmed Mitwalli Sumayah Askandarani

Panel members recused as a result of risk of conflicts of interest:

None

Assessment

Problem **Is the problem a priority?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	• The global burden of CKD remains a major public health problem as the worldwide prevalence is currently estimated at 7.2% to 13.4% (2). • Early identification of CKD by screening for kidney disease, followed by risk stratification and treatment, offers the potential to substantially reduce the morbidity and mortality from CKD and its related complications, such as cardiovascular disease (3). • Despite effective methods to diagnose and treat CKD at its earliest stages, there is a lack of consensus on whether health systems and governments should implement CKD screening programs (3). • In children with CKD, reports indicate that mortality among children who progress to end-stage renal disease (ESRD) is 30 to 50 times higher compared to that in the general population (4)(5). • The main causes of CKD in this population of patients were congenital abnormalities of the renal system, in 50% of patients, followed by neurogenic bladder in almost 20% of the children, acquired causes (14%), and hereditary conditions (12%) (6).	
Desirable Effects **How substantial are the desirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1*	The panel noted that a moderate effect of the intervention can be present considering their clinical expertise.

Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgment	**Research evidence**	**Additional considerations**
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	*See Appendix 1*	
Certainty of evidence **What is the overall certainty of the evidence of effects?**		
Judgment	**Research evidence**	**Additional considerations**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty in the evidence is reduced as a result of imprecision and risk of bias for the assessment of one outcome of one study.	Based on the lowest certainty of the critical outcomes.
Values **Is there important uncertainty about or variability in how much people value the main outcomes?**		
Judgment	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not identify primary studies addressing the relative importance of the outcomes for this specific question. **An international report described the following regarding the relative importance of outcomes and patients' preferences for the screening and diagnosis of CKD** Patient representatives and advocates described that there is a strong belief that patients overwhelmingly prefer earlier CKD screening and diagnosis and that patient education has the potential to improve self-management and disease prognosis (2). Individual and population-level risk of having CKD and experiencing its complications should inform whether persons should be screened for CKD. Decisions concerning the age to initiate	

	testing, the frequency of repeat testing, and the time to forgo or end testing should all be individualized based upon risk factors, preferences, and life expectancy (2). **One systematic review described the following regarding the relative importance of outcomes and patients' preferences for hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT):** Patients highly value the benefits of HD, PD, and KT (7). The utility values for HD ranged from 0.44 to 0.72; for PD from 0.53 to 0.81; for KT from 0.57 to 0.90. In seven of the nine studies, KT utility was higher than PD utility, and PD utility was higher than HD utility. In two of the nine studies, KT utility was higher than PD and HD utility, with PD and HD utility being equal. One study suggests that conflicting results of utility valuations existed among different valuation methods. For example, continuous ambulatory PD patients' Euro-QoL-5Dimension (EQ-5D) scores were higher than those of center HD patients, while continuous ambulatory PD patients' standard gamble (SG) and time tradeoff (TTO) scores were lower than those of center HD patients (7).	
Balance of effects **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel judged the balance as probably favoring the intervention because of uncertainty about the effects.
Resources required **How large are the resource requirements (costs)?**		
Judgment	**Research evidence**	**Additional considerations**

○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not identify primary studies addressing the resources required to manage CKD patients with renal replacement therapy. **Cost of disease** • Chronic kidney disease (CKD) affects about 10 percent of the population worldwide, including an estimated 1 in 7 adult Americans.1 In the United States, Medicare spending totals more than $64 billion each year to care for Americans with CKD and an additional $34 billion to care for patients with end-stage renal disease (ESRD) (Initiative, 2018). • The impact of kidney disease extends well beyond the United States; over 2 million people worldwide have ESRD. In higher-income countries, treatment costs are enormous: a 2010 report from the UK National Health Service estimates its annual CKD spending at £1.45 billion—more than half of which was for RRT (Jha V, 2013)—while Australia has estimated it will spend over $12 billion on ESRD patients through 2020 (Australia, 2020). At the same time, renal replacement therapy (RRT) remains entirely unaffordable to the majority of ESRD patients in low- and middle-income countries throughout the world, with over 1 million people dying annually from lack of treatment (Couser WG, 2011). **Cost of interventions** • Initial assessment clinic: annual cost per patient £2,537 (Saudi Riyals [SAR] 13,137), annual expenditure £6,421,018 (SAR 33,238,174). • The mean total cost per HD session was calculated as 297 US dollars (USD) (1,114 SAR), and the mean total cost of dialysis per patient per year was 46,332 USD (173,784 SAR) (8). • One study conducted in Saudi Arabia described that an average annual cost of medical care per patient after transplantation in the first, second, third, and fourth-year was US $133,291, US $14,233, US $5,536, and US $4,402; respectively. The average 4-year actual total cost per patient was US $210,779 and US $317,186.3 in the kidney transplant group and the HD group; respectively (p=0.017) (9). • One systematic review reported annual costs of HD and PD in low and middle-income countries. The annual cost per patient for hemodialysis (HD) ranged from Int$ 3,424 to Int$ 42,785, and peritoneal dialysis (PD) ranged from Int$ 7,974 to Int$ 47,971. Direct medical cost especially drugs and consumables for HD and dialysis solutions and tubing for PD were the main cost drivers (10).	The panel agreed that though early assessment decreases disease progression, it may result in an increase in costs considering clinical test and medical appointments.

Certainty of evidence of required resources **What is the certainty of the evidence of resource requirements (costs)?**		
Judgment	**Research evidence**	**Additional considerations**

○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify direct evidence to address the certainty of the evidence of resource requirements.	

Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**One systematic review directly addresses the cost-effectiveness of different renal replacement therapy (RRT)** (7)**.** Kidney transplant (KT) was the most cost-effective RRT modality and peritoneal dialysis (PD) was more cost-effective than hemodialysis (HD). Most studies suggested that KT held a dominant position over HD and PD with both lower costs and higher effectiveness. Five studies suggested that increased uptake of KT and PD by new end-stage renal disease (ESRD) patients would reduce costs and improve health outcomes or would be more cost-effective than current practice patterns.	Renal replacement therapy (RRT) was cost-effective, although no date was reported that compare early vs. late assessment.

Equity **What would be the impact on health equity?**		
Judgment	**Research evidence**	**Additional considerations**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify evidence to address equity for this specific question.	The panel judgment of probably no impact was related to a system of full healthcare coverage in Saudi Arabia.

Acceptability **Is the intervention acceptable to key stakeholders?**		
Judgment	**Research evidence**	**Additional considerations**

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address acceptability for this specific question. Indirect evidence (11) for the implementation of the multidisciplinary care (MDC) clinic for patients with advanced CKD suggested possible improvement in adherence to CKD intervention targets and good participants' acceptability of the MDC program. The program included clinical outcomes assessment, self-care advice, and kidney replacement therapy (KRT) options.	
Feasibility **Is the intervention feasible to implement?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question.	

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			

	Judgment						
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation
In patients with CKD, the CKD Task Force suggests using early assessment (i.e., eGFR 20 mL/min/1.73m2) for KRT rather than late assessment (i.e., eGFR <20 mL/min/1.73m2) for KRT (conditional recommendation, very low certainty in the evidence of effects).

Justification

The panel judged that the balance of desirable and undesirable consequences favors the use of early assessment (i.e., eGFR 20 mL/min/1.73m2) for KRT over late assessment (i.e., eGFR <20 mL/min/1.73m2) for KRT in this population. Specifically, the panel felt that most patients will get benefit due to a balance that proabaly favors early assessment (i.e., eGFR 20 mL/min/1.73m2) for KRT in the context of very low certainty evidence, moderate savings, and cost-effectiveness that probably favours early assessment (i.e., eGFR 20 mL/min/1.73m2) for KRT.

Subgroup considerations

No subgroup considerations were made for this recommendation.

Implementation considerations

The panel suggested using doubling serum creatinine as an indicator for early assessment of CKD, especially in the remote areas of the Kingdom, where hospital infrastructure and proper laboratory facilities may be limited, and the use of GFR may not be possible.

Monitoring and evaluation

No monitoring and evaluation considerations were made for this recommendation.

Research priorities

There were no future research needs prioritized by the panel.

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Appendix 1 - Summary of findings

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with late assessment (i.e., eGFR <20 mL/min/1.73m2)	Risk difference with early assessment (i.e., eGFR 20 mL/min/1.73m2)
Mortality follow-up: 90 days	3015 (1 observational study)[1]	⨁◯◯◯ Very low[a,b]	**RR 0.67** (0.60 to 0.76)	Study population	
				349 per 1,000	**115 fewer per 1,000** (140 fewer to 84 fewer)
				Low	
				103 per 1,000[2,c]	**34 fewer per 1,000** (41 fewer to 25 fewer)
Mortality follow-up: range 90 days to 1 years	2178 (1 observational study)[1]	⨁◯◯◯ Very low[a,b]	**RR 0.97** (0.84 to 1.13)	Study population	
				281 per 1,000	**8 fewer per 1,000** (45 fewer to 37 more)
				Low	
				103 per 1,000[2,c]	**3 fewer per 1,000** (16 fewer to 13 more)
Patient, family/caregiver health related quality of life - not reported	-	-	-	-	-
Impact late referral rates - not reported	-	-	-	-	-
Pre-emptive transplantation rates - not reported	-	-	-	-	-
Proportion patients receiving renal replacement therapy after assessment - not reported	-	-	-	-	-
Symptom scores - not reported	-	-	-	-	-
Cognitive impairment - not reported	-	-	-	-	-
Growth - not reported	-	-	-	-	-
Adverse events - not reported	-	-	-	-	-

References

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Explanations

a. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.
b. Study that carried all weight for the overall effect estimate rated as high risk of bias due to residual confounding arising from limited characterization of the severity of comorbid conditions. We, therefore, downgraded by two levels.
c. Mortality attributable to chronic kidney disease from a cohort study of 462 293 individuals aged older than 20 years in Taiwan.

Question 6. Should any late preparation strategy (based on eGFR or by anticipated time to start of KRT) versus any early preparation strategy (based on eGFR or by anticipated time to start of KRT) be used in patients with CKD stage 4 to 5 to prepare the patient for the start of KRT?*

Population:	patients with CKD stage 4 to 5 to prepare the patient for the start of KRT
Intervention:	any late preparation strategy (based on eGFR or by anticipated time to start of KRT)
Comparison:	any early preparation strategy (based on eGFR or by anticipated time to start of KRT)
Main outcomes:	Mortality (HD access, adults > 70 years) [fistula placement within 1 month before initiation vs 1-2 months before initiation]; Cognitive impairment; Growth; Impact late referral rates; Patient, family/caregiver health related QoL; Pre-emptive transplantation rates; Proportion receiving RRT after assessment; Symptom scores; Adverse events (HD access): AVF failure [time from creation to use <30 days vs >30 days]; Adverse events (PD access, 1 week vs 4 weeks from access creation use, adults 18 - 70 years): Modality failure; Adverse events (PD access, 1 week vs 4 weeks from access creation use, adults 18 - 70 years): Infections (PD related/tunnel/peritonitis); Adverse events (PD access, 1 week vs 4 weeks from access creation use, adults 18 - 70 years): Leak; Adverse events (PD access, 1 week vs 2 weeks from access creation use, adults 18 - 70 years): Modality failure ; Adverse events (PD access, 1 week vs 2 weeks from access creation use, adults 18 - 70 years): Infections (PD related/tunnel/peritonitis) ; Adverse events (PD access, 1 week vs 2 weeks from access creation use, adults 18 - 70 years): Leak ; Adverse events (PD access, 2 weeks vs 4 weeks from access creation use, adults 18 - 70 years): Modality failure; Adverse events (PD access, 2 weeks vs 4 weeks from access creation use, adults 18 - 70 years): Infections (PD related/tunnel/peritonitis) ; Adverse events (PD access, 2 weeks vs 4 weeks from access creation use, adults 18 - 70 years): Leak
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (1).
Conflict of interests:	**KSA conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dalbhi Muneera Rashid Al-Jelaify Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari Ahmed Mitwalli Mohammed Alghonaim **Panel members recused as a result of risk of conflicts of interest:** None.

Assessment

Problem **Is the problem a priority?**		
Judgment	**Research evidence**	**Additional considerations**
● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	• The global burden of CKD remains a major public health problem as the worldwide prevalence is currently estimated at 7.2% to 13.4% (KDIGO, 2021). Early identification of CKD by screening for kidney disease, followed by risk stratification and treatment, offers the potential to substantially reduce the morbidity and mortality from CKD and its related complications, such as cardiovascular disease (Shlipak MG et al., 2021). • Despite effective methods to diagnose and treat CKD at its earliest stages, there is a lack of consensus on whether health systems and governments should implement CKD screening programs (Shlipak MG et al., 2021). In children with CKD, reports indicate that mortality among children who progress to ESRD is 30 to 50 times higher compared to that in the general population (Mitsnefes et al., 2013)(Harambat et al., 2012). • The main causes of CKD in this population of patients were congenital abnormalities of the renal system, in 50% of patients, followed by neurogenic bladder in almost 20% of the children, acquired causes (14%), and hereditary conditions (12%) (Kari, 2006).	
Desirable Effects **How substantial are the desirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1*	
Undesirable Effects **How substantial are the undesirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**

○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	*See Appendix 1*	

Certainty of evidence
What is the overall certainty of the evidence of effects?

Judgment	Research evidence	Additional considerations
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty in the evidence is reduced as a result of risk of bias and imprecision for the assessment of outcomes. of three studies.	Based on the lowest certainty of the critical outcomes.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgment	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not identify primary studies addressing the relative importance of the outcomes for this specific question.**International report described the following regarding the relative importance of outcomes and patients' preferences for the screening and diagnosis of CKD**Patient representatives and advocates described that there is a strong belief that patients overwhelmingly prefer earlier CKD screening and diagnosis and that patient education has the potential to improve self-management and disease prognosis (2).Individual and population-level risk of having CKD and experiencing its complications should inform whether persons should be screened for CKD. Decisions concerning the age to initiate testing, the frequency of repeat testing, and the time to forgo or end testing should all be individualized based upon risk factors, preferences, and life expectancy (2).**One systematic review described the following regarding the relative importance of outcomes and patients' preferences for hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT)**:Patients highly value the benefits of HD, PD, and KT (3). The utility values for HD ranged from 0.44 to 0.72; for PD from 0.53 to 0.81; for KT from 0.57 to 0.90.In seven of the nine studies, KT utility was higher than PD utility, and PD utility was higher than HD utility. In two of the nine studies, KT utility was higher than PD and HD utility, with PD and HD utility being equal. One study suggests that conflicting results of utility valuations existed among different valuation methods. For example, continuous ambulatory PD patients' EQ-5D scores were higher than those of center HD	

	patients, while continuous ambulatory PD patients' SG and TTO scores were lower than those of center HD patients (3).	
Balance of effects **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**
● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel noted that the balance of effects between early vs late preparation favors the early preparation of RRT.
Resources required **How large are the resource requirements (costs)?**		
Judgment	**Research evidence**	**Additional considerations**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not identify primary studies addressing the resources required to manage chronic kidney disease patients with renal replacement therapy. **Cost of disease** • Chronic kidney disease (CKD) affects about 10 percent of the population worldwide, including an estimated 1 in 7 adult Americans.1 In the United States, Medicare spending totals more than $64 billion each year to care for Americans with CKD and an additional $34 billion to care for patients with end-stage renal disease (ESRD) (Initiative, 2018). • The impact of kidney disease extends well beyond the United States; over 2 million people worldwide have ESRD. In higher-income countries, treatment costs are enormous: a 2010 report from the UK National Health Service estimates its annual CKD spending at £1.45 billion—more than half of which was for RRT (Jha V, 2013)—while Australia has estimated it will spend over $12 billion on ESRD patients through 2020 (Australia, 2020). At the same time, RRT remains entirely unaffordable to the majority of ESRD patients in low- and middle-income countries	

	throughout the world, with over 1 million people dying annually from lack of treatment (Couser WG, 2011). **Cost of interventions** • Initial assessment clinic: annual cost per patient £2,537 (SAR 13,137), annual expenditure £6,421,018 (SAR 33,238,174). • The mean total cost per HD session was calculated as 297 US dollars (USD) [1,114 Saudi Riyals (SR)], and the mean total cost of dialysis per patient per year was 46,332 USD (173,784 SR) (Al Saran K, 2012). • One study conducted in Saudi Arabia described that an average annual cost of medical care per patient after transplantation in the first, second, third, and fourth-year was US $133,291, US $14,233, US $5,536, and US $4,402; respectively. The average 4-year actual total cost per patient was US $210,779 and US $317,186.3 in the kidney transplant group and the HD group; respectively (p=0.017) (Al-Jedai A, 2012). • One systematic review reported annual costs of HD and PD in low and middle-income countries. The annual cost per patient for hemodialysis (HD) ranged from Int$ 3,424 to Int$ 42,785, and peritoneal dialysis (PD) ranged from Int$ 7,974 to Int$ 47,971. Direct medical cost especially drugs and consumables for HD and dialysis solutions and tubing for PD were the main cost drivers (Mushi L, 2015).	
Certainty of evidence of required resources **What is the certainty of the evidence of resource requirements (costs)?**		
Judgment	**Research evidence**	**Additional considerations**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify primary studies addressing the resources required to manage CKD patients with renal replacement therapy.	
Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**One systematic review directly addresses the cost-effectiveness of different renal replacement therapy (RRT)** (Yang, 2021). Kidney transplant (KT) was the most cost-effective RRT modality and peritoneal dialysis (PD) was more cost-effective than hemodialisys (HD). Most studies suggested that KT held a dominant position over HD and PD with both lower costs and higher effectiveness. Five studies suggested that increased uptake of KT and PD by new end-stage kidney disease patients would reduce costs and improve health outcomes or would be more cost-effective than current practice patterns.	The panel noted that early preparatory strategy is more cost-effective than any late strategy.
Equity **What would be the impact on health equity?**		
Judgment	**Research evidence**	**Additional considerations**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify evidence to address equity for this specific question. Two studies suggest that there are Iranian studies assessed local geographical barriers to access to hemodialysis. The reason for the disadvantage is a and found that they may be a factor in the distribution of resources (4, 5).	The panel judged this contextual factor based on the lack of evidence.
Acceptability **Is the intervention acceptable to key stakeholders?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address acceptability for this specific question.	
Feasibility **Is the intervention feasible to implement?**		
Judgment	**Research evidence**	**Additional considerations**

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question.	The panel agreed that it is feasible to implement an early strategy but it is not advisable or recommended.

Summary of judgments

	Judgment						
Problem	**No**	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	**Trivial**	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	**Moderate**	Small	Trivial		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	**Probably no**	Probably yes	Yes		Varies	Don't know

	Judgment						
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

Conclusions

Recommendation

In patients with CKD stage 4 to 5, the CKD Task Force suggests using an early preparation strategy* (based on eGFR or by anticipated time to start of KRT) over late preparation strategy (by eGFR or by anticipated time to start of KRT) to prepare the patient for the start of KRT (conditional recommendation, very low certainty in the evidence of effects).

*Estimated glomerular filtration rate: 20 mL/min/1.73m2; anticipated time for PD (2-4 weeks); hemodialysis (4-8 weeks for arteriovenous fistula [AVF] to heal).

Justification

The panel judged that the balance of desirable and undesirable consequences does not favor the use of late preparation strategy (by eGFR or by anticipated time to start of KRT) to prepare the patient for the start of KRT over early preparation strategy* (based on eGFR or by anticipated time to start of KRT) in this population. Specifically, the panel felt that most patients will get benefit due to a balance that favors early preparation strategy* (based on eGFR or by anticipated time to start of KRT) in the context of very low certainty evidence, moderate savings, and cost-effectiveness that probably favours early preparation strategy* (based on eGFR or by anticipated time to start of KRT).

Subgroup considerations

No subgroup considerations were made for this recommendation.

Implementation considerations

- Discuss the risks and/or benefits with the person, their family members, and caregivers (as appropriate) for the different types of dialysis access, for example, fistula, graft, central venous, or peritoneal dialysis catheter.

- Two weeks before the anticipated dialysis, plan to create access for peritoneal dialysis via a catheter using an open surgical technique.
- Six months before the planned start of HDF or HD via an arteriovenous fistula, create the fistula to allow for maturation. Consider that the first fistula may fail and need further interventions before actual initiation and use.
- Discuss ultrasound scanning with the patient to determine vascular access sites for creating arteriovenous fistulae for HDF or HD.

Monitoring and evaluation

No monitoring and evaluation considerations were made for this recommendation.

Research priorities

With regard to research needs, the panel identified:

- The timing of creating percutaneous and laparoscopic PD access for different RRT options.
- The clinical and cost-effectiveness of initial hemodialysis versus initial peritoneal dialysis for people who start dialysis in an unplanned approach.
- The best timing for transplant listing for those on RRT considering transplantation.

The CKD Task Force also accepted the following research needs listed in the NICE guideline (6): What is the most clinical and cost-effective strategy for timing of preemptive transplantation, and what is the optimum timing of listing for transplantation?

References

1. Gadelkarim AH, Mohammed AFS,AHK Ali,et al. Etiology of chronic kidney disease (CKD) in Saudi Arabia. Int J Med Res & Health Sci; 2019.
2. KDIGO, . KDIGO conferences. https://kdigo.org/conferences/early-identification/; 2021.
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4. Kiani, B,Bagheri,N,Tara,A,Hoseini,B.,Tara,M. Haemodialysis services in the northeastern region of Iran. Geospatial Health; 2017.
5. Kiani, Behzad, Bagheri, Nasser, Tara, Ahmad, Hoseini, Benyamin, Hashtarkhani, Soheil, Tara, Mahmood. Comparing potential spatial access with self-reported travel times and cost analysis to haemodialysis facilities in North-eastern Iran. 2018.
6. NG107, NICE,guideline. Qualitative evidence review. RRT and conservative management Evidence review for symptom recognition. 2018.

Appendix 1 – Summary of findings

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with any early preparation strategy (based on eGFR or by anticipated time to start of KRT)	Risk difference with any late preparation strategy (based on eGFR or by anticipated time to start of KRT)
Mortality (HD access, adults > 70 years) [fistula placement within 1 month before initiation vs 1-2 months before initiation] follow-up: 4 years	419 (1 observational study)[1]	⨁◯◯◯ Very low[a,b]	**HR 1.26** (1.03 to 1.54)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)
				Low	
				103 per 1,000[2,c]	**25 more per 1,000** (3 more to 51 more)
Cognitive impairment - not reported	-	-	-	-	-
Growth - not reported	-	-	-	-	-
Impact late referral rates - not reported	-	-	-	-	-
Patient, family/caregiver health related QoL - not reported	-	-	-	-	-
Pre-emptive transplantation rates - not reported	-	-	-	-	-
Proportion receiving RRT after assessment - not reported	-	-	-	-	-
Symptom scores - not reported	-	-	-	-	-
Adverse events (HD access): AVF failure [time from creation to use <30 days vs >30 days] follow-up: 5 years	184 (1 observational study)[3]	⨁◯◯◯ Very low[b]	**HR 1.94** (1.34 to 2.82)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)
Adverse events (PD access, 1 week vs 4 weeks from access creation use, adults 18 - 70 years): Modality failure follow-up: 6 months	80 (1 RCT)[4]	⨁⨁◯◯ Low[d,e]	**RR 0.15** (0.02 to 1.17)	Study population	
				171 per 1,000	**145 fewer per 1,000** (167 fewer to 29 more)
Adverse events (PD access, 1 week vs 4 weeks from access creation use, adults 18 - 70 years): Infections (PD related/tunnel/peritonitis) follow-up: 2 months	80 (1 RCT)[4]	⨁⨁◯◯ Low[d,f]	**RR 5.26** (0.64 to 43.00)	Study population	
				24 per 1,000	**104 more per 1,000** (9 fewer to 1,024 more)
				Study population	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with any early preparation strategy (based on eGFR or by anticipated time to start of KRT)	Risk difference with any late preparation strategy (based on eGFR or by anticipated time to start of KRT)
Adverse events (PD access, 1 week vs 4 weeks from access creation use, adults 18 - 70 years): Leak follow-up: 2 months	80 (1 RCT)[4]	⨁⨁◯◯ Low[a,d]	**RR 11.56** (1.57 to 85.42)	24 per 1,000	**258 more per 1,000** (14 more to 2,059 more)
Adverse events (PD access, 1 week vs 2 weeks from access creation use, adults 18 - 70 years): Modality failure follow-up: 6 months	81 (1 RCT)[4]	⨁⨁◯◯ Low[d,g]	**RR 1.08** (0.07 to 16.63)	Study population	
				24 per 1,000	**2 more per 1,000** (22 fewer to 372 more)
Adverse events (PD access, 1 week vs 2 weeks from access creation use, adults 18 - 70 years): Infections (PD related/tunnel/peritonitis) follow-up: 2 months	81 (1 RCT)[4]	⨁⨁◯◯ Low[d,f]	**RR 5.38** (0.66 to 44.07)	Study population	
				24 per 1,000	**104 more per 1,000** (8 fewer to 1,025 more)
Adverse events (PD access, 1 week vs 2 weeks from access creation use, adults 18 - 70 years): Leak follow-up: 2 months	81 (1 RCT)[4]	⨁⨁◯◯ Low[4,h]	**RR 2.96** (1.03 to 8.53)	Study population	
				95 per 1,000	**187 more per 1,000** (3 more to 717 more)
Adverse events (PD access, 2 weeks vs 4 weeks from access creation use, adults 18 - 70 years): Modality failure follow-up: 6 months	83 (1 RCT)[4]	⨁⨁◯◯ Low[d,i]	**RR 0.14** (0.02 to 1.08)	Study population	
				171 per 1,000	**147 fewer per 1,000** (167 fewer to 14 more)
Adverse events (PD access, 2 weeks vs 4 weeks from access creation use, adults 18 - 70 years): Infections (PD related/tunnel/peritonitis) follow-up: 2 months	83 (1 RCT)[4]	⨁⨁◯◯ Low[d,g]	**RR 0.98** (0.06 to 15.09)	Study population	
				24 per 1,000	**0 fewer per 1,000** (23 fewer to 344 more)
Adverse events (PD access, 2 weeks vs 4 weeks from access creation use, adults 18 - 70 years): Leak follow-up: 2 months	83 (1 RCT)[4]	⨁⨁◯◯ Low[d,j]	**RR 3.90** (0.46 to 33.48)	Study population	
				24 per 1,000	**71 more per 1,000** (13 fewer to 792 more)

References

1. Ishani A, Gilbertson DT,Kim D,Bradbury BD,Collins AJ.. Predialysis care and dialysis outcomes in hemodialysis patients with a functioning fistula. American Journal of Nephrology; 2014.
2. Wen CP, Cheng TY,Tsai MK,Chang YC,Chan HT,Tsai SP,Chiang PH,Hsu CC,Sung PK,Hsu YH,Wen SF.. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan.. Lancet; 2008.
3. Ravani P, Brunori G,Mandolfo S,Cancarini G,Imbasciati E,Marcelli D et al.. Cardiovascular comorbidity and late referral impact arteriovenous fistula survival: A prospective multicenter study. . Journal of the American Society of Nephrology. ; 2004.

4. Ranganathan D, John GT,Yeoh E,Williams N,O'Loughlin B,Han T et al.. A randomized controlled trial to determine the appropriate time to initiate peritoneal dialysis after insertion of catheter (Timely PD Study). . Peritoneal Dialysis International; 2017.

Explanations

a. Serious imprecision. One study with a small sample size did not meet OIS criteria.
b. Study that carried all weight for the overall effect estimate rated as high risk of bias due to bias due to confounding and selection of participants into the study. We, therefore, downgraded by two levels.
c. Mortality attributable to chronic kidney disease for national population was calculated based on a cohort study of 462 293 individuals aged older than 20 years in Taiwan.
d. Study that carried all weight for the overall effect estimate rated as high risk of bias due to lack of blinding.
e. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.
f. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 6 events in total.
g. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 2 events in total.
h. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 15 events in total.
i. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 8 events in total.
j. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference with only 5 events in total.

Question 7. Should a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms that he/she is experiencing versus not using such strategy be used in patients who are undergoing or being assessed for KRT or conservative management of established kidney failure?

Population:	patients who are being assessed for or are undergoing KRT or conservative management of established kidney failure
Intervention:	a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms he/she is experiencing
Comparison:	no such a strategy
Main outcomes:	Fatigue (Pre-RRT, adults aged 25 to <70); Itching (Pre-RRT, adults aged 25 to <70); Nausea and vomiting (Pre-RRT, adults aged 25 to <70); Weight loss (Pre-RRT, adults aged 25 to <70); Tiredness (Aching body, conservative management, adults aged 25 to <70, 70+); Psychological distress and mental wellbeing (Confusion, conservative management, adults aged 25 to <70, 70+); Psychological distress and mental wellbeing (Depression, conservative management, adults aged 25 to <70, 70+); Itching (Conservative management, adults aged 25 to <70, 70+); Tiredness (Lack of energy, conservative management, adults aged 25 to <70, 70+); Tiredness (Fatigue, conservative management, adults aged 25 to <70, 70+); Nausea and vomiting (Conservative management, adults aged 25 to <70, 70+); Anorexia (Poor appetite, conservative management, adults aged 25 to <70, 70+); Psychological distress and mental wellbeing (Cognitive fluctuations, conservative management, adults aged 25 to <70, 70+); Weight loss (Conservative management, adults aged 25 to <70, 70+); Psychological distress and mental wellbeing (Cognitive fluctuations, HD, adults aged 70+); Psychological distress and mental wellbeing (Anxiety, HD, People aged 25 to <70, 70+); Psychological distress and mental wellbeing (Cognitive fatigue, HD, adults aged 25 to <70, 70+); Psychological distress and mental wellbeing (Depression, HD, People aged 2 to <16, 25 to <70, 70+); Tiredness (Exhaustion, HD, People aged 16 to <25, 25 to <70, 70+); Tiredness (Fatigue, HD, People aged 2 to <16, 25 to <70, 70+); Tiredness (Malaise, HD, People aged 25 to <70, 70+); Itching (HD, People aged 25 to <70, 70+); Nausea and vomiting (HD, People aged 2 to <16, 16 to <25, 25 to <70, 70+); Weight loss (HD, People aged 25 to <70); Psychological distress and mental wellbeing (Cognitive fatigue, PD, adults aged 25 to <70, 70+); Tiredness (Fatigue, PD, People aged 25 to <70, 70+); Itching (PD, People aged 25 to <70, 70+); Nausea and vomiting (PD, People aged 2 to <16, 16 to <25, 25 to <70, 70+); Weight loss (PD, People aged 25 to <70); Psychological distress and mental wellbeing (Cognitive fatigue, Transplant, People aged 25 to <70); Psychological distress and mental wellbeing (Depression, Transplant, People aged 25 to <70); Tiredness (Fatigue, Transplant, People aged 16 to 25, 25 to <70, 70+); Itching (Transplant, People aged 25 to <70); Nausea and vomiting (Transplant, People aged 2 to <16, 16 to <25, 25 to <70, 70+); Weight loss (Transplant, People aged 25 to <70);
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (1).
Conflict of interests:	**KSA conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dalbhi Muneera Rashid Al-Jelaify

	Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari Ahmed Mitwalli Mohammed Alghonaim **Panel members recused as a result of risk of conflicts of interest:** None.

Assessment

Problem **Is the problem a priority?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	• The global burden of CKD remains a major public health problem as the worldwide prevalence is currently estimated at 7.2% to 13.4% (KDIGO, 2021). • When people approach or have progressed to later stages CKD they need to decide whether to undergo renal replacement therapy or to choose conservative management (NG107, 2018). • Renal replacement therapy includes the following modalities: hemodialysis, haemodiafiltration, peritoneal dialysis, and renal transplantation. Haemodialysis can be delivered at home, in a satellite unit, or in hospital. Peritoneal dialysis can be continuous ambulatory or automated. Transplantation may be pre-emptive (before dialysis) or not and may be from a living or deceased donor (NG107, 2018). • Conservative management is the full supportive management (including the control of symptoms and complications and advance care planning) for those in the later stages of CKD who, in conjunction with carers and the clinical team, decide against renal replacement therapy. Conservative management will generally (although not always) be less appropriate for younger, healthier people. Conservative management is rarely an option for children (NG107, 2018).	
Desirable Effects **How substantial are the desirable anticipated effects?**		

Judgment	Research evidence	Additional considerations
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	*See Appendix 1*	The panel noted that the judgment of large desirable effect was made on the basis of the panel's clinical expertise and experience.
Undesirable Effects **How substantial are the undesirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	*See Appendix 1*	
Certainty of evidence **What is the overall certainty of the evidence of effects?**		
Judgment	**Research evidence**	**Additional considerations**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty in the evidence is reduced as a result of methodological limitations and concerns regarding adequacy for the assessment of outcomes.	Based on the lowest certainty of the critical outcomes.
Values **Is there important uncertainty about or variability in how much people value the main outcomes?**		
Judgment	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or	We did not identify primary studies addressing the relative importance of the outcomes for this specific question.**International report described the following regarding the relative importance of outcomes and patients' preferences for the screening and diagnosis of**	

variability ○ No important uncertainty or variability	**CKD**Patient representatives and advocates described that there is a strong belief that patients overwhelmingly prefer earlier CKD screening and diagnosis and that patient education has the potential to improve self-management and disease prognosis (2). Individual and population-level risk of having CKD and experiencing its complications should inform whether persons should be screened for CKD. Decisions concerning the age to initiate testing, the frequency of repeat testing, and the time to forgo or end testing should all be individualized based upon risk factors, preferences, and life expectancy (2).**One systematic review described the following regarding the relative importance of outcomes and patients' preferences for hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT)**Patients highly value the benefits of HD, PD, and KT (3). The utility values for HD ranged from 0.44 to 0.72; for PD from 0.53 to 0.81; for KT from 0.57 to 0.90. In seven of the nine studies, KT utility was higher than PD utility, and PD utility was higher than HD utility. In two of the nine studies, KT utility was higher than PD and HD utility, with PD and HD utility being equal. One study suggests that conflicting results of utility valuations existed among different valuation methods. For example, continuous ambulatory PD patients' EQ-5D scores were higher than those of center HD patients, while continuous ambulatory PD patients' SG and TTO scores were lower than those of center HD patients (3).	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgment	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel judged the balance as probably favoring the intervention because of uncertainty about the effects.

Resources required
How large are the resource requirements (costs)?

Judgment	Research evidence	Additional considerations

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not identify direct evidence to address resources use for this question.	The panel agreed on the judgment varies because resources required vary from patient to patient based on severity of the condition and presence of comorbidities. If there are symptoms, then there would be implications and dialysis would need to be initiated. The presence of comorbidities can increase the costs associated with RRT.
Certainty of evidence of required resources **What is the certainty of the evidence of resource requirements (costs)?**		
Judgment	**Research evidence**	**Additional considerations**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		
Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	We did not identify direct evidence to address cost effectiveness for this question.	The panel agreed that cost-effectiveness vary because resources required vary from patient to patient based on severity of the condition and presence of comorbidities. If there are symptoms, then there would be implications and dialysis would need to be initiated. The presence of comorbidities can increase the costs associated with RRT.
Equity **What would be the impact on health equity?**		
Judgment	**Research evidence**	**Additional considerations**

○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify evidence to address equity for this specific question.	The judgment of probably no impact was related to a system of full healthcare coverage in Saudi Arabia.
Acceptability **Is the intervention acceptable to key stakeholders?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not identify direct evidence to address acceptability for this specific question. Indirect evidence (Al-Jedai A, 2012) for the implementation of the multidisciplinary care (MDC) clinic for patients with advanced CKD suggested possible improvement in adherence to CKD intervention targets and good participants' acceptability of the MDC program. The program included clinical outcomes assessment, self-care advice, and KRT options	
Feasibility **Is the intervention feasible to implement?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question.	

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	Judgment						
Desirable Effects	Trivial	Small	Moderate	**Large**		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

In patients who are undergoing or being assessed for KRT or conservative management of established kidney failure, the CKD Task Force suggests using a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms he/she is experiencing rather than not using such a strategy (conditional recommendation, very low certainty in the evidence of effects).

Justification

The panel judged that the balance of desirable and undesirable consequences favors the use of a strategy of asking patients (and/or their families and/or their caregivers) about the symptoms he/she is experiencing over no such a strategy in this population. Specifically, the panel felt that most patients will get benefit due to a balance that probably favors ca strategy of asking patients (and/or their families and/or their caregivers) about the symptoms he/she is experiencing in the context of very low certainty evidence.

Subgroup considerations

No subgroup considerations were made for this recommendation.

Implementation considerations

No implementation considerations were made for this recommendation.

Monitoring and evaluation

No monitoring and evaluation considerations were made for this recommendation.

Research priorities

There were no future research needs prioritized by the panel.

References

1. Gadelkarim AH, Mohammed AFS,AHK Ali,et al. Etiology of chronic kidney disease (CKD) in Saudi Arabia. Int J Med Res & Health Sci; 2019.
2. KDIGO, . KDIGO conferences. https://kdigo.org/conferences/early-identification/; 2021.

3. Yang, F.,Liao,M.,Wang,P. et al.. The Cost-Effectiveness of Kidney Replacement Therapy Modalities: A Systematic Review of Full Economic Evaluations. Appl Health Econ Health Policy; 2021.

Appendix 1 - Summary of findings

Outcomes	Impact
Fatigue (Pre-RRT, adults aged 25 to <70)	Symptom reported with no additional details. [a]
Itching (Pre-RRT, adults aged 25 to <70)	This symptom was reported relatively infrequently and as intense. [b]
Nausea and vomiting (Pre-RRT, adults aged 25 to <70)	Symptom reported with no additional details. [c]
Weight loss (Pre-RRT, adults aged 25 to <70)	Symptom reported with no additional details. [a]
Tiredness (Aching body, conservative management, adults aged 25 to <70, 70+)	Symptom reported with no additional details. [a]
Psychological distress and mental wellbeing (Confusion, conservative management, adults aged 25 to <70, 70+)	Symptom reported with no additional details. [a]
Psychological distress and mental wellbeing (Depression, conservative management, adults aged 25 to <70, 70+)	Participants reported feeling depressed as they were unable to do things they were previously able to do. [a]
Itching (Conservative management, adults aged 25 to <70, 70+)	Most participants found this problematic and persistent. [a]
Tiredness (Lack of energy, conservative management, adults aged 25 to <70, 70+)	Symptom reported with no additional details. [a]
Tiredness (Fatigue, conservative management, adults aged 25 to <70, 70+)	Most participants reported feeling tired and finding it debilitating. [a]
Nausea and vomiting (Conservative management, adults aged 25 to <70, 70+)	Most participants suffered from this symptom. [a]

Outcomes	Impact
Anorexia (Poor appetite, conservative management, adults aged 25 to <70, 70+)	Symptom reported with no additional details. [a]
Psychological distress and mental wellbeing (Cognitive fluctuations, conservative management, adults aged 25 to <70, 70+)	Symptom reported with no additional details. [a]
Weight loss (Conservative management, adults aged 25 to <70, 70+)	Symptom reported with no additional details. [a]
Psychological distress and mental wellbeing (Cognitive fluctuations, HD, adults aged 70+)	Participants reported concern about their memory and remembering to carry out day-to-day tasks. [c]
Psychological distress and mental wellbeing (Anxiety, HD, People aged 25 to <70, 70+)	Symptom reported with no additional details. [a]
Psychological distress and mental wellbeing (Cognitive fatigue, HD, adults aged 25 to <70, 70+)	Participants mentioned how weakness and fatigue affected their cognitive abilities, causing difficulty in concentrating after dialysis. [a]
Psychological distress and mental wellbeing (Depression, HD, People aged 2 to <16, 25 to <70, 70+)	Participants reported feeling depressed during and after dialysis. [b]
Tiredness (Exhaustion, HD, People aged 16 to <25, 25 to <70, 70+)	Participants reported feeling exhausted after dialysis. [a]
Tiredness (Fatigue, HD, People aged 2 to <16, 25 to <70, 70+)	This symptom was reported by most participants as both habitual and following dialysis. [b]
Tiredness (Malaise, HD, People aged 25 to <70, 70+)	A common symptom mentioned by participants associated with dialysis. [a]
Itching (HD, People aged 25 to <70, 70+)	This was a common symptom reported by participants as usually intense. [b]
Nausea and vomiting (HD, People aged 2 to <16, 16 to <25, 25 to <70, 70+)	This symptom was reported relatively infrequently. [a]
Weight loss (HD, People aged 25 to <70)	Symptom reported with no additional details. [a]

Outcomes	Impact
Psychological distress and mental wellbeing (Cognitive fatigue, PD, adults aged 25 to <70, 70+)	Some participants reported sensations of being mentally tired more dominant than physical tiredness. [a]
Tiredness (Fatigue, PD, People aged 25 to <70, 70+)	Participants reported this symptom following dialysis. [b]
Itching (PD, People aged 25 to <70, 70+)	This was a common symptom reported by participants as usually intense. [d]
Nausea and vomiting (PD, People aged 2 to <16, 16 to <25, 25 to <70, 70+)	This symptom was reported relatively infrequently. [c]
Weight loss (PD, People aged 25 to <70)	Symptom reported with no additional details. [a]
Psychological distress and mental wellbeing (Cognitive fatigue, Transplant, People aged 25 to <70)	Symptom reported with no additional details. [b]
Psychological distress and mental wellbeing (Depression, Transplant, People aged 25 to <70)	Symptom reported with no additional details. [c]
Tiredness (Fatigue, Transplant, People aged 16 to 25, 25 to <70, 70+)	This symptom was reported by most participants as a side effect to transplant medication. [b]
Itching (Transplant, People aged 25 to <70)	This symptom was reported relatively infrequently and as intense. [b]
Nausea and vomiting (Transplant, People aged 2 to <16, 16 to <25, 25 to <70, 70+)	This symptom was reported relatively infrequently. [b]
Weight loss (Transplant, People aged 25 to <70)	Symptom reported with no additional details. [a]

Explanations

a. Overall assessment of certainty: LOW
b. Overall assessment of certainty: VERY LOW
c. Overall assessment of certainty: MODERATE
d. Qualitative studies; individual interviews.

Question 8. Should initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms versus initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms be used in previously KRT-naive adults requiring KRT for deteriorating CKD?

Population:	previously KRT-naive adults requiring KRT for deteriorating CKD
Intervention:	initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms
Comparison:	initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*
Main outcomes:	All-cause mortality - HD or PD; All-cause mortality: age<18 years - HD or PD; Cognitive impairment - HR or PD (assessed with: early vs late dialysis initiation based on eGFR); Growth age<18 years - HD or PD; Impact late referral rates - HR or PD (assessed with: early vs late dialysis initiation based on eGFR); Patient, family/caregiver health related QoL - HD or PD; Pre-emptive transplantation rates: age<18 years - HD or PD; Proportion receiving RRT after assessment - HR or PD (assessed with: early vs late dialysis initiation based on eGFR); Symptom scores - HR or PD (assessed with: early vs late dialysis initiation based on eGFR); Adverse events - HD or PD; Mortality: Transplant at eGFR>/=15ml/min vs <10ml/min; Mortality: Transplant at eGFR 10 -14.9 ml/min vs <10ml/min.
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (1).
Conflict of interests:	**KSA conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dalbhi Muneera Rashid Al-Jelaify Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari Ahmed Mitwalli Sumayah Askandarani **Panel members recused as a result of risk of conflicts of interest:**

	None

Assessment

Problem **Is the problem a priority?**		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	• The global burden of CKD remains a major public health problem as the worldwide prevalence is currently estimated at 7.2% to 13.4% (KDIGO, 2021). • Early identification of CKD by screening for kidney disease, followed by risk stratification and treatment, offers the potential to substantially reduce the morbidity and mortality from CKD and its related complications, such as cardiovascular disease (Shlipak MG et al., 2021). • Despite effective methods to diagnose and treat CKD at its earliest stages, there is a lack of consensus on whether health systems and governments should implement CKD screening programs (Shlipak MG et al., 2021). • In children with CKD, reports indicate that mortality among children who progress to end-stage renal disease (ESRD) is 30 to 50 times higher compared to that in the general population (Mitsnefes et al., 2013)(Harambat et al., 2012). • The main causes of CKD in this population of patients were congenital abnormalities of the renal system, in 50% of patients, followed by neurogenic bladder in almost 20% of the children, acquired causes (14%), and hereditary conditions (12%) (Kari, 2006).	
Desirable Effects **How substantial are the desirable anticipated effects?**		
Judgement	**Research evidence**	**Additional considerations**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1*	

Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	**Research evidence**	**Additional considerations**
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	*See Appendix 1*	Financial considerations may influence time of initiation and/or choice of renal replacement therapy, internationally. Lifestyle is a consideration in choice of renal replacement therapy (RRT) e.g., peritoneal dialysis or hemodialysis. Physician education may also play a role in choice of RRT. In children, there could be undesirable efects of starting late including cognitive decline; in adults, it can cause encephalopathy and loss of consciousness. Studies show that late vs early initiation, however, does not show much difference in mortality and morbidity.
Certainty of evidence **What is the overall certainty of the evidence of effects?**		
Judgement	**Research evidence**	**Additional considerations**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty in the evidence is reduced as a result of imprecision and risk of bias for the assessment of outcomes.	Based on the lowest certainty of the critical outcomes.
Values **Is there important uncertainty about or variability in how much people value the main outcomes?**		
Judgement	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not identify primary studies addressing the relative importance of the outcomes for this specific question.**An international report described the following regarding the relative importance of outcomes and patients' preferences for the screening and diagnosis of CKD** Patient representatives and advocates described that there is a strong belief that patients overwhelmingly prefer earlier CKD screening and diagnosis and that patient education has the potential to improve self-management and disease prognosis (2). Individual and population-level risk of having CKD and experiencing its complications should inform whether persons should be screened for CKD. Decisions concerning the age to initiate testing, the frequency of	

	repeat testing, and the time to forgo or end testing should all be individualized based upon risk factors, preferences, and life expectancy (2). **One systematic review described the following regarding the relative importance of outcomes and patients' preferences for hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT)** Patients highly value the benefits of HD, PD, and KT (3). The utility values for HD ranged from 0.44 to 0.72; for PD from 0.53 to 0.81; for KT from 0.57 to 0.90. In seven of the nine studies, KT utility was higher than PD utility, and PD utility was higher than HD utility. In two of the nine studies, KT utility was higher than PD and HD utility, with PD and HD utility being equal. One study suggests that conflicting results of utility valuations existed among different valuation methods. For example, continuous ambulatory PD patients' Euro-QoL-5 Dimension (EQ-5D) scores were higher than those of center HD patients, while continuous ambulatory PD patients' standard gamble (SG) and time tradeoff (TTO) scores were lower than those of center HD patients (3).	
Balance of effects **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**		
Judgement	**Research evidence**	**Additional considerations**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel judged the balance as probably favoring the comparison because of uncertainty about the effects.
Resources required **How large are the resource requirements (costs)?**		
Judgement	**Research evidence**	**Additional considerations**

● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not identify primary studies addressing the resources required to manage CKD patients with renal replacement therapy. **Cost of disease** • Chronic kidney disease (CKD) affects about 10 percent of the population worldwide, including an estimated 1 in 7 adult Americans.1 In the United States, Medicare spending totals more than $64 billion each year to care for Americans with CKD and an additional $34 billion to care for patients with end-stage renal disease (ESRD) (4). • The impact of kidney disease extends well beyond the United States; over 2 million people worldwide have ESRD. In higher-income countries, treatment costs are enormous: a 2010 report from the UK National Health Service estimates its annual CKD spending at £1.45 billion—more than half of which was for renal replacement therapy (RRT) (5)—while Australia has estimated it will spend over $12 billion on ESRD patients through 2020 (6). At the same time, RRT remains entirely unaffordable to the majority of ESRD patients in low- and middle-income countries throughout the world, with over 1 million people dying annually from lack of treatment (7). **Cost of interventions** • Initial assessment clinic: annual cost per patient £2,537 (Saudi Riyals [SAR] 13,137), annual expenditure £6,421,018 (SAR 33,238,174). • The mean total cost per hemodialysis (HD) session was calculated as 297 US dollars (USD) (1,114 SAR), and the mean total cost of dialysis per patient per year was 46,332 USD (173,784 SAR) (8). • One study conducted in Saudi Arabia described that an average annual cost of medical care per patient after transplantation in the first, second, third, and fourth-year was US $133,291, US $14,233, US $5,536, and US $4,402; respectively. The average 4-year actual total cost per patient was US $210,779 and US $317,186.3 in the kidney transplant group and the HD group; respectively (p=0.017) (9).	The panel agreed that initiating early RRT will add additional costs to the health care system. The panel expressed that KSA is seeing a linear increase in the number of patients on dialysis. They agreed that there are large costs to start dialysis early. However, delaying dialysis and starting only when extremely urgent if needed, will overload the health care system.
Certainty of evidence of required resources **What is the certainty of the evidence of resource requirements (costs)?**		
Judgement	**Research evidence**	**Additional considerations**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify direct evidence to address the certainty of the evidence of resource requirements.	
Cost effectiveness		

Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Judgement	**Research evidence**	**Additional considerations**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**One systematic review directly addresses the cost-effectiveness of different renal replacement therapy (RRT)** (3) Kidney transplant (KT) was the most cost-effective RRT modality and peritoneal dialysis (PD) was more cost-effective than hemodialysis (HD). Most studies suggested that KT held a dominant position over HD and PD with both lower costs and higher effectiveness. Five studies suggested that increased uptake of KT and PD by new end-stage renal disease (ESRD) patients would reduce costs and improve health outcomes or would be more cost-effective than current practice patterns.	
Equity **What would be the impact on health equity?**		
Judgement	**Research evidence**	**Additional considerations**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify evidence to address equity for this specific question.	Equity might be affected due availability of centers and resources to allow all patients to start dialysis early. This will impact patient perceptions of good quality of dialysis care.
Acceptability **Is the intervention acceptable to key stakeholders?**		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address acceptability for this specific question.	

Feasibility Is the intervention feasible to implement?		
Judgement	**Research evidence**	**Additional considerations**
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question.	Early hemodialysis is costly and challenging to implement. The number of people requiring hemodialysis is increasing in Saudi Arabia. Efforts are being made towards early prevention. Peritoneal dialysis may include lower costs and higher quality of life than hemodialysis.

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies

	Judgment						
Equity	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	**Probably no**	Probably yes	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

Conclusions

Recommendation

In previously KRT-naive adults requiring KRT for deteriorating CKD, the CKD Task Force suggests initiating KRT late (i.e., eGFR 5-7 mL/min/1.73m2) or based on severe symptoms* over initiating KRT early (i.e., eGFR 10-15 mL/min/1.73m2) or based on moderate symptoms (conditional recommendation, very low certainty in the evidence of effects).

*** Severe uremic symptoms and/or uncontrollable fluid overload**

Justification

The panel judged that the balance of desirable and undesirable consequences does not favor the use of initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms over initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms* in this population. Specifically, the panel felt that most patients will get benefit due to a balance that probably favors initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms* in the context of very low certainty evidence, large costs in the context of initiating early KRT, cost-effectiveness that probably favours initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*, and probably reduce equity.

* Severe uremic symptoms and/or uncontrollable fluid overload

Subgroup considerations

No subgroup considerations were made for this recommendation.

Implementation considerations

No implementation considerations were made for this recommendation because there was no research evidence identified.

Monitoring and evaluation

No monitoring and implementation considerations were made for this recommendation.

Research priorities

The NICE guideline [2] identified a research need for the following question: What is the most clinical and cost-effective strategy for timing of pre-emptive transplantation? A question raised by the CKD Task Force was whether initiation of dialysis can be delayed safely with aggressive medical management [24].

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Appendix 1 - Summary of findings

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*	**Risk difference with initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms**
Mortality - HD or PD assessed with: early vs late dialysis initiation based on eGFR follow-up: mean 3.6 years[a]	828 (1 RCT)[1]	⨁⨁◯◯ Low[b,c]	**RR 1.04** (0.87 to 1.24)	Study population	
				366 per 1,000	**15 more per 1,000** (48 fewer to 88 more)
				Low	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*	Risk difference with initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms
				257 per 1,000[2,d]	**10 more per 1,000** (33 fewer to 62 more)
				High	
				516 per 1,000[2,e]	**21 more per 1,000** (67 fewer to 124 more)
Mortality: age<18 years - HD or PD follow-up: 1.3 years	18133 (2 observational studies)[3,4]	⨁◯◯◯ Very low[b,f]	**HR 1.25** (0.96 to 1.64)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)
Cognitive impairment - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[a]	-	-	-	-	-
Growth age<18 years - HD or PD assessed with: early vs late dialysis initiation based on eGFR[a]	2963 (1 observational study)[3]	⨁◯◯◯ Very low[b,c]	-	The mean growth age<18 years - HD or PD was **0**	MD **0.03 lower** (0.15 lower to 0.09 higher)
Impact late referral rates - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[a]	-	-	-	-	-
Patient, family/caregiver health related QoL - HD or PD assessed with: assessed with: early vs late dialysis initiation based on eGFR[a]	642 (1 RCT)[1]	⨁◯◯◯ Very low[b,c]	-	The mean patient, family/caregiver health related QoL - HD or PD was **0**	MD **0** (0.03 lower to 0.03 higher)
Pre-emptive transplantation rates: age<18 years - HD or PD assessed with: assessed with: early vs late dialysis initiation based on eGFR[a]	2963 (1 observational study)[3]	⨁◯◯◯ Very low[b,c]	**HR 0.97** (0.89 to 1.06)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)
Proportion receiving RRT after assessment - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[a]	-	-	-	-	-
Symptom scores - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[a]	-	-	-	-	-

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*	Risk difference with initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms
Adverse events - HD or PD assessed with: assessed with: early vs late dialysis initiation based on eGFR follow-up: 3.6 years[a,g]	828 (1 RCT)[1]	⨁⨁◯◯ Low[b,c]	**RR 0.89** (0.75 to 1.06)	Study population	
				410 per 1,000	**45 fewer per 1,000** (103 fewer to 25 more)
Mortality: Transplant at eGFR>/=15ml/min vs <10ml/min	454 (1 observational study)[5]	⨁◯◯◯ Very low[b,c]	**HR 1.35** (0.89 to 2.05)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)
				Low	
				87 per 1,000	**29 more per 1,000** (9 fewer to 84 more)
Mortality: Transplant at eGFR 10 -14.9 ml/min vs <10ml/min	541 (1 observational study)[5]	⨁◯◯◯ Very low[b,c]	**HR 0.99** (0.69 to 1.42)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)
				Low	
				87 per 1,000	**1 fewer per 1,000** (26 fewer to 34 more)

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Explanations

a. Early=10-14 ml/min, late=5-7 ml/min
b. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.
c. One study that carried all weight for the overall effect estimate rated as high risk of bias.
d. Mortality rate based on a population-based cohort study of 725 Swedish adult patients with CKD that received peritoneal dialysis.
e. Mortality rate based on a population-based cohort study of 1791 Swedish adult patients with CKD that received hemodialysis.
f. Studies that carried large weight for the overall effect estimate rated as high risk of bias.
g. Infection events

Question 9. Should any KRT modality versus conservative management be used in certain groups of patients requiring KRT for CKD?*

Population:	adults requiring KRT for deteriorating CKD
Intervention:	initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms
Comparison:	initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*
Main outcomes:	All-cause mortality - HD or PD; All-cause mortality: age<18 years - HD or PD; Cognitive impairment - HR or PD (assessed with: early vs late dialysis initiation based on eGFR); Growth age<18 years - HD or PD; Impact late referral rates - HR or PD (assessed with: early vs late dialysis initiation based on eGFR); Patient, family/caregiver health related QoL - HD or PD; Pre-emptive transplantation rates: age<18 years - HD or PD; Proportion receiving RRT after assessment - HR or PD (assessed with: early vs late dialysis initiation based on eGFR); Symptom scores - HR or PD (assessed with: early vs late dialysis initiation based on eGFR); Adverse events - HD or PD; Mortality: Transplant at eGFR>/=15ml/min vs <10ml/min; Mortality: Transplant at eGFR 10 -14.9 ml/min vs <10ml/min.
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (1).
Conflict of interests:	**KSA conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dalbhi Muneera Rashid Al-Jelaify Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari Ahmed Mitwalli Sumayah Askandarani

	Panel members recused as a result of risk of conflicts of interest: None

Assessment

Problem **Is the problem a priority?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	• The global burden of CKD remains a major public health problem as the worldwide prevalence is currently estimated at 7.2% to 13.4% (KDIGO, 2021). • Early identification of CKD by screening for kidney disease, followed by risk stratification and treatment, offers the potential to substantially reduce the morbidity and mortality from CKD and its related complications, such as cardiovascular disease (Shlipak MG et al., 2021). • Despite effective methods to diagnose and treat CKD at its earliest stages, there is a lack of consensus on whether health systems and governments should implement CKD screening programs (Shlipak MG et al., 2021). • In children with CKD, reports indicate that mortality among children who progress to end-stage renal disease (ESRD) is 30 to 50 times higher compared to that in the general population (Mitsnefes et al., 2013)(Harambat et al., 2012). • The main causes of CKD in this population of patients were congenital abnormalities of the renal system, in 50% of patients, followed by neurogenic bladder in almost 20% of the children, acquired causes (14%), and hereditary conditions (12%) (Kari, 2006).	
Desirable Effects **How substantial are the desirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies	*See Appendix 1*	

○ Don't know		

Undesirable Effects
How substantial are the undesirable anticipated effects?

Judgment	Research evidence	Additional considerations
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	*See Appendix 1*	Financial considerations may influence time of initiation and/or choice of renal replacement therapy, internationally. Lifestyle is a consideration in choice of renal replacement therapy (RRT) e.g., peritoneal dialysis or hemodialysis. Physician education may also play a role in choice of RRT. In children, there could be undesirable efects of starting late including cognitive decline; in adults, it can cause encephalopathy and loss of consciousness. Studies show that late vs early initiation, however, does not show much difference in mortality and morbidity.

Certainty of evidence
What is the overall certainty of the evidence of effects?

Judgment	Research evidence	Additional considerations
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty in the evidence is reduced as a result of imprecision and risk of bias for the assessment of outcomes.	Based on the lowest certainty of the critical outcomes.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgment	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not identify primary studies addressing the relative importance of the outcomes for this specific question.**An international report described the following regarding the relative importance of outcomes and patients' preferences for the screening and diagnosis of CKD** Patient representatives and advocates described that there is a strong belief that patients overwhelmingly prefer earlier CKD screening and diagnosis and that patient education has the potential to improve self-management and disease prognosis (2). Individual and population-	

	level risk of having CKD and experiencing its complications should inform whether persons should be screened for CKD. Decisions concerning the age to initiate testing, the frequency of repeat testing, and the time to forgo or end testing should all be individualized based upon risk factors, preferences, and life expectancy (2). **One systematic review described the following regarding the relative importance of outcomes and patients' preferences for hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT)** Patients highly value the benefits of HD, PD, and KT (3). The utility values for HD ranged from 0.44 to 0.72; for PD from 0.53 to 0.81; for KT from 0.57 to 0.90. In seven of the nine studies, KT utility was higher than PD utility, and PD utility was higher than HD utility. In two of the nine studies, KT utility was higher than PD and HD utility, with PD and HD utility being equal. One study suggests that conflicting results of utility valuations existed among different valuation methods. For example, continuous ambulatory PD patients' Euro-QoL-5 Dimension (EQ-5D) scores were higher than those of center HD patients, while continuous ambulatory PD patients' standard gamble (SG) and time tradeoff (TTO) scores were lower than those of center HD patients (3).	
Balance of effects **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel judged the balance as probably favoring the comparison because of uncertainty about the effects.
Resources required **How large are the resource requirements (costs)?**		
Judgment	**Research evidence**	**Additional considerations**

● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not identify primary studies addressing the resources required to manage CKD patients with renal replacement therapy. **Cost of disease** • Chronic kidney disease (CKD) affects about 10 percent of the population worldwide, including an estimated 1 in 7 adult Americans.1 In the United States, Medicare spending totals more than $64 billion each year to care for Americans with CKD and an additional $34 billion to care for patients with end-stage renal disease (ESRD) (4). • The impact of kidney disease extends well beyond the United States; over 2 million people worldwide have ESRD. In higher-income countries, treatment costs are enormous: a 2010 report from the UK National Health Service estimates its annual CKD spending at £1.45 billion—more than half of which was for renal replacement therapy (RRT) (5)—while Australia has estimated it will spend over $12 billion on ESRD patients through 2020 (6). At the same time, RRT remains entirely unaffordable to the majority of ESRD patients in low- and middle-income countries throughout the world, with over 1 million people dying annually from lack of treatment (7). **Cost of interventions** • Initial assessment clinic: annual cost per patient £2,537 (Saudi Riyals [SAR] 13,137), annual expenditure £6,421,018 (SAR 33,238,174). • The mean total cost per hemodialysis (HD) session was calculated as 297 US dollars (USD) (1,114 SAR), and the mean total cost of dialysis per patient per year was 46,332 USD (173,784 SAR) (8). • One study conducted in Saudi Arabia described that an average annual cost of medical care per patient after transplantation in the first, second, third, and fourth-year was US $133,291, US $14,233, US $5,536, and US $4,402; respectively. The average 4-year actual total cost per patient was US $210,779 and US $317,186.3 in the kidney transplant group and the HD group; respectively (p=0.017) (9).	The panel agreed that initiating early RRT will add additional costs to the health care system. The panel expressed that KSA is seeing a linear increase in the number of patients on dialysis. They agreed that there are large costs to start dialysis early. However, delaying dialysis and starting only when extremely urgent if needed, will overload the health care system.

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
Judgment	**Research evidence**	**Additional considerations**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify direct evidence to address the certainty of the evidence of resource requirements.	
Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**One systematic review directly addresses the cost-effectiveness of different renal replacement therapy (RRT)** (3) Kidney transplant (KT) was the most cost-effective RRT modality and peritoneal dialysis (PD) was more cost-effective than hemodialysis (HD). Most studies suggested that KT held a dominant position over HD and PD with both lower costs and higher effectiveness. Five studies suggested that increased uptake of KT and PD by new end-stage renal disease (ESRD) patients would reduce costs and improve health outcomes or would be more cost-effective than current practice patterns.	
Equity **What would be the impact on health equity?**		
Judgment	**Research evidence**	**Additional considerations**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify evidence to address equity for this specific question.	Equity might be affected due availability of centers and resources to allow all patients to start dialysis early. This will impact patient perceptions of good quality of dialysis care.

Acceptability Is the intervention acceptable to key stakeholders?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address acceptability for this specific question.	
Feasibility **Is the intervention feasible to implement?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question.	Early hemodialysis is costly and challenging to implement. The number of people requiring hemodialysis is increasing in Saudi Arabia. Efforts are being made towards early prevention. Peritoneal dialysis may include lower costs and higher quality of life than hemodialysis.

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			

	Judgment						
Balance of effects	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	**Probably no**	Probably yes	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

Conclusions

Recommendation

In previously adults requiring KRT for deteriorating CKD, the CKD Task Force suggests initiating KRT late (i.e., eGFR 5-7 mL/min/1.73m2) or based on severe symptoms* over initiating KRT early (i.e., eGFR 10-15 mL/min/1.73m2) or based on moderate symptoms (conditional recommendation, very low certainty in the evidence of effects).

*** Severe uremic symptoms and/or uncontrollable fluid overload**

Justification

The panel judged that the balance of desirable and undesirable consequences does not favor the use of initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms over initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms* in this population. Specifically, the panel felt that most patients will get benefit due to a balance that probably favors initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms* in the context of very low certainty evidence, large costs in the context of initiating early KRT, cost-effectiveness that probably favours initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*, and probably reduce equity.

* Severe uremic symptoms and/or uncontrollable fluid overload

Subgroup considerations

No subgroup considerations were made for this recommendation.

Implementation considerations

No implementation considerations were made for this recommendation because there was no research evidence identified.

Monitoring and evaluation

No monitoring and implementation considerations were made for this recommendation.

Research priorities

The NICE guideline [2] identified a research need for the following question: What is the most clinical and cost-effective strategy for timing of pre-emptive transplantation? A question raised by the CKD Task Force was whether initiation of dialysis can be delayed safely with aggressive medical management [24].

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Appendix 1 - Summary of findings

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*	Risk difference with initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms
Mortality - HD or PD assessed with: early vs late dialysis initiation based on eGFR follow-up: mean 3.6 years[a]	828 (1 RCT)[1]	⨁⨁◯◯ Low[b,c]	**RR 1.04** (0.87 to 1.24)	Study population	
				366 per 1,000	**15 more per 1,000** (48 fewer to 88 more)
				Low	
				257 per 1,000[2,d]	**10 more per 1,000** (33 fewer to 62 more)
				High	
				516 per 1,000[2,e]	**21 more per 1,000** (67 fewer to 124 more)
Mortality: age<18 years - HD or PD follow-up: 1.3 years	18133 (2 observational studies)[3,4]	⨁◯◯◯ Very low[b,f]	**HR 1.25** (0.96 to 1.64)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)
Cognitive impairment - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[a]	-	-	-	-	-
Growth age<18 years - HD or PD assessed with: early vs late dialysis initiation based on eGFR[a]	2963 (1 observational study)[3]	⨁◯◯◯ Very low[b,c]	-	The mean growth age<18 years - HD or PD was **0**	MD **0.03 lower** (0.15 lower to 0.09 higher)
Impact late referral rates - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[a]	-	-	-	-	-
Patient, family/caregiver health related QoL - HD or PD assessed with: assessed with: early vs late dialysis initiation based on eGFR[a]	642 (1 RCT)[1]	⨁◯◯◯ Very low[b,c]	-	The mean patient, family/caregiver health related QoL - HD or PD was **0**	MD **0** (0.03 lower to 0.03 higher)
Pre-emptive transplantation rates: age<18 years - HD or PD assessed with: assessed with: early vs late dialysis initiation based on eGFR[a]	2963 (1 observational study)[3]	⨁◯◯◯ Very low[b,c]	**HR 0.97** (0.89 to 1.06)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with initiation of KRT at late eGFR (5-7 mL/min/1.73m2) or based on severe symptoms*	Risk difference with initiation of KRT at early eGFR (10-15 mL/min/1.73m2) or based on moderate symptoms
Proportion receiving RRT after assessment - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[a]	-	-	-	-	-
Symptom scores - HR or PD (assessed with: early vs late dialysis initiation based on eGFR) - not reported[a]	-	-	-	-	-
Adverse events - HD or PD assessed with: assessed with: early vs late dialysis initiation based on eGFR follow-up: 3.6 years[a,g]	828 (1 RCT)[1]	⨁⨁◯◯ Low[b,c]	**RR 0.89** (0.75 to 1.06)	Study population	
				410 per 1,000	**45 fewer per 1,000** (103 fewer to 25 more)
Mortality: Transplant at eGFR>/=15ml/min vs <10ml/min	454 (1 observational study)[5]	⨁◯◯◯ Very low[b,c]	**HR 1.35** (0.89 to 2.05)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)
				Low	
				87 per 1,000	**29 more per 1,000** (9 fewer to 84 more)
Mortality: Transplant at eGFR 10 -14.9 ml/min vs <10ml/min	541 (1 observational study)[5]	⨁◯◯◯ Very low[b,c]	**HR 0.99** (0.69 to 1.42)	Study population	
				0 per 1,000	**-- per 1,000** (-- to --)
				Low	
				87 per 1,000	**1 fewer per 1,000** (26 fewer to 34 more)

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Explanations

h. Early=10-14 ml/min, late=5-7 ml/min

i. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.
j. One study that carried all weight for the overall effect estimate rated as high risk of bias.
k. Mortality rate based on a population-based cohort study of 725 Swedish adult patients with CKD that received peritoneal dialysis.
l. Mortality rate based on a population-based cohort study of 1791 Swedish adult patients with CKD that received hemodialysis.
m. Studies that carried large weight for the overall effect estimate rated as high risk of bias.
n. Infection events

Question 10. Should transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators versus not transferring between modalities of KRT or discontinuing KRT based on suitable clinical indicators* or doing either at a later stage be used in patients with CKD currently receiving KRT?*

Population:	patients with CKD currently receiving KRT
Intervention:	transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators*
Comparison:	not transferring between KRT modalities or discontinuing KRT, or doing either at a later stage (any clinical indications)
Main outcomes:	Mortality; Cognitive impairment (dichotomous) and new outcome: school performance in children; Growth; Impact late referral rates; Patient, family/caregiver health related QoL; Pre-emptive transplantation rates; Proportion receiving RRT after assessment; Symptom scores; Adverse events
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (1).
Conflict of interests:	**KSA conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dalbhi Muneera Rashid Al-Jelaify Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari **Panel members recused as a result of risk of conflicts of interest:** None.

Assessment

Problem Is the problem a priority?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	• Different options are available to patients with end-stage kidney disease (ESKD) to replace the function of their failing kidneys. Over the years, the search for the optimal renal replacement therapy (RRT) has progressively given way to the understanding that most patients will use different modalities at different time points of their disease (2). • "Integrated care" is a model that intends to consider treatment pathways rather than individual RRT techniques (2). • RRT modalities that should be made available within an integrated care program should not be restricted to PD and CHD, but should also include home-based HD, satellite HD, conservative care, and the different modalities of transplantation (2). • Given that more than one-third of patients will experience a transition to another RRT modality, particularly to facility-based conventional hemodialysis (CHD), within the first 3 years on PD, a better understanding of morbidity and mortality associated with this transition is critically important for the care of patients with ESKD (2)	
Desirable Effects **How substantial are the desirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	*See Appendix 1*	The panel noted that there was uncertainty around the benefits of the interventions. The choice of the RRT modality varies according to the type or severity of the patient.
Undesirable Effects **How substantial are the undesirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**

○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	*See Appendix 1*	The panel noted that there was uncertainty around the harms of the interventions. The choice of the RRT modality varies according to the severity of the clinical condition.

Certainty of evidence
What is the overall certainty of the evidence of effects?

Judgment	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No direct research evidence identified to address the certainty of the evidence of benefits and harms of interventions.	The panel agreed that there is insufficient evidence since it can be unethical to conduct a study under the characteristics of the intervention and comparison.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgment	Research evidence	Additional considerations
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not identify primary studies addressing the relative importance of the outcomes for this specific question. • Transitioning from one modality to another can have an enormous impact on the well-being and lifestyle of patients and their caregivers (2). • One study reported six categories of transitions of care during advanced CKD: (1) transition from non-dialysis-dependent CKD to de novo dialysis therapy; (2) transition from non-dialysis dependent CKD to pre-emptive transplantation; (3) transition among or across dialysis modalities, formats and frequency (hemodialysis to peritoneal dialysis or vice versa, in-center to home; (4) transition from dialysis therapy to kidney transplantation; (5) transition from a gradually failing kidney transplantation back to dialysis therapy; and (6) transition from any of the above stages to partial or full transitions can be present in patients with CKD (3). • There is uncertainty regarding what factors make patients' transition and their caregivers' experiences successful, stressful, or even unsuccessful. Moreover, data are lacking on how patients and their caregivers perceive such a transition, what their ideas and emotions are, and how they cope with them (2).	

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know		

Resources required How large are the resource requirements (costs)?		
Judgment	**Research evidence**	**Additional considerations**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	We did not identify primary studies addressing the resources required to manage CKD patients with renal replacement therapy.**Cost of disease** • Chronic kidney disease (CKD) affects about 10 percent of the population worldwide, including an estimated 1 in 7 adult Americans.1 In the United States, Medicare spending totals more than $64 billion each year to care for Americans with CKD and an additional $34 billion to care for patients with end-stage renal disease (ESRD) (4). • The impact of kidney disease extends well beyond the United States; over 2 million people worldwide have ESRD. In higher-income countries, treatment costs are enormous: a 2010 report from the UK National Health Service estimates its annual CKD spending at £1.45 billion—more than half of which was for RRT (5)—while Australia has estimated it will spend over $12 billion on ESRD patients through 2020 (6). At the same time, RRT remains entirely unaffordable to the majority of ESRD patients in low- and middle-income countries throughout the world, with over 1 million people dying annually from lack of treatment (7). **Cost of interventions** • Initial assessment clinic: annual cost per patient £2,537 (SAR 13,137), annual expenditure £6,421,018 (SAR 33,238,174).	

	• The mean total cost per HD session was calculated as 297 US dollars (USD) [1,114 Saudi Riyals (SR)], and the mean total cost of dialysis per patient per year was 46,332 USD (173,784 SR) (8). • One study conducted in Saudi Arabia described that an average annual cost of medical care per patient after transplantation in the first, second, third, and fourth year was US $133,291, US $14,233, US $5,536, and US $4,402; respectively. The average 4-year actual total cost per patient was US $210,779 and US $317,186.3 in the kidney transplant group and the HD group; respectively (p=0.017) (9). • One systematic review reported annual costs of HD and PD in low and middle-income countries. The annual cost per patient for hemodialysis (HD) ranged from Int$ 3,424 to Int$ 42,785, and peritoneal dialysis (PD) ranged from Int$ 7,974 to Int$ 47,971. Direct medical cost especially drugs and consumables for HD and dialysis solutions and tubing for PD were the main cost drivers (10).	
Certainty of evidence of required resources **What is the certainty of the evidence of resource requirements (costs)?**		
Judgment	**Research evidence**	**Additional considerations**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify direct evidence to address the certainty of the evidence of resource requirements.	
Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**

● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**One systematic review directly addresses the cost-effectiveness of different RRT.** KT was the most cost-effective KRT modality and PD was more cost-effective than HD. Most studies suggested that KT held a dominant position over HD and PD with both lower costs and higher effectiveness. Five studies suggested that increased uptake of KT and PD by new ESKD patients would reduce costs and improve health outcomes or would be more cost-effective than current practice patterns (11). According to a NICE 2018 review, "given the lack of clinical or cost-effectiveness evidence, specific recommendations about indicators for switching or discontinuing were not made, however, it was felt that it was appropriate to make some recommendations based on current good practice. These were not expected to have a substantial resource impact on the NHS in England. The committee confirmed that the recommendations were applicable to children and young people. The committee noted people with failing transplants may not be offered regular opportunities to discuss the option to switch modality, which may result in a delay in planning for other forms of RRT." (12) One SR reported the cost of dialysis from different countries in the low and middle-income countries. In this review, six articles adopted a provider perspective, two—the patient perspective, and one—the societal perspective. The review demonstrated that economic evaluation of RRT in low and middle-income countries faces methodological challenges. Due to this, the cost of dialysis was found to differ from one author to another, and in some countries, the cost differences between HD and PD were reported to be insignificant. However, even the limited knowledge about the cost of dialyzes in low- and middle-income countries clearly indicates that the cost is beyond the capability of the average individual to pay for these services. Dialyses will have to be included in the national social protection or they will not be available for the majority of cases. (10)	The panel observed that cost-effectiveness would favor the comparison. However, that would also mean the eventual death due to disease progression (terminal illness). Switching modalities is cost-incurring in nature.

Equity **What would be the impact on health equity?**		
Judgment	**Research evidence**	**Additional considerations**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify evidence to address equity for this specific question.	The panel noted that clinical decisions about discontinuing or transferring between any RRT, are supported by the health care system.

Acceptability Is the intervention acceptable to key stakeholders?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	We did not identify direct evidence to address acceptability for this specific question. Indirect evidence for the implementation of the multidisciplinary care (MDC) clinic for patients with advanced CKD suggested possible improvement in adherence to CKD intervention targets and good participants' acceptability of the MDC program. The program included clinical outcomes assessment, self-care advice, and KRT options (13).	The panel judged it to vary based on the severity of the condition across different types of patients.
Feasibility **Is the intervention feasible to implement?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question.	The panel observed that there was insufficient evidence to decide the feasibility of implementing RRT interventions. From clinical experience, the panel agreed that switching modalities is based on clinical needs. For example, a membrane failure in PD can facilitate a need to switch over to HD. The panel also agreed that discontinuing dialysis is a very difficult decision for clinicians worldwide, including in Saudi Arabia. The decision to start dialysis is easier than the decision to discontinue it.

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	Judgment						
Desirable Effects	Trivial	Small	Moderate	Large		**Varies**	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		**Varies**	Don't know
Certainty of evidence	Very low	Low	Moderate	High			**No included studies**
Values	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		**Varies**	Don't know
Feasibility	No	**Probably no**	Probably yes	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

Conclusions

Recommendation

In patients with CKD currently receiving KRT, the CKD Task Force suggests transferring between KRT modalities or discontinuing KRT based on suitable clinical indicators*, or doing either at a later stage (any clinical indications*) (conditional recommendation).

***Vascular access failure, peritoneal membrane failure or failure of kidney graft.**

Justification

The panel judged that the balance of desirable and undesirable consequences does not favor or favor the use of transferring between modalities of KRT or discontinuing KRT based on any suitable indicator over transferring between forms of KRT or discontinuing KRT (any clinical indications*) in this population. Specifically, the panel felt that most patients will get benefit due to cost-effectiveness that favours conservative management.

*Vascular access failures, peritoneal membrane failure or failure of kidney graft.

Subgroup considerations

No subgroup considerations were made for this recommendation.

Implementation considerations

No implementation considerations were made for this recommendation.

Monitoring and evaluation

No monitoring and evaluation considerations were made for this recommendation.

Research priorities

The NICE guideline [2] identified the following research need, confirmed by the CKD Task Force: What is the clinical and cost effectiveness of strategies for switching KRT modality?

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Appendix 1 - Summary of findings

No relevant clinical studies comparing various strategies for transferring or discontinuing KRT were identified.

Question 11. Should any frequency of regular review for any KRT modality or conservative management versus any other frequency of regular review be used in patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice?

Population:	patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice
Intervention:	any frequency of regular review for any KRT modality or conservative management
Comparison:	any other frequency of regular review
Main outcomes:	Mortality; Cognitive impairment; Growth ; Impact late referral rates; Patient, family/caregiver health related QoL; Pre-emptive transplantation rates; Proportion receiving RRT after assessment; Symptom scores; Adverse events
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (1).
Conflict of interests:	**KSA conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dalbhi Muneera Rashid Al-Jelaify Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari **Panel members recused as a result of risk of conflicts of interest:** None.

Assessment

Problem Is the problem a priority?		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	• The incidence and prevalence of CKD has been steadily rising in the KSA, even surpassing the estimates for Western Europe and North America (2)(3). • Complications from CKD and CKD itself cause a high disease and economic burden on the population and strain healthcare systems. Based on current estimated cost of a dialysis session as well as manpower and overhead and utility costs, the estimated total direct cost for managing RRT patients in the KSA is $506,723,847 per year (4). • The high burden of renal disease is also reflected by the growing number of people requiring RRT. According to SCOT estimates, the net increase in the population requiring dialysis is 7.7% annually. Among the dialysis treatment modalities, hemodialysis is the most commonly used by patients (80%), and hemodiafiltration is used by the remaining 20% (5)	
Desirable Effects **How substantial are the desirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	*See Appendix 1*	The panel agreed that a quarterly (every 2 or 3 months) review is advisable, especially for CKD patients stage 4 to 5. However, patients with a declining eGFR, should be reviewed more frequently. Overall, the panel considered that patients need to have more frequent reviews. This strategy can help to reduce mortality and morbidity.
Undesirable Effects **How substantial are the undesirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**

○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	*See Appendix 1*	The undesirable effects varies according to the decline of eGFR and how rapidly it declines.
Certainty of evidence **What is the overall certainty of the evidence of effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified to address the certainty of the evidence of benefits and harms of interventions.	
Values **Is there important uncertainty about or variability in how much people value the main outcomes?**		
Judgment	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	We did not identify primary studies addressing the relative importance of the outcomes for this specific question.**International report described the following regarding the relative importance of outcomes and patients' preferences for the screening and diagnosis of CKD**Patient representatives and advocates described that there is a strong belief that patients overwhelmingly prefer earlier CKD screening and diagnosis and that patient education has the potential to improve self-management and disease prognosis (6).Individual and population-level risk of having CKD and experiencing its complications should inform whether persons should be screened for CKD. Decisions concerning the age to initiate testing, the frequency of repeat testing, and the time to forgo or end testing should all be individualized based upon risk factors, preferences, and life expectancy (6).**One systematic review described the following regarding the relative importance of outcomes and patients' preferences for hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT)**Patients highly value the benefits of HD, PD, and KT (7). The utility values for HD ranged from 0.44 to 0.72; for PD from 0.53 to 0.81; for KT from 0.57 to 0.90. In seven of the nine studies, KT utility was higher than PD utility, and PD utility was higher than HD utility. In two of the nine studies, KT utility was higher than PD and HD utility, with PD and HD utility being equal. One study suggests that conflicting results of utility valuations existed among different valuation methods. For example, continuous ambulatory PD patients' EQ-5D scores were higher than those of center	

	HD patients, while continuous ambulatory PD patients' SG and TTO scores were lower than those of center HD patients (7).	
Balance of effects **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know		
Resources required **How large are the resource requirements (costs)?**		
Judgment	**Research evidence**	**Additional considerations**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We did not identify primary studies addressing the resources required to address resources required for this specific question.**Cost of interventions** • Initial assessment clinic: annual cost per patient £2,537 (SAR 13,137), annual expenditure £6,421,018 (SAR 33,238,174). • The mean total cost per HD session was calculated as 297 US dollars (USD) [1,114 Saudi Riyals (SR)], and the mean total cost of dialysis per patient per year was 46,332 USD (173,784 SR) (8). • One study conducted in Saudi Arabia described that an average annual cost of medical care per patient after transplantation in the first, second, third, and fourth-year was US $133,291, US $14,233, US $5,536, and US $4,402; respectively. The average 4-year actual total cost per patient was US $210,779 and US $317,186.3 in the kidney transplant group and the HD group; respectively (p=0.017) (9).	The panel agreed that it depends on patients severity of the disease and the rate of disease progression. More severe decline in eGFR warrants more frequent review which can impact the cost and resources.
Certainty of evidence of required resources **What is the certainty of the evidence of resource requirements (costs)?**		

Judgment	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No direct research evidence identified to address the certainty of the evidence of resource requirements.	
Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	One study assessed the value for money and budget impact of offering hemodialysis (HD) as a first-line treatment, or the HD-first policy, and the peritoneal dialysis (PD) first policy compared to a supportive care option in patients with end-stage renal disease (ESRD) in Indonesia (10). The PD-first policy was found to be more cost-effective compared to the HD-first policy. Budget impact analysis provided evidence on the enormous financial burden for the country if the current practice, where HD dominates PD, continues for the next five years. **Costs:** *Life years saved*- Supportive care option: 0.21- PD first option: 5.93- HD first option: 5.93*Quality-adjusted life years (QALY)*- Supportive care option: 0.076- PD first option: 4.40- HD first option: 4.34*Incremental cost-effectiveness ratio (ICER)*- Supportive care: Not reported- PD first option: 193.2 million IDR- HD first option: 2017.4 million IDR*Cost-effectiveness acceptability*- At the threshold of willingness to pay 43 million IDR (1 GDP), supportive care was the best option. (probability = 1.00)- At willingness to pay > 190million IDR, PD first was the most cost-effective option (probability > 0.5)- HD first was not the best cost-effective option at any level of willingness to pay. *A CADTH Review* (11) *demonstrated the results from the cost effectiveness acceptability curve that, supportive care remained the most cost-effective option up to a threshold of < 200 Million IDR, after which PD first option was the most cost effective. HD first option was not the best cost-effective option at any level of willingness to pay (43 million IDR equates roughly to $4,000 CAD).*	The panel described that the intervention costs and frequency in reviewing patients can increase costs.
Equity **What would be the impact on health equity?**		
Judgment	**Research evidence**	**Additional considerations**

○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify evidence to address equity for this specific question.	The judgment of probably no impact was related to a system of full healthcare coverage in Saudi Arabia.

Acceptability **Is the intervention acceptable to key stakeholders?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address acceptability for this specific question. One evidence from a study favors the concept of the conservative management program to patients who have chosen to forego dialysis. Evidence provided information on the survival in a large cohort of CM patients in comparison to patients who received RRT and demonstrated that in patients aged >75 years with high extra-renal comorbidity, the survival advantage conferred by RRT over CM is likely to be small (12) . A protocol for a pilot RCT is set to explore the feasibility and acceptability of Conservative Kidney Management Options and Advance Care Planning Education—COPE, change in communication of preferences, and differences in the intervention's effects on knowledge and communication of preferences by race (13).	

Feasibility **Is the intervention feasible to implement?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question.	- Te panel described that the Saudi Arabia health care system supports different RRT strategies.

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		**Varies**	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		**Varies**	Don't know
Certainty of evidence	Very low	Low	Moderate	High			**No included studies**
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

Conclusions

Recommendation

In patients requiring KRT for CKD or opting for conservative management once they are established on their option of choice, the CKD Task Force suggests regular review at a frequency tailored to the KRT modality or conservative management (conditional recommendation).

Justification

The panel judged that the balance of desirable and undesirable consequences does not favor or favor the use of any frequency of review for any KRT modality or conservative management over any other review strategy in this population. Specifically, the panel felt that most patients will probably accept any other review strategy, and it will probably be feasible to implement.

Subgroup considerations

No subgroup considerations were made for this recommendation.

Implementation considerations

No implementation considerations were made for this recommendation.

Monitoring and evaluation

No monitoring and evaluation considerations were made for this recommendation.

Research priorities

The NICE guideline [2] identified the following research needs, confirmed by the CKD Task Force:

- What is the most clinical and cost-effective frequency of review for people on PD, hemodiafiltration, hemodialysis or conservative management? [2]
- Could a CKD Frailty Index be used to identify clinically important changes over time in individuals before dialysis and after initiation of dialysis? [24]
- Are the changes different with hemodialysis versus PD? [24]
- Is it possible to predict which patients improve and which get worse? [24]
- To what extent do uremic symptoms change after initiation of dialysis? [24]

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Appendix 1 - Summary of findings

No relevant clinical studies comparing how frequently people on different forms of KRT should be reviewed were identified.

Question 12. Should any type of information, education, or support versus any other type of information, education, or support be used in patients requiring KRT or conservative management (and their families or caregivers as appropriate)?

Population:	patients requiring KRT or conservative management (and their families or caregivers as appropriate)
Intervention:	any type of information, education, or support
Comparison:	any other type of information, education, or support
Main outcomes:	Content of information: Symptoms; Content of information: Prognosis; Content of information: Mode of access; Content of information: Services; Content of information: Adherence; Content of information: Transplant listing; Content of information: How to approach potential living donors; Content of information: Acute situations; Content of information: Kidney function and CKD; Content of information: End of life care; Preferred format of information provision: Depth and timing of information; Preferred format of information provision: Personalisation; Preferred format of information provision: Classes and tours; Preferred format of information provision: Multiple formats; Preferred format of information provision: Target of education/information; Decision making: Availability of choice; Decision making: Reversibility; Impact of transport on care; Psychological support; Barriers to good care; Facilitators of good care; Impact of treatment on lifestyle; Information sources other than healthcare professionals (e.g. support groups, online resources); Information around transitions between forms of RRT; Modality of RRT;
Setting:	Outpatients
Perspective:	Clinical recommendation - population perspective
Background:	International guidelines define chronic kidney disease (CKD) by a reduced glomerular filtration rate (GFR) of <60 mL/min per 1.73 m2 or by markers of kidney damage, or both, lasting at least three months. CKD may result in end-stage renal disease (ESRD) and is often complicated by cardiovascular disease. Early detection of CKD may allow for interventions to help prevent progression or complications (1).
Conflict of interests:	**KSA conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation):** Khalid Alhasan Sultan Al Dalbhi Muneera Rashid Al-Jelaify Khalid Ibrahim Almatham Yasser Sami Amer Jameela Kari Ahmed Mitwalli

	Mohammed Alghonaim **Panel members recused as a result of risk of conflicts of interest:** None.

Assessment

Problem **Is the problem a priority?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The NICE guideline on patient experience in adult NHS services (CG138) outlines the key principles of general care. It is important to identify and address the unique needs of people with specific conditions and those following the identification that an adult, child or young person may require renal replacement therapy or conservative management. Information and support is required to enable people to make the decision of whether to commence renal replacement therapy or not and if RRT, what modality of renal replacement therapy to use. Information and support can help to ensure that the person makes the right decision for themselves or their child and this in turn can lead to better outcomes including adherence to treatment (2)	
Desirable Effects **How substantial are the desirable anticipated effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		
Undesirable Effects		

How substantial are the undesirable anticipated effects?		
Judgment	**Research evidence**	**Additional considerations**
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
Certainty of evidence **What is the overall certainty of the evidence of effects?**		
Judgment	**Research evidence**	**Additional considerations**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The certainty in the evidence is reduced as a result of methodological limitations and concerns regarding adequacy for the assessment of outcomes.	Based on the lowest certainty of the critical outcomes.
Values **Is there important uncertainty about or variability in how much people value the main outcomes?**		
Judgment	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The pre-dialysis education program (PDEP) has been generally introduced as an acceptable tool in increasing the rates of peritoneal dialysis (PD) in ESRD patients. A retrospective cohort study showed that PDEP was associated with a significant reduction in hemodialysis (HD) rates [OR (95% CI) = 0.11 (0.05-0.24); P-value < 0.001]. The PDEP positively impacted the rate of PD while PD was associated with favorable outcomes and lower infection rates, emphasizing the importance of an educational program [Alghamdi 2020]. Moreover, a series of structured PDEP sessions for the patients progressing to ESRD have facilitated their selection of RRT [Mirza 2020]. Educating health promotion strategies have proven effective in improving self-esteem and quality of life in patients undergoing hemodialysis [Poorgholami 2015, Ghadam 2015].	
Balance of effects		

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		The panel agreed on the judgment favors of the intervention based on their clinical experience.

Resources required How large are the resource requirements (costs)?		
Judgment	**Research evidence**	**Additional considerations**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not identify primary studies addressing the resources required to manage CKD patients with conservative management or renal replacement therapy.**Cost of interventions** • Initial assessment clinic: annual cost per patient £2,537 (SAR 13,137), annual expenditure £6,421,018 (SAR 33,238,174). The mean total cost per HD session was calculated as 297 US dollars (USD) [1,114 Saudi Riyals (SR)], and the mean total cost of dialysis per patient per year was 46,332 USD (173,784 SR) (Al Saran K, 2012). • One study conducted in Saudi Arabia described that an average annual cost of medical care per patient after transplantation in the first, second, third, and fourth-year was US $133,291, US $14,233, US $5,536, and US $4,402; respectively. The average 4-year actual total cost per patient was US $210,779 and US $317,186.3 in the kidney transplant group and the HD group; respectively (p=0.017) (Al-Jedai A, 2012).	

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
Judgment	**Research evidence**	**Additional considerations**

○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify direct evidence to address the certainty of the evidence of resource requirements.	
Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
Judgment	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We did not identify direct evidence to address cost-effectiveness of this specific question.	
Equity **What would be the impact on health equity?**		
Judgment	**Research evidence**	**Additional considerations**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not identify direct evidence to address equity for this specific question.	
Acceptability **Is the intervention acceptable to key stakeholders?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes	We did not identify direct evidence to address acceptability for this specific question. Quality-of-life issues for people with CKD include depression and anxiety, which are prevalent among people undergoing hemodialysis (3). Small studies addressed whether screening, counseling or education might support social interactions, [Kazami 2011] self-esteem (one	

○ Varies ○ Don't know	quasi-experimental study of 50 people), [Poorghalami 2015] or the families of children undergoing peritoneal dialysis (4).	

Feasibility **Is the intervention feasible to implement?**		
Judgment	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We did not identify direct evidence to address feasibility for this specific question. Studies that examined areas for improvement in the delivery of care included a cross-sectional study in Palestine that found self-reported adherence to diet, fluid restriction, medications, and hemodialysis sessions to be optimal in about 56% of 220 people with end-stage renal disease (5). A record review in New York found that lack of motivation, dialysis dependence, and comorbidities predicted failure to complete pre-transplantation preparation (6). These authors suggested that interventions such as timely referral, educational resources, counseling, and support might increase workup completion rates or improve therapeutic outcomes	The panel agreed that CKD educators are present in most institutions and hospitals within the Kingdom. They encourage having a dialogue with the patient to explain the options, the procedures and familiarise them with life on RRT. The panel also endorsed that doctors should initiate the initial education with the patient and provide materials and resources to them. This is not always the case in rural hospitals or institutions along the periphery of the Kingdom.

Summary of judgments

	Judgment						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know

	Judgment						
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

In patients requiring KRT or conservative management (and their families or caregivers as appropriate), the CKD Task Force suggests using individualized information, education, or support rather than other types of information, education, or support (conditional recommendation, moderate certainty in the evidence of effects).

Justification

The panel judged that the balance of desirable and undesirable consequences favors the use of information, education, or support over no information, education, or support in this population. Specifically, the panel felt that most patients will get benefit due to a balance that favors information, education, or support in the context of moderate certainty evidence, moderate savings, and cost-effectiveness that probably favours information, education, or support.

Subgroup considerations

No subgroup considerations were made for this recommendation.

Implementation considerations

- CKD educators are provided in hospitals and different institutions in KSA.
- Doctors should also educate patients, which is the current practice in KSA.
- Scouting/follow-up patients and their conditions.
- Patients should be educated and that should be documented in their medical records as required by the Saudi National Accreditation (CBAHI) which is also checked in their accreditation surveys and is mandatory.

Monitoring and evaluation

No monitoring and evaluation considerations were made for this recommendation.

Research priorities

The NICE guideline [2] identified the following research needs, confirmed by the CKD Task Force, were:

- What is the clinical and cost effectiveness of having keyworkers present in the context of KRT? [2]
- What is the clinical and cost effectiveness of using decision aids in the context of KRT? [2].
- Can an integrated care model improve quality and decrease costs for patients with kidney disease as they transition from CKD G5 to G5D? [24].
- What is the preferred timing for educating patients regarding dialysis modalities? Does the optimal time vary based on patient characteristics? [24].
- What is the optimal content and format for educating patients regarding the advantages and disadvantages of each modality? How do we check their understanding? [24]

The CKD Task Force proposes that researchers develop studies (RCTs) to assess the impact of interventions, namely education and support to patients, families, and caregivers to evaluate the effectiveness and impact on outcomes like morbidity and mortality. .

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Appendix 1 - Summary of findings

Outcomes	Impact
Content of information: Symptoms	People mentioned information on what they may experience and how to manage them as an area they appreciated or would have appreciated. [a]
Content of information: Prognosis	People mentioned information on the likely long term consequences of their disease and life expectancy, particularly in the context of transplant as an area they appreciated or would have appreciated. [a]
Content of information: Mode of access	People mentioned information on the benefits and harms of different types of vascular access as an area they appreciated or would have appreciated. [a]
Content of information: Services	People mentioned information on the availability of support and transition from paediatric to adult as an area they appreciated or would have appreciated A study identified functional needs and home environmental barriers to social engagement through focus groups; mapped findings onto aspects of an established program, which includeshome visits with an occupational therapist, nurse,and handyman to provides ≤$1,300 worth of repairs,modifications, and devices; and piloted the program(Seniors Optimizing Community Integration toAdvance Better Living with ESRD [SOCIABLE])among 12 older adult HD patients. A home-based intervention addressing physical and social functioning of low socioeconomic status older adults on HD therapy was feasible and acceptable. [1,b]
Content of information: Adherence	People mentioned information on the importance of adherence and consequences of non-adherence as an area they appreciated or would have appreciated. [b]
Content of information: Transplant listing	People mentioned information on the actual practicalities of listing an area they appreciated or would have appreciated [b]
Content of information: How to approach potential living donors	People mentioned information on how to approach potential living donors in an area they appreciated or would have appreciated. [b]
Content of information: Acute situations	People mentioned information on what to expect with acute situations and how to handle them as areas they appreciated or would have appreciated A mixed method study demonstrated content gaps that included prognosis, decisionsupport, mental health and cognition, advance care planning, cost, and diet. Slide presentations used did not consistently reflect best practices related to health literacy. [2,b]
Content of information: Kidney function and CKD	People mentioned information to gain a basic understanding of their disease as an area they appreciated or would have appreciated. In a study, mean scores of the emotional and instrumental social support were 3.92 (± 0.78) and 3.81 (± 0.69) respectively, an indication of good support received. The most frequent sources of instrumental and emotional social support mentioned by participants were partners, spouse, companion or boyfriend and friends. [3,b]
Content of information: End of life care	People mentioned information on end of life care as an area they appreciated or would have appreciated. [b]
Preferred format of information provision: Depth and timing of information	People appreciate more complete information, provided in stages from an earlier starting point to avoid being overwhelmed. Patients with CKD stages 3 to 4 wanted information on slowing diseaseprogression and avoiding transplant Increasing access to culturally responsive transplant education in multiple languages, pairing appropriate content to the disease stage, and increasing system-wide follow-up as the disease progresses might help patients make more informed choices about transplant (Waterman, 2020).A study highlights the importance of improving pre-hemodialysis education to ensure that patients' expectations are realistic, as well as identifying individualized coping strategies by patients (Balogun, 2019). All participants were reluctant to initiate HD, but

Outcomes	Impact
	made the decision on advice from their physicians for varying reasons.Even though the majority of participants identified several difficulties with being on HD, they also had positive coping strategies, and the majority indicated that they would make the same decision to initiate HD.[a]
Preferred format of information provision: Personalisation	People appreciated when information provided to them was individualised and tailored to their circumstances.Multidisciplinary education (MDE) enhanced participants' disease-specific knowledge and ability for coping. It also improved sympathy, helpfulness, and the mutual responsibilities of family members (Polner 2021)[a]
Preferred format of information provision: Classes and tours	People appreciated formal education methods like pre-dialysis classes and tours of facilities before beginning RRT.[a]
Preferred format of information provision: Multiple formats	People noted that they found it useful when information/education was provided in multiple formats, for example, oral and written Educational videos were well utilized with nearly half of the participants (42.5%) reporting that they watched at least one of the videos, and the majority reporting that the videos seen had an overall positive impact on health (Magnus, 2017)[a]
Preferred format of information provision: Target of education/information	People and their family/carers both noted that it was useful to have information and education with aspects tailored to each individual. In a semi-structured interview, self-care requirements, self-care deficit, and education and information management for self-care emerged as three categories. People were aware of the importance of carrying out their self-care. They also stated not to carry out the care actions rigorously enough showing some limitations. Finally, people's knowledge about their condition was usually acquired from the Internet and from their own experience rather than through consultations with a health team (Santana, 2020) Preliminary findings emphasized thar strengthening patient education strategies in the clinics,hospitals, and community settings should be given due attention by relevant healthcare professionals (Sowtali, 2020)[b]
Decision making: Availability of choice	People reported that they did not always feel like all options that should have been available to them, were available . Evidence suggests that various personal, family-related, psychological, social, and economic factors could affect the decision on the type of dialysis in patients. Therefore, basic infrastructures such as social support, education, and even the specialist and positive perspective of the Ministry of Health are required to choose this therapeutic method. (Ahmadi, 2018) According to an evidence (Cassidy , 2018), three themes influenced dialysis modality decision making: (i) Patient Factors: individualization, autonomy, and emotions; (ii) Educational Factors: tailored education, time and preparation, and available resources; and (iii) Support Systems: partnership with health care team, and family and friends. When providing decisional support to pre-dialysis stage patients, practitioners need to increase patients' decision self-efficacy, provide both haemodialysis and peritoneal dialysis pre-dialysis education, increase dialysis knowledge and provide professional support (Chen, 2018). Comparing patients who chose peritoneal dialysis (PD) and hemodialysis (HD), there were no differences on anxiety (p= 0.55), and depressionscores (p= 0.467), and stress (p= 0.854). Anxious (p= 0.007) and depressive (p= 0.030) patients presented lower levels ofphosphate than those not affected. There was a significant correlation between anxiety and depressionscores, anxiety and stress scores, depression and stress scores (Bezerra, 2018) Patients from low-GDP countries reported later in-formation provision, less information about other modalitiesthan CHD and lower satisfaction with information. The major-ity of modality decisions were made involving both patient andnephrologist. Patients reported subjective (e.g. quality of life andfears) and objective reasons (e.g. costs and availability of treat-ments) for modality choice (Jong, 2021)[b]
Decision making: Reversibility	People felt it was particularly important that the reversibility of any decisions they made was made clear[b]

Outcomes	Impact
Impact of transport on care	People noted that the availability of transport affected their ability to engage with RRT and was a significant psychological stressor during RRT [a]
Psychological support	People reported that they felt healthcare professionals were not always aware of the emotional and social distress associated with their RRT. People reported that having someone to talk to was important. Caregivers were found to be moderately burdened and their lives hadchanged for the worst as a result of caregiving. There were significant differences incaregiving outcome scores before and after the intervention (Alnazly , 2018)A study identified main themes like “immersion in an ocean of psychological tension,” which suggests that the mothers of the children undergoing hemodialysis are overwhelmed by the numerouspsychological pressures that they encounter during their children’s treatment. This theme was constituted by the subthemes “bewilderment between hope and despair,” “endless concerns,” “agony and sorrow,” and “a sense of being ignored (Pourghaznein, 2021) The findings from the dyadic perspective (Sousa, 2021) were conceptualized into twomajor themes: negative impacts (emotional distress, constraints on leisure and dailyactivities, impacts on couples’dynamics, and difficulties in meal planning) andunmet needs (educational, relational, financial, instrumental, and supportive needs). [a]
Barriers to good care	The most commonly cited barriers to home dialysis were lack of a care partner, lack of home space, and patient preference (Shamy 2021). Many participants felt that dialysis center technicians treated them poorly (Salter, 2015). Financial barrier: Some of the participants encountered periods of limited funds. Some of the participants experienced the effects of the hidden costs of dialysis, such as specific dietary requirements including specific, more costly food groups (Small, 2010). Many felt disempowered by the system, and worn down by the need to continually justify their requirement for assistance. For some, the time and expense that was required to gather all the documentation to apply for assistance resulted in them not completing this process and not receiving the assistance to which they were entitled (Walker, 2016). Some felt healthcare professionals underestimated their ability to accept and cope with their illness (Wells, 2013). Lack of information and dissatisfaction with their healthcare providers regarding perceptions of their care. Lack of explanation of results, not being completely honest, kept in the dark about the seriousness of the problem and not being clear about when dialysis would occur were problems patients described (Harwood, 2005) [b]
Facilitators of good care	Patients thought 1:1 time with transplant team members was helpful. Patients wanted additional information sources as well, without losing 1:1 time(Korus, 2011). Hospital staff also played a key role, including teachers, youth workers and nurses. Being able to trust healthcare staff was valued highly (Wells, 2013). Patients identified needing time to absorb information and adjust to the approaching dialysis. Some reported how it was hard difficult to grasp and absorb the information (Harwood, 2005). The importance/effect of a good nurse/patient relationship. Most patients wanted to discuss the importance of good care received by nurses and how it affected their condition. It is valuable for the nurse to listen to the dialysis patients and hear their views, and incorporate these views in care planning (KABA, 2007) [b]
Impact of treatment on lifestyle	People mentioned information on of any modality choice, including limitations on travel, and sexual activity as areas they appreciated or would have appreciated. [b]
Information sources other than healthcare professionals (e.g. support groups, online resources)	People valued peer support as a useful format of providing information or education when presented in an open, unbiased and supportive manner [b]
Information around transitions between forms of RRT - not reported	

Outcomes	Impact
Modality of RRT	People mentioned information on the benefits and harms of different modalities of RRT and conservative management as an area they appreciated or would have appreciated. There was a significant impact of PDEP on reducing HD choice. Most of the PD patients (81.8%) did not have an infection as compared to 42.3% of the HD patients. HD was also associated with increased admission days.(Alghamdi, 2020). Five themes related to continuation or discontinuation of HHD emerged: (1) degree of independence (increasedflexibility, burden of therapy), (2) availability of support (emotional andphysical support and caregiver burden), (3) technical aspects (familiarity with machine), (4) home environment (ability to organize supplies, space in home), and (5) attitude and expectations (positive or negative outlook about performing HHD). For each theme, positive aspects facilitated continuation of HHD and negative aspects contributed to discontinuation of HHD (Seshasai, 2019)[b]

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Explanations

a. Overall assessment of certainty: HIGH
b. Overall assessment of certainty: MODERATE

14.9. Cost tables

Class	Drug	Strength	Cost per package size	
			Lowest price	Highest price
Angiotensin converting enzyme inhibitors	Lisinopril	5 mg	12 SAR	26 SAR
		10mg	40 SAR	20 SAR
		20 mg	15 SAR	65 SAR
	Captopril	mg/ml	140 SAR	165 SAR
		25 mg	15 SAR	20 SAR
		50 mg	25 SAR	35 SAR
	Enalapril	5mg	12 SAR	26 SAR
		10 mg	20 SAR	44 SAR
		20mg	14 SAR	60 SAR
	Fosinopril	10 mg	42 SAR	52 SAR
		20 mg	78 SAR	
	Perindopril	5 mg	34 SAR	
		10 mg	45 SAR	
Angiotensin receptor blocker	Azilsartan	40 mg	65 SAR	
		80 mg	100 SAR	
	Candesartan	8 mg	23 SAR	50 SAR
		16 mg	55 SAR	
		32 mg	77 SAR	
	Losartan	50 mg	42 SAR	55 SAR
		100 mg	80 SAR	98 SAR
	Olmesartan	20 mg	37 SAR	71 SAR
		40 mg	50 SAR	70 SAR
	Valsartan	80, 160, 320 mg	35 SAR	
	Telmisartan	40, 80 mg	50 SAR	
	Irbesartan	150, 300 mg	45 SAR	60 SAR
	Eprosartan	600 mg	100 SAR	
Aldosterone antagonists	Spironolactone	25, 100 mg	9 SAR	25 SAR
	Eplerenone	50 mg	61 SAR	
Calcium channel blockers	Amlodipine	2.5, 5, 10 mg	13 SAR	70 SAR
	Nifedipine	10, 20,30, 50mg	6 SAR	50 SAR
	Nimodipine			
Diuretics	Indapamide	1.5 mg	25 SAR	
	Hydrochlorothiazide	depends on the combination		

SAR: Saudi Riyal.

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Attributions

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For Questions 5-12, this guideline draws on NICE guidance © NICE (2018) Renal replacement therapy and conservative management (NICE-NG107, 2018). Available from www.nice.org.uk/guidance/ng107 All rights reserved. Subject to Notice of rights.

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14.11. Approvals

Approval	Details
Approval Authority	Saudi Health Council Scientific Committee
Final Approval Authority	Ministry of Health, Saudi Arabia
Administrator	Fatima Alsinan
Final Approval Date	To be confirmed