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The Saudi Center for
Evidence Based Health Care

Hemodialysis

Clinical Practice Guideline on the Timing of Initiation of Dialysis

April 2014

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Executive summary

Introduction

Initiating chronic dialysis has major implications for patients and health care systems around the world and in Saudi Arabia. Global prevalence of renal replacement therapy has almost doubled within the past two decades. In Saudi Arabia, the rate of increase in prevalence has been more pronounced. The prevalence of hemodialysis has almost doubled within the past decade.

When patients reach advanced stages of chronic kidney disease (CKD), there is a need to identify a dialysis threshold. Before this proposed threshold starting dialysis will add no benefits but beyond it there may be risks to patients.

Methodology

This clinical practice guideline is a part of the larger initiative of the Ministry of Health of the Kingdom of Saudi Arabia (KSA) to establish a program of rigorous adaptation and de novo development of guidelines. The ultimate goals are to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For the selected question we updated existing systematic reviews that were used for the Canadian Society of Nephrology 2014 clinical practice guidelines for timing the initiation of chronic dialysis.[1] We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment,
Development and Evaluation) approach.[2] We used this information to prepare *evidence to recommendation tables* used by the guideline panel to follow a structured consensus process and transparently document all decisions made during the meeting (see **Appendix 1**). The guideline panel met in Riyadh on December 4th and 5th, 2013 and formulated the recommendation during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[3]

How to use these guidelines

The guideline panel developed and graded the recommendations and assessed the quality of the supporting evidence according to the GRADE approach.[4] Quality of evidence (confidence in the available estimates of treatment effects) is categorized as: high, moderate, low, or very low based on consideration of risk of bias, directness, consistency and precision of the estimates. High quality evidence indicates that we are very confident that the *true* effect lies close to that of the estimate of the effect. Moderate quality evidence indicates moderate confidence, and that the *true* effect is likely close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality evidence indicates that our confidence in the effect estimate is limited, and that the *true* effect may be substantially different. Finally, very low quality evidence indicates that the estimate of effect of interventions is very uncertain, the *true* effect is likely to be substantially different from the effect estimate and further research is likely to have important potential for reducing the uncertainty.

The strength of recommendations is expressed as either strong ('guideline panel recommends…') or conditional/weak ('guideline panel suggests…') and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades is essential for sagacious clinical decision making.

Table 1: 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 a quality criterion or performance indicator.	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 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.

Key question

Among adult patients (age 18 years or older) with advanced (stage 5) chronic kidney disease, what are the effects of an intent-to-initiate dialysis early (eGFR 10-14 ml/min) strategy compared with an intent-to-defer dialysis (eGFR 5-7 ml/min) strategy?

Recommendation

The Kingdom of Saudi Arabia Ministry of Health guideline panel recommends against an "intent- to- start-early" and recommends for an "intent-to-defer" strategy for initiating dialysis in adult patient (age 18 years or older) with stage 5 CKD (an eGFR <15 ml/min/1.73m^2) (strong recommendation, moderate quality evidence)

Remarks:

- This recommendation applies to adult patients who are 18 years old or older and does not apply to adolescence between 13 and 18 years old. The KSA MoH panel agreed that patients aged 13-18 years are likely to behave clinically different than adults for many reasons including small body size and going through maturity period. This group of patients (13-18 years old) is considered adult by the KSA MoH regulations and they are typically admitted to adult inpatient services. This creates a challenge in managing dialysis patients in this age group due to variation in comfort level among adult nephrologists who are expected to deal with this group especially when admitted.

- This recommendation applies to patients planning to use either chronic hemodialysis or chronic peritoneal dialysis. We do not consider pre-emptive transplantation, initiation of dialysis after failed transplant, urgent initiation of dialysis for acute kidney failure, conservative management without dialysis, or paediatric populations.

- Patients comorbidities and age, modality education and selection, rate of decline in eGFR, local waiting time for access (vascular access creation and maturation or peritoneal dialysis catheter insertion), access to interventional radiology and diagnostic imaging and availability of staff, physical space, equipment, or other resources re-

quires for provision of a chosen modality are all factors that may influence the decision about timing of initiation of dialysis.

- Adherence to this recommendation requires availability of timely follow-up with a nephrologist to closely monitor clinical indications for dialysis initiation. These clinical indications for the initiation of dialysis include: symptoms of uremia, fluid overload, hyperkalemia or academia that are refractory to medical management, or other conditions or symptoms that are likely to be ameliorated by dialysis. In the absence of these factors, eGFR should not serve as a sole criterion for the initiation of dialysis unless it is ≤ 6 ml/min/1.72m^2.
- The 'intent-to-defer' strategy pertains specifically to timing of dialysis initiation, and does not mean that patients should be referred to nephrologists at a later stage (lower level of kidney function).

Introduction

Initiating chronic dialysis has major implications for patients and health care systems around the world and in Saudi Arabia. Global prevalence of renal replacement therapy has almost doubled within the past two decades at a rate of > 6% per year. This growth is far beyond what is anticipated secondary to population growth and aging and it adds enormous burden on global health resources.

When patients reach advanced stages of chronic kidney disease (CKD), there is a need to identify a dialysis threshold. Before this proposed threshold starting dialysis will add no benefits but beyond it there may be risks to patients. Identifying this threshold is challenging due to: 1. Strong beliefs among some physicians and investigators that early start of dialysis is beneficial to patients, 2. Limited number of studies that explored effect of timing of dialysis on patient important outcomes (e.g. quality of life, hospitalization, etc.), 3. Inaccuracy among different formulae in determining kidney function based on creatinine, 4. Limitations in the body of evidence exploring this question due to confounding factors in observational studies. All these factors may explain the recent trend in increase in "earlier" (at a higher level of kidney function) initiation of dialysis in Canada and the United States.[5]

In 2012, there were 14171 dialysis patients out of a population of 28.4 million in Saudi Arabia[6]. Total number of ESRD patients on HD was 12844 in 2012. This number has almost doubled in one decade (was 3357 in 1993 and 7004 in 2003). In 2012, 3187 new cases of hemodialysis were registered (was 1733 in 2000). The limited available dialysis slots Saudi Arabia hospitals and dialysis units emphasize the importance of this guideline to individual patients' care and the healthcare system in general.

Given the importance of this topic, the Ministry of Health (MoH) of Saudi Arabia with the methodological support of the McMaster University working group produced clinical practice guidelines to assist health care providers in evidence-based clinical decision-making. This Ministry of Health of Saudi Arabia and McMaster University Clinical Practice Guideline was adapted from the Canadian Society of Nephrology timing of initiation of dialysis guideline,[1] and is part of the larger initiative of the MoH to establish a program of rigorous adaptation and de novo development of guidelines in the Kingdom; the ultimate goal being to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

Scope

Our target audience includes Saudi nephrologists, general internists and other internal medicine subspecialists who care for patients with CKD and who play a critical role in referring and co-managing patients with CKD.

The target population includes adult patients (>18 years) with Stage 5 CKD (eGFR<15 ml/min/1.73m^2) planning an elective chronic dialysis start. This guideline applies to patients planning to use either chronic hemodialysis or chronic peritoneal dialysis. This guideline does not consider pre-emptive transplantation, initiation of dialysis after failed transplant, urgent initiation of dialysis for acute kidney failure, conservative management without dialysis, or paediatric populations.

Methodology

To facilitate the interpretation of these guidelines; we briefly describe the methodology we used to develop and grade recommendations and quality of the supporting evidence. We present the detailed methodology in a separate publication.[7]

For the selected question for this guideline we updated existing systematic reviews that were used for the Canadian Society of Nephrology 2014 clinical practice guidelines for timing the initiation of chronic dialysis.[1] We also conducted systematic searches for information

that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach (see **Appendix 2**).[2]

We assessed the quality of evidence using the system described by the GRADE working group.[4]
Quality of evidence is classified as "high", "moderate", "low", or "very low" based on decisions about methodological characteristics of the available evidence for a specific health care problem. The definition of each category is as follows:

- *High*: We are very confident that the true effect lies close to that of the estimate of the effect.
- *Moderate*: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- *Low*: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- *Very low*: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

According to the GRADE approach, the strength of a recommendation is either strong or conditional (weak) and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades – either strong or conditional – of the strength of recommendations is essential for sagacious clinical decision-making.

Based on this information and the input of KSA MoH panel members we prepared the *evidence-to-recommendation* tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see **Appendix 1**). The guideline panel met in Riyadh on December 4th and 5th, 2013 and formulated the recommendation during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[3]

How to use these guidelines

The Ministry of Health of Saudi Arabia and McMaster University Clinical Practice Guidelines provide clinicians and their patients with a basis for rational decisions in the management of timing of initiating dialysis in patients with advanced CKD. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No guidelines and recommendations can take into account all of the often-compelling unique features of individual clinical circumstances. Therefore, nobody charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines as rote or in a blanket fashion.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate an accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines.

Key question

The clinical question covered in this guideline was adapted from the Canadian Society of Nephrology timing of initiation of dialysis guideline.[1] This key question was chosen for its importance as it has major implications for care of individual patients and healthcare systems in general.

Recommendations

Question 1: Among adult patients (age 18 years or older) with advanced (stage 5) chronic kidney disease, what are the effects of an intent-to-initiate dialysis early (eGFR 10-14 ml/min) strategy compared with an intent-to-defer dialysis (eGFR 5-7 ml/min) strategy?

Summary of Findings:
We updated the systematic review used for the Canadian Society of Nephrology guideline. We identified 26 observational studies (29 reports) one randomized controlled trial (RCT)(4 reports from 1 RCT)[8-11] and a published systematic review[12] comparing the effect of early vs late dialysis start on survival. We summarized the evidence informing each of the critical and important outcomes (mortality, quality of life and hospitalization) in a GRADE evidence profile (Appendix 1 Table1).

The IDEAL trial demonstrated no effect on mortality between patients randomized to the intent-to-start early versus intent-to-defer groups (hazard ratio [HR] 1.04, 95% CI=0.83 to 1.30). The pooled effect estimate from systematic review of observational studies was identical, but with a narrower confidence interval HR =1.04 (95%CI 1.03 to 1.05), and suggested a harmful effect with early initiation of dialysis. Residual confounding was, however, likely severe in this body of evidence. Of note, the patients randomised in the IDEAL trial are generally healthier (have fewer comorbidities) than the advanced CKD patients typically initiating dialysis in Saudi Arabia. (Appendix 1 Table 3)

The IDEAL trial reported no significant difference in quality of life between patients randomized to the intent-to-start early versus intent-to-defer groups. This was similar to the finding of the 2 observational studies[10,13] that reported quality of life. In one of the observational studies[13], although patients who initiated dialysis early had higher baseline health-related quality of life, there was no significant difference in SF-36 scores at 12 months follow-up. (Appendix 1 Table 4)

We identified a total of 6 studies (5 observational[14-18] and 1 RCT) that assessed the effect of earlier versus later initiation of dialysis on risk of hospitalization. The IDEAL trial found no significant difference in hospitalization days between early and late start of dialysis. We were not able to pool the effects on hospitalization due to variation in measures and reporting of this outcome. 3 studies found no significant difference in the number of days spent in hospital in the early vs. late initiation of dialysis groups. One study found that late initiation of dialysis was associated with a reduced risk of all-cause hospitalization, though indication bias and residual confounding may have been present. Another study reported fewer hospitalizations per person-year among "intent-to-start early", 2.13 ± 1.13 as compared with "intent-to-start late" 3.14 ± 1.17 (p=0.05). (Appendix 1 Table 5)

We found no evidence to support a subgroup effect for patients: 1. initiating peritoneal or hemodialysis, 2. patients with or without diabetes, or 3. patients with cardiovascular disease vs no cardiovascular disease for intent-to-defer versus intent-to-start early strategies (Table 6). Specifically, the IDEAL trial did not detect significant interactions between type on dialysis and diabetes and treatment effect although the trial was underpowered to detect any. We did not identify any studies evaluating a subgroup effect for patients with hemoglobinopathies vs no hemoglobinubathies.

Benefits of the Option:
None

Harms of the Option:
Potential increase in mortality with no improvement in quality of life or hospitalization.
Quality of Evidence:
The risk of bias among all observational studies was significant, primarily due to confounding. Patients who started earlier may have had a poorer baseline prognosis than those who were healthy enough to defer. Risk of bias in

the IDEAL trial was lower. The quality of evidence (QoE) for observational studies evaluating critical outcomes (mortality and QoL) was very low, while the QoE for outcomes reported in the single RCT was moderate (mortality outcome rated down for imprecision); we therefore considered the overall QoE to be moderate. QoE ratings are summarized in Appendix 1 Table 1.

Values and Preferences:
The KSA MoH panel assumed that patients place a high value on ameliorating symptoms associated with uremia and hypervolemia, but that they also place a high value on avoiding the inconvenience associated with initiating dialysis. Hence, the panel assumed that an asymptomatic patient would favour delaying initiation of dialysis until a clear indication emerged, or until a low threshold (e.g. 5-7 ml/min) was reached. Although there were no published studies characterizing values and preferences in this population, panel members were confident, based on their experience with patients, that these values and preferences are likely to be uniform across the target population and relevant patient subgroups.

Resource Use:
One report, from the IDEAL trial, examined resource use.[10] The intent-to-start early group initiated dialysis a median of 5.6 months (mean 3.8 months) earlier from the time of randomization, compared with the intent-to-defer group. This was associated with higher dialysis costs. Costs of transport to dialysis were also greater. The number and costs of hospitalizations and outpatient visits were not significantly different between groups. There is no evidence assessing the effects of early vs late dialysis on resources in the Saudi context. The cost of a single hemodialysis session in Saudi Arabia ranges between 1140-1360 SR based on available published and unpublished data.[19] We were not able to perform micro costing using the Australian study due to lack of details about cost of peritoneal dialysis and other dialysis associated cost.

Implementation Considerations:

- The lack of guidance about timing of initiation of dialysis in paediatric and adolescence group is a major challenge and guideline panel recommends that this should be addressed in the near future.

Other considerations:

- The KSA MoH panel members assumed based on their experience that late start dialysis is more acceptable to most patients and is less acceptable to most physicians.
- Given variability in access to dialysis care and availability of dialysis slots in KSA, an "intent-to-start-early" strategy is likely to increase inequity as it may lead to more competition on dialysis slots.

Monitoring and Evaluation:

- A prospective data collection of eGFR at the time of elective initiation of dialysis is needed for monitoring and evaluation of the effects of this guideline. This information can be collected through a national CKD registry.

Research Priorities:

- Formal evaluation of physicians' values and preferences with assessment of potential barriers to implementing the guidelines.
- Assessing the percentage of patients that get their first dialysis in emergency setting and reasons for variability in this figure.
- Assess patients' values and preferences and predictors of non-adherence to physicians' recommendations.
- Assessing the prevalence and burden of non-eligible patients to the health care system
- Establish a national registry for CKD including important outcomes, comorbidities and related variables.
- Policies to regulate and enforce registering CKD patients to available registries.

Recommendation:

The Kingdom of Saudi Arabia Ministry of Health guideline panel recommends against an "intent- to- start-early" and recommends for an "intent-to-defer" strategy for initiating dialysis in adult patient (age 18 years or older) with stage 5 CKD (an eGFR <15 ml/min/1.73m^2) (strong recommendation, moderate quality of evidence)

Remarks:

- This recommendation applies to adult patients who are 18 years old or older and does not apply to adolescence between 13 and 18 years old. The KSA MoH panel agreed that patients aged 13-18 years are likely to behave clinically different than adults for many reasons including small body size and going through maturity period. This group of patients (13-18 years old) is considered adult by the KSA MoH regulations and they are typically admitted to adult inpatient services. This creates a challenge in managing dialysis patients in this age group due to variation in comfort level among adult nephrologists who are expected to deal with this group especially when admitted.

- This recommendation applies to patients planning to use either chronic hemodialysis or chronic peritoneal dialysis. We do not consider pre-emptive transplantation, initiation of dialysis after failed transplant, urgent initiation of dialysis for acute kidney failure, conservative management without dialysis, or paediatric populations.

- Patients comorbidities and age, modality education and selection, rate of decline in eGFR, local waiting time for access (vascular access creation and maturation or peritoneal dialysis catheter insertion), access to interventional radiology and diagnostic imaging and availability of staff, physical space, equipment, or other resources requires for provision of a chosen modality are all factors that may influence the decision about timing of initiation of dialysis.

- Adherence to this recommendation requires availability of timely follow-up with a nephrologist to closely monitor clinical indications for dialysis initiation. These clinical indications for the initiation of dialysis include: symptoms of uremia, refractory fluid overload, hyperkalemia or acidemia, or other conditions or symptoms that are likely to be ameliorated by dialysis. In the absence of these factors, eGFR should not serve as a sole criterion for the initiation of dialysis unless it is ≤ 6 ml/min/1.72m^2.

- The 'intent-to-defer' strategy pertains specifically to timing of dialysis initiation, and does not mean that patients should be referred to nephrologists at a later stage (lower level of kidney function).

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Appendices

1. Evidence-to-Recommendation Table and Evidence Profiles
2. Search Strategies and Results

Appendix 1: Evidence-to-Recommendation Table and Evidence Profiles

Evidence to recommendation framework

Among adult patients (age >= 18 years) with advanced (stage V) chronic kidney disease, what are the effects of an intent-to-initiate dialysis early (eGFR 10-14 ml/min) strategy compared with an intent-to-defer dialysis (eGFR 5-7 ml/min) strategy?

Problem: adult patients (>=18 years of age) with an eGFR <15 ml/min/1.73m^2
Option: "intent-to-start-early"
Comparison: "Intent-to-defer"
Setting: Outpatient
Perspective: Health system (*might not be applicable from an individual decision making perspective)

Background: Initiating chronic dialysis has major implications for patients and health care systems around the world and in Saudi Arabia. When patients reach advanced stages of chronic kidney disease (CKD), there is a need to identify a dialysis threshold. Before this proposed threshold starting dialysis will add no benefits but beyond it there may be risks to patients. The limited available dialysis slots Saudi Arabia hospitals and dialysis units emphasize the importance of this guideline to individual patients' care and the healthcare system in general.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	Global prevalence of renal replacement therapy has almost doubled within the past two decades at a rate of > 6% per year. This growth is far beyond what is anticipated secondary to population growth and aging and it adds enormous burden on global health resources. KSA specific evidence (SCOT database)[6] In 2012, there were 14171 dialysis patients out of a population of 28.4 million. Total number of ESRD patients on HD was 12844 in 2012. This number has almost doubled in one decade (was 3357 in 1993 and 7004 in 2003). In 2012, 3187 new cases of HD were registered (was 1733 in 2000).	The prevalence of CKD with its different stages is unknown in KSA. There is large variation in incidence and prevalence among different regions.[20] Increase availability of dialysis services may also have played a role in increasing ESRD population.

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS
What is the overall certainty of this evidence?	No included studies ☐ | Very low ☐ | Low ☐ | Moderate ☒ | High ☐
Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability ☐ | Possibly important uncertainty or variability ☐ | Probably no important uncertainty or variability ☐ | No important uncertainty or variability ☒ | No known undesirable outcomes ☐
Are the desirable anticipated effects large?	No ☐ | Probably No ☒ | Uncertain ☐ | Probably Yes ☐ | Yes ☐ | Varies ☐
Are the undesirable anticipated effects small?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☒ | Yes ☐ | Varies ☐
Are the desirable effects large relative to undesirable effects?	No ☒ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☐ | Varies ☐

RESEARCH EVIDENCE

The relative importance or values of the main outcomes of interest:

Outcome	Relative importance	Certainty of the evidence
Mortality	Cretical	Moderate ⊕⊕⊕⊖
Quality of Life	Cretical	
Hospitalization	Important	
Nutritional status	Not important	

Summary of findings: "Intent-to-defer" dialysis compared to "intent-to-start-early" in adult patients with CKD stage 5

Outcome	"intent-to-start-early" (# of patients)	"intent-to-defer" (# of patients)	Difference Per 1000 (95%CI)	Relative effect (95%CI)	Certainty of the evidence (GRADE)
Mortality	152 out of 404	155 out of 424	11 more (from 51 fewer to 81 more)	HR 1.04 (0.83 to 1.3)	Moderate ⊕⊕⊕⊖
Quality of Life (better indicated by lower)	307	355	MD 1 higher (no CI provided)	-	High ⊕⊕⊕⊕
Hospitalization	307	355	MD 8 higher (2 lower to 17 higher)	-	Moderate ⊕⊕⊕⊖

Link to detailed evidence profile (Table 1,3,4,5)

Subgroup considerations:

1. DM vs No DM
2. HD vs PD
3. CVD vs no CVD
4. Hemoglobinuria vs no hemoglobinuria

Link to summary of findings and judgments for subgroups (Table 6)

ADDITIONAL CONSIDERATIONS

We updated the SR done by the Canadian Society of Nephrology. We identified 26 observational studies (29 reports) one randomized controlled trial (RCT)(4 reports)[8,9,10,11] and a published systematic review[12] comparing the effect of early vs late dialysis start on survival. We summarized the evidence informing each of the critical and important outcomes (mortality, quality of life and hospitalization) in GRADE evidence profile (Table1).

The IDEAL trial demonstrated no effect on mortality between patients randomized to the intent-to-start early versus intent-to-defer groups (hazard ratio [HR] 1.04, 95% CI=0.83 to 1.30). The pooled effect estimate from systematic review of observational studies was identical, but with a narrower confidence interval HR =1.04 (95%CI 1.03 to 1.05), and suggested a harmful effect with early initiation of dialysis. Residual confounding was, however, likely severe in this body of evidence. Of note, the patients randomised in the IDEAL trial are generally healthier (have fewer comorbidities) than the advanced CKD patients typically initiating dialysis in Saudi Arabia. (Table 3)

The IDEAL trial reported no significant difference in quality of life between patients randomized to the intent-to-start

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			Summary of the evidence for patients' values and preferences: *We assume that patients place a high value on ameliorating symptoms associated with uremia and hypervolemia, but that they also place a high value on avoiding the inconvenience associated with initiating dialysis. Therefore, we assumed that an asymptomatic patient would favour delaying initiation of dialysis until a clear indication emerged, or until a low threshold (e.g. 5-7 ml/min) was reached. Although there were no published studies characterizing values and preferences in this population, panel members are confident that these values and preferences are likely to be uniform across the target population and relevant patient subgroups.*	early versus intent-to-defer groups. This was similar to the finding of the 2 observational studies[10,13] that reported quality of life. In one of the observational studies[13], although patients who initiated dialysis early had higher baseline health-related quality of life, there was no significant difference in SF-36 scores at 12 months follow-up. (Table 4) We identified a total of 6 studies (5 observational[14-18] and 1 RCT) that assessed the effect of earlier versus later initiation of dialysis on risk of hospitalization. The IDEAL trial found no significant difference in hospitalization days between early and late start of dialysis. We were not able to pool the effects on hospitalization due to variation in measures and reporting of this outcome. 3 studies found no significant difference in the number of days spent in hospital in the early vs. late initiation of dialysis groups. One study found that late initiation of dialysis was associated with a reduced risk of all-cause hospitalization, though indication bias and residual confounding may have been present. Another study reported fewer hospitalizations per person-year among "intent-to-start early", 2.13 ± 1.13 as compared with "intent-to-start late" 3.14 ± 1.17 (p=0.05). (Table 5) We found no evidence to

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
				support a subgroup effect for patients: 1. initiating peritoneal or hemodialysis, 2. patients with or without diabetes, or 3. patients with cardiovascular disease vs no cardiovascular disease for intent-to-defer versus intent-to-start early strategies (Table 6). Specifically, the IDEAL trial did not detect significant interactions between type on dialysis and diabetes and treatment effect although the trial was underpowered to detect any. We did not identify any studies evaluating a subgroup effect for patients with hemoglobinopathies vs no hemoglobinubathies. *The preference to delay dialysis may be stronger in Saudi patients compared to non-Saudi patients (i.e. Saudi patients are more hesitant/resistant to start dialysis).* *Patient waiting for preemptive transplantation would prefer to delay dialysis as much as possible to avoid the inconvenience of all the preparation for dialysis.*

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / **Varies** ☐	One report, from the IDEAL trial, examined resource use. The intent-to-start early group initiated dialysis median of 5.6 (mean 3.8) months earlier from the time of randomization, compared with the intent-to-defer group. This was associated with higher dialysis costs. Costs of transport to dialysis were also greater. The number and costs of hospitalizations and outpatient visits were not significantly different between groups. Link to detailed evidence profile (Table 2)	-Cost of single HD session is 1140[19]-1360 SR (unpublished data, report accessed by Dr. Adnan Alfi) -Cost of hemodialysis is about 180,000 SR per year/pt
	Is the incremental cost small relative to the net benefits?	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / **Varies** ☐	There is evidence of increase cost and no evidence of benefit but rather evidence of potential harm.	
EQUITY	**What would be the impact on health inequities?**	Increased ☒ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☐ / **Varies** ☐	Given variability in access to dialysis care and availability of dialysis slots, an 'intent-to-start-early" strategy is likely to increase inequity as it may lead to more competition on dialysis slots	-Access to dialysis care is likely to vary by region and by proximity to central areas/cities -Limited transportation is a barrier to access to dialysis especially to elderly and female patients - About 500 Saudi patients out of the 14171 who require dialysis do not have access to regular dialysis slot which may vary among regions in KSA -Eligible patients (including Saudi and insured non-Saudis) have easier access to dialysis compared to non-eligible (non-insured non-Saudis)
ACCEPTABILITY	**Is the option acceptable to key stakeholders ?**	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / **Varies** ☒	KSA MoH panel members assumed based on their experience that late start dialysis is more acceptable to most patients. KSA MoH panel members assumed based on their experience that early start dialysis is more acceptable to nephrologists	There is considerable variation in the rate of elective initiation of dialysis among different centers, regions and patient populations. KSA MoH panel members reported the current figures in different practices: elective (clinic) versus Emergency dialysis start a. Panelist 1: ER 85% Vs. 15% elective b. Panelist 2: ER 50 % Vs. 50% elective c. Panelist 3: ER 30% Vs 70% elective

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☒ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	There are limited dialysis slots in Saudi Arabia. Hence, an "intent-to-start early" will be less feasible to implement.	About 500 Saudi patients out of the 14171 who require dialysis do not have access to regular dialysis slot which may vary among regions in KSA

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☒	☐	☐	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☒	☐	☐	☐

Recommendation (text)

The KSA MoH guideline panel recommends against "intent- to- start-early" rather than "intent-to-defer" strategy for initiating dialysis in adult patient (age 18 years or more) with stage 5 CKD (an eGFR <15 ml/min/1.73m^2)

Justification

- This recommendation applies to adult patients who are 18 years old or older and does not apply to adolescence between 13 and 18 years old. The KSA MoH panel agreed that patients aged 13-18 years are likely to behave clinically different than adults for many reasons including small body size and going through maturity period. This group of patients (13-18 years old) is considered adult by the KSA MoH regulations and they are typically admitted to adult inpatient services. This creates a challenge in managing dialysis patients in this age group due to variation in comfort level among adult nephrologists who are expected to deal with this group especially when admitted.
- This recommendation applies to patients planning to use either chronic hemodialysis or chronic peritoneal dialysis. We do not consider pre-emptive transplantation, initiation of dialysis after failed transplant, urgent initiation of dialysis for acute kidney failure, conservative management without dialysis, or paediatric populations.
- Patients comorbidities and age, modality education and selection, rate of decline in eGFR, local waiting time for access (vascular access creation and maturation or peritoneal dialysis catheter insertion), access to interventional radiology and diagnostic imaging and availability of staff, physical space, equipment, or other resources requires for provision of a chosen modality are all factors that may influence the decision about timing of initiation of dialysis.
- Adherence to this recommendation requires availability of timely follow-up with a nephrologist to closely monitor clinical indications for dialysis initiation. These clinical indications for the initiation of dialysis include: symptoms of uremia, refractory fluid overload, hyperkalemia or acidemia, or other conditions or symptoms that are likely to be ameliorated by dialysis. In the absence of these factors, eGFR should not serve as a sole criterion for the initiation of dialysis unless it is ≤ 6 ml/min/1.72m^2.
- The 'intent-to-defer' strategy pertains specifically to timing of dialysis initiation, and does not mean that patients should be referred to nephrologists at a later stage (lower level of kidney function).

Subgroup considerations

We found no evidence to support a subgroup effect for patients:
1. initiating peritoneal or hemodialysis, 2. patients with or without diabetes, or 3. patients with high vs. low levels of comorbidity and outcome for intent-to-defer versus intent-to-start early strategies

Implementation considerations	The lack of guidance about timing of initiation of dialysis in pediatric and adolescence group is a major challenge and KSA MoH panel recommends that this should be addressed in the near future
Monitoring and evaluation	A prospective data collection of eGFR at the time of elective initiation of dialysis is needed for monitoring and evaluation of the effects of this guideline. This information can be collected through a national CKD registry.
Research priorities	• Formal evaluation of physicians' values and preferences with assessment of potential barriers to implementing the guidelines. • Assessing the percentage of patients that get their first dialysis in emergency setting and reasons for variability in this figure. • Assess patients' values and preferences and predictors of non-adherence to physicians' recommendations. • Assessing the prevalence and burden of non-eligible patients to the health care system • Establish a national registry for CKD including important outcomes, comorbidities and related variables including serial eGFR. • Policies to regulate and may be enforce registering CKD patients to available registries

Table 1: GRADE Evidence Profile – 'Intent-to-Start Early' versus 'Intent-to-Defer'

Author(s): Adapted with permission from the Canadian Society of Nephrology timing of initiation of chronic dialysis guidelines[1]

Date: Updated by Reem Mustafa 2013-12-28

Question: Should an intent-to-start late vs. an intent-to-start early strategy be used in in chronic kidney disease patients? Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Early start dialysis	Late start dialysis	Relative (95% CI)	Absolute		
Mortality (RCT) (follow-up mean 3.59 years; assessed with: All cause mortality)												
1[a]	randomised trials	no serious risk of bias	no serious in-consistency	no serious indirectness	serious[b]	none	152/404 (37.6%)	155/424 (36.6%)[c]	HR 1.04 (0.83 to 1.3)	11 more per 1000 (from 51 fewer to 81 more)	⊕⊕⊕O MODERATE	CRITICAL
Mortality (Observational) (follow-up 1 - 11 years; assessed with: All cause mortality)												
15[d]	observational studies	very serious[e]	very serious[f]	no serious indirectness	no serious imprecision	none	-	36.6%[c]	HR 1.04 (1.03 to 1.05)[g]	11 more per 1000 (from 9 more to 14 more)	⊕OOO VERY LOW	CRITICAL
Quality of Life (RCT) (follow-up mean 6 months; measured with: SF-36 at 0.5, 1, 2, and 3 years; Better indicated by lower values)												
1[h]	randomised trials	no serious risk of bias	no serious in-consistency	no serious indirectness	no serious imprecision	none	307	335	-	MD 1 higher (no CI provided)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of Life (Observational) (follow-up 1 years; measured with: SF-36; Better indicated by lower values)												
1[i]	observational studies	serious[j]	no serious in-consistency	serious[k]	no serious imprecision[l]	none	147	90	-	MD 2.5 higher (no CI provided)	⊕OOO VERY LOW	CRITICAL
Hospitalizations (RCT) (follow-up median 4.15 years; measured with: Hospitalization (days); (early - late); Better indicated by lower values)												
1[h]	randomised trials	no serious risk of bias	no serious in-consistency	no serious indirectness	serious[m]	none	307	335	-	MD 8 higher (2 lower to 17 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Hospitalizations (Observational) (follow-up 1-6 years; measured with: Number of hospitalizations; Better indicated by lower values)												
5[n]	observational studies	serious[o]	serious[p]	serious[q]	no serious imprecision	none	-	-	-	See narrative summary	⊕OOO VERY LOW	IMPORTANT

[a] Cooper et al.

[b] Rated down for imprecision. We assumed a control event rate of 40% and RRR of 25%; which met the optimal information size criteria, however, 95% CI crosses 25% decision threshold (HR 1.30.

[c] We used the IDEAL trial control group event rate of 36.6%,

[d] Susantitaphong et al.[12]

[e] Indication bias was a major issue in this body of literature. Most studies did not adjust for information related to indication for starting dialysis like symptoms of uremia or hypervolemia.

[f] Unexplained sever heterogeneity present with I^2 of 97%. Attempt to explain heterogeneity included subgroup analyses that assessed: adjustment for nutritional markers, hemodialysis patients only, peritoneal dialysis patients only, calculated GFR, and estimated GFR.

[g] Hazard ratio is per 1mL/min/1.73 m^2 GFR increment.
[h] Harris et al.[10]
[i] Korevaar et al.[13]
[j] Likely unmeasured baseline prognostic factors leading to indication bias.
[k] Early and late dialysis groups defined as GFR 7.1 +/- 2.5 and 4.9 +/-1.7 ml/min; recent studies, including the IDEAL trial, would consider both groups 'late' start.
[l] No difference between groups on the Kidney Disease Quality of Life Physical and Mental Component summaries; statistical comparisons provided only when individual components were significant. Study adequately powered to detect minimal important difference of 3 points assuming SD=12, alpha 0.05 and power 0.8.
[m] Study may have been underpowered to detect clinically meaningful differences in hospitalization; CSN was unable to obtain normalized hospitalization data from authors.
[n] Pupim et al.[14], Tang et al.[15], Shiao et al.[17], Kim et al.[16], Coronel et al.[18]
[o] 2/5 studies[14,17] had serious risk of indication bias.
[p] Effect estimates ranged between beneficial and harmful association with later initiation of dialysis. Unable to pool due to variability in reported measures of effect and clinical heterogeneity.
[q] In consistent definition of early vs. late cohorts across 3 studies: ‘elective starter’ vs ‘initial refuser’[15]; GFR as greater or less than 5ml/min[17]; and highest vs. lowest quartile of serum albumin and creatinine[14].

Table 2: GRADE Evidence Profile for Resource Use

Author(s): Adapted with permission from the Canadian Society of Nephrology timing of initiation of chronic dialysis guidelines[1]
Date: Updated by Reem Mustafa 2013-12-28

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intent for early start dialysis	Intent for late start dialysis	Absolute (MD = early – late)		
Dialysis months (follow-up mean 4.15 years; Better indicated by lower values)											
1[a]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	335	MD 3.8 higher (0.3 to 7.3 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Dialysis costs (follow-up mean 4.15 years; measured with $CAD Better indicated by lower values)											
1[b]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	335	MD 10777 higher (313 to 22801 higher)[b,c]	⊕⊕⊕⊕ HIGH	IMPORTANT
Hospitalization days (follow-up mean 4.15 years; Better indicated by lower values)											
1[a]	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness[d]	serious[e]	none	307	335	MD 8 higher (2 lower to 17 higher)	⊕⊕⊕O LOW	IMPORTANT
Hospitalization costs (follow-up mean 4.15 years; measured with $AUS Better indicated by lower values)											
1[a]	randomised trials	no serious risk of bias	no serious inconsistency	serious	serious[e]	none	307	335	MD 5112 higher (3662 lower to 13247 higher)	⊕⊕⊕O LOW	IMPORTANT
Transportation costs (follow-up mean 4.15; measured with $AUS; Better indicated by lower values)											
1[a]	randomised trials	no serious risk of bias	no serious inconsistency	serious[f]	no serious imprecision[g]	none	307	335	MD 3610 higher (1111 to 9959 higher)[g]	⊕⊕⊕O MODERATE	IMPORTANT
Outpatient visits non-admitted (follow-up mean 4.15 years; Better indicated by lower values)											
1[a]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[e]	none	307	335	MD 0 higher (3 lower to 3 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Outpatient costs non-admitted (follow-up mean 4.15 months; measured with $AUS Better indicated by lower values)											
1[a]	randomised trials	no serious risk of bias	no serious inconsistency	serious[h]	serious[e,i]	none	307	335	MD 129 lower (1155 lower to 1070 higher)	⊕⊕OO LOW	IMPORTANT
Outpatient visits GP/HP (follow-up mean 4.15 years; Better indicated by lower values)											
1[a]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[e]	none	307	335	MD 0 higher (6 lower to 5 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Outpatient costs GP/HP (follow-up mean 4.15 years; measured with $AUS Better indicated by lower values)											
1[a]	randomised trials	no serious risk of bias	no serious inconsistency	serious[h]	serious[e]	none	307	335	MD 259 lower (722 lower to 242 higher)	⊕⊕OO LOW	IMPORTANT

[a] Harris et al.[10]
[b] Canadian dialysis costs used microcosting data from Lee[21] inflated to 2008 CAD $. Cost of $10,440 2008 CAD $ if a blend of 50% PD and 50% HD as per Harris et al.[10]; cost of $12,219 2008 CDN$ if a blend of 25% PD and 75% HD as per current Canadian estimates. Both scenarios assume 3.8 months of dialy-

sis difference between groups.
[c] Results are likely to be similar in direction if local KSA data were used.
[d] Hospitalization rates were derived from an Australian population[10]. It is likely that this effect varies significantly in a Saudi population, therefore, we rated down for indirectness.
[e] Serious imprecision as CI ranges between trivial and significant incremental costs that would lead to different decisions regarding strength of recommendation. Only 78% of IDEAL trial participants were in the economic study. Primarily stated reason was delay in ethics approval. Attrition may have decreased precision of estimate.
[f] Australian setting; may differ from Saudi setting due to mix of home dialysis [22]
[g] Travel costs estimated using distance travelled with application of unit costs for mode of transportation used. This may differ from Saudi context.
[h] Reported in 2008 AUS $.
[i] CI ranges between greater incremental costs and significant cost savings.

Table 3: Summary of studies assessing effect on mortality

– not included in review by Susantitaphong et al.[12]

Adapted with permission from the Canadian Society of Nephrology timing of initiation of chronic dialysis guidelines[1]

Study	Year	Quality assessment	Outcome Measures	Notes
Fink[23]	1999	Serious RoB		Need additional data; GFR not presented. Number lost to follow up not detailed.
Kim[16]	2009	Serious to very serious RoB	Early and late starters defined as greater and less than 5 mL/min/1.73m^2. No difference in crude survival between groups (p=0.096). No difference in survival curves between early and late starters (p=0.27).	Unadjusted analysis. No information on patients excluded.
Rosansky[5]	2009	Difficult to assess	Patients ages 65–74 years with an eGFR of 5–9.9 at the initiation of dialysis have a 25% first year mortality rate and similarly aged patients with an eGFR of >15 at initiation of dialysis have a 41.5% first year mortality.	No information on characteristics of patients. No information on those lost to follow-up.
Sjolander[24]	2011	Serious RoB	From initiation method: 0.81 (0.51-1.21) and 0.77 (0.48-1.25) for intermediate and late (compared to early) From threshold method: 0.62 (0.39-0.98) and 0.56 (0.35-0.91) for intermediate and late (compared to early) Inverse probability weighting method: equal trend for early and intermediate starters; better survival for late starters	Re-analysis of the study done by Evans et al.[25] From threshold examines from the time renal function dropped below a fixed threshold. From initiation refers to the baseline at which dialysis is initiated. Inverse probability weighting was used as a method to correct for lead time and immortal time bias. Many patient exclusions due to lack of repeated measures.
Collins[8]	2011	Little RoB	HR with early initiation = 0.97 (0.66 – 1.41).	Sub-group analysis of IDEAL study.
Oh[26]	2012	Little RoB due to PS based matching	For the overall population, 5-yr patient survival rate was 84.3%. For median follow-up of 27 months, 14 of 136 patients in early starter group and 10 of 136 patients in the late starter group died (adjusted HR with early initiation 0.47, 95% CI 0.16 to 1.35, P = 0.17)	After PS 272 patients (n = 136, for each group) out of 491 patients originally included.
Johnson[11]	2012	Little RoB	Death occurred in 102 early-start patients and 96 late-start patients [hazard ratio: 1.04; 95% CI: 0.79 – 1.37]	Sub-group analysis of IDEAL study.
Chang[27]	2012	Little RoB due to PS based matching	At the start of dialysis, the mean eGFR was 11.1 ± 3.9 mL/min/1.73 m2 in the early-start group compared with 6.1 ± 1.2 mL/min/1.73 m2 in the late-start group. Overall survival was similar for the early start and late-start groups (HR: 1.32; 95% CI: 0.87-1.99, P = 0.186)	After PS, 450 patients (225 in each group) remained out of 831 patients originally included.
Yamagata[28]	2012	Serious RoB	After adjustments for age, gender, underlying renal diagnosis, and symptom at dialysis initiation, both late and early initiation of RRT did not affect long-term survival.	

Abbreviations: RoB, risk of bias; PS, propensity-score based matching; HR, Hazard Ratio; CI, confidence interval

Table 4: Summary of studies assessing effect on quality of life

Adapted with permission from the Canadian Society of Nephrology timing of initiation of chronic dialysis guidelines[1]

Study	Year	Quality assessment	Outcome Measures	Notes
Korevaar[13]	2002	Little RoB	Compared with patients who started dialysis later, patients who started earlier had significantly higher HRQOL for a number of dimensions immediately after start of treatment. After 12 months, the differences in HRQOL disappeared.	No CI presented.
Harris[10]	2011	Little RoB	No significant difference in QOL between early and late starters (no further details for SF-36).	Almost half the patients did not complete 4 year follow-up.

Abbreviations: RoB, risk of bias; HRQOL, Health related quality of life; QOL, Quality of Life; CI, confidence interval

Table 5: Summary of studies assessing effect on hospitalization

Adapted with permission from the Canadian Society of Nephrology timing of initiation of chronic dialysis guidelines[1]

Study	Year	Quality assessment	Outcome Measures	Notes
Pupim[14]	2003	Serious RoB	Unadjusted analysis: 9.61±15.46 days vs 8.78±9.84 for lowest vs. highest quartile for number of days in hospital.	Only 50% of sample reported 24 hour creatinine clearance. Lack of detail on lost to follow up by group. Lowest and highest quartile not defined.
Tang[15]	2007	Serious RoB	Unadjusted analysis: 2.13±1.13 episodes/person-year vs. 3.14±1.17 for elective starters vs. initial refusers (p=0.05).	Elective starters defined as people who chose to start dialysis early compared with those who refused. Baseline differences of eGFR between groups is negligible and standard deviations overlap.
Shiao[17]	2008	Serious RoB	Adjusted analysis: Late start of dialysis was associated with reduced risk for all-cause hospitalization (log rank, p = 0.025).	Potential selection bias as initial drop outs not detailed by group. Early vs late started defined as greater and less than 5 mL/min/1.73^2 respectively.
Kim[16]	2009	Serious to very serious RoB	Unadjusted analysis: 1.6 days (±2.2) vs. 1.8 days (±1.8) for late vs. early starters (p=0.340).	Early and late started defined as greater or less than 5 mL/min/1.73^2 respectively.
Coronel[18]	2009	Serious RoB	1.3 (±1.0) days for early start compared to 1.5 (±1.2) days in late start; no significance. 23.1 (±29 days) compared to 20 (±22) days/pt/year, not significant.	
Harris[10]	2011	Little RoB	48±64 days vs. 40±54 for early vs. late start group.	Sub-study of IDEAL trial. Not all participants enrolled due to delay in obtaining ethics approval.

Abbreviations: RoB, risk of bias;

Table 6: Studies examining mortality among subgroups

Adapted with permission from the Canadian Society of Nephrology timing of initiation of chronic dialysis guidelines[1]

Studies examining mortality among subgroups					
Author	Subgroup	eGFR category	No. patients	HR (95% CI)	Adjustment variables
Traynor[29]	Nondiabetics	≥ 8 mL/min GFR < 8 mL/min GFR	97 87	Not reported	
Kazmi[30]	Age > 67 y	Per ↑ 1 mL/min GFR	91 083	M1: 1.040 (1.038–1.042) M2: 1.028 (1.026–1.030) M3: 1.028 (1.025–1.031) M4: 1.028 (1.025–1.031)	M1: adjusted for age, sex, race, Hispanic ethnicity, BMI, cause of kidney failure, year of initiation of dialysis, network; M2: M1 + comorbid conditions; M3: M2 + hematocrit and albumin; M4: M3 + employment and insurance status
	Low-risk population	Per ↑ 1 mL/min GFR	90 540	M1: 1.047 (1.044–1.050) M2: 1.041 (1.038–1.044) M3: 1.034 (1.029–1.039) M4: 1.031 (1.026–1.036)	M1: adjusted for age, sex, race, Hispanic ethnicity, BMI, cause of kidney failure, year of initiation of dialysis, network; M2: M1 + comorbid conditions; M3: M2 + hematocrit and albumin; M4: M3 + employment and insurance status
Coronel[18]	Diabetics on PD	> 7.7 mL/min/1.73 m^2 ≤ 7.7 mL/min/1.73 m^2	56 44	Not reported	
Stel (1999 cohort)	Age 20–44 y 45–64 y 65–74 y > 75 y	Per ↑ 1 mL/min/1.73 m^2	4644†‡	 1.04 (0.99–1.09) 1.05 (1.03–1.06) 1.04 (1.03–1.06) 1.03 (1.02–1.04)	Age at start of dialysis, gender, primary renal disease, treatment modality, and country
	Sex Female Male	Per ↑ 1 mL/min/1.73 m^2	4644	 1.03 (1.01–1.05) 1.04 (1.03–1.05)	Same as above
	Comorbidity DM RVD/HTN GN Other	Per ↑ 1 mL/min/1.73 m^2	4644	 1.04 (1.02–1.05) 1.05 (1.03–1.06) 1.03 (1.00–1.06) 1.05 (1.03–1.06)	Same as above

Studies examining mortality among subgroups					
Author	Subgroup	eGFR category	No. patients	HR (95% CI)	Adjustment variables
Stel (2003 cohort)	Age 20–44 y 45–64 y 65–74 y > 75 y	Per ↑ 1 mL/min/1.73 m^2	M1: 6613† M2: 3375‡	 M1: 1.11 (1.05–1.17); M2: 1.12 (1.03–1.22) M1: 1.04 (1.02–1.06); M2: 1.05 (1.03–1.07) M1: 1.02 (1.01–1.04); M2: 1.02 (0.99–1.04) M1: 1.02 (1.01–1.03); M2: 1.01 (0.98–1.03)	M1: age at start of dialysis, gender, primary renal disease, treatment modality, and country; M2: M1 + diabetes, heart disease, PVD, cerebrovascular disease, malignancy
	Sex Female Male	Per ↑ 1 mL/min/1.73 m^2	M1: 6613 M2: 3375	 M1: 1.02 (1.00–1.03); M2: 1.01 (0.99–1.04) M1: 1.03 (1.02–1.04); M2: 1.03 (1.01–1.05)	Same as above
	Comorbidity DM RVD/HTN GN Other	Per ↑ 1 mL/min/1.73 m^2	M1: 6613 M2: 3375	 M1: 1.02 (1.00–1.04); M2: 1.00 (0.99–1.04) M1: 1.02 (1.00–1.05); M2: 1.03 (1.00–1.07) M1: 1.10 (1.05–1.15); M2: 1.11 (1.05–1.18) M1: 1.02 (1.01–1.03); M2: 1.02 (1.00–1.04)	Same as above
	Dialysis HD PD	Per ↑ 1 mL/min/1.73 m^2	M1: 6613 M2: 3375	 M1: 1.02 (1.02–1.04); M2: 1.02 (1.01–1.04) M1: 1.03 (1.01–1.05); M2: 1.03 (1.00–1.05)	Same as above

Studies examining mortality among subgroups					
Author	Subgroup	eGFR category	No. patients	HR (95% CI)	Adjustment variables
Lassalle[31]	Planned HD	Per ↑ 5 mL/min/1.73 m^2	6672	M1: 1.26 (1.19–1.34); M2: 1.13 (1.07–1.20); M3: 1.12 (1.06–1.19)	M1: age and gender; M2: M1 + diabetes, heart failure, dysrhythmia, PVD, CHD, malignancy, severe disability; M3: M2 + predialysis anemia care, initial treatment condition, wait listing or transplantation
	Planned PD		1367	M1: 1.16 (1.05–1.29); M2: 0.98 (0.88–1.10); M3: 1.00 (0.89–1.12)	
	Unplanned		3646	M1: 1.20 (1.13–1.26); 1.09 (1.03–1.15); M3: 1.08 (1.03–1.15)	
Cooper[9]	Age				Unadjusted
	< 60 y	10–14	180	39/180§	
		5–7	194	38/194 (not significant)	
	≥ 60 y				
		10–14	224	113/224	
		5–7	230	117/230 (not significant)	
	Sex				
	Female	10–14	143	55/143	
		5–7	143	58/143 (not significant)	
	Male	10–14	261	97/261	
		5–7	281	97/281 (not significant)	
	Diabetes				
	No	10–14	232	65/232	
		5–7	241	63/241 (not significant)	
	Yes	10–14	172	87/172	
		5–7	183	92/183 (not significant)	
	Albumin				
	< 35 g/L	10–14	68	38/68	
		5–7	81	44/81 (not significant)	
	≥ 35 g/L	10–14	325	110/325	
		5–7	336	109/336 (not significant)	

Studies examining mortality among subgroups					
Author	Subgroup	eGFR category	No. patients	HR (95% CI)	Adjustment variables
Wright[32]	Age				Age at ESRD onset, height and weight at ESRD onset, race, sex, diabetic status, Charlson comorbidity index, duration of predialysis nephrology care, type of dialysis, type of vascular access, cause of ESRD
	< 75 y	> 15	651 304	1.48 (1.46–1.49)	
		10–15		1.17 (1.16–1.17)	
		5–10		Reference	
		≤ 5		0.86 (0.85–0.86)	
	≥ 75 y	> 15	243 989	1.35 (1.33–1.37)	Same as above
		10–15		1.11 (1.10–1.26)	
		5–10		Reference	
		≤ 5		0.96 (0.94–0.97)	
	Dialysis				Same as above
	PD	> 15	63 691	1.42 (1.37–1.47)	
		10–15		1.10 (1.07–1.12)	
		5–10		Reference	
		≤ 5		0.96 (0.93–0.99)	
	HD	> 15	801 685	1.49 (1.47–1.50)	Same as above
		10–15		1.17 (1.16–1.17)	
		5–10		Reference	
		≤ 5		0.87 (0.86–0.87)	
	Charlson comorbidity index				
	< 6	> 15	204 208	1.46 (1.42–1.5)	Same as above
		10–15		1.18 (1.16–1.21)	
		5–10		Reference	
		≤ 5		0.84 (0.83–0.85)	
	6–8	> 15	468 446	1.46 (1.44–1.48)	Same as above
		10–15		1.15 (1.14–1.16)	
		5–10		Reference	
		≤ 5		0.90 (0.89–0.91)	

Studies examining mortality among subgroups					
Author	Subgroup	eGFR category	No. patients	HR (95% CI)	Adjustment variables
	> 8	> 15 10–15 5–10 ≤ 5	222 639	1.37 (1.35–1.39) 1.13 (1.11–1.14) Reference 0.94 (0.92–0.95)	Same as above
Rosansky (2011)[33]	Albumin ≥ 3.5 g/dL-HD only	0–4.9 5.0–9.9 10.0–14.9 ≥ 15.0	35 665†	Reference 1.27 1.53 2.18‖	Not specified
Kim[16]	Dialysis				
	HD	< 5 ≥ 5	47 61	Not detailed–(read off graph); significant difference at 60 months	Unadjusted
	PD	< 5 ≥ 5	52 50	Not detailed (read off graph); no significant difference at 60 months	Unadjusted
Collins[8]	HD	10–14 5–7	171 191	Reference 0.97 (0.66–1.41)	
Rosansky (2009)[34]	Age 65-74 y	5–9.9 > 15		Not provided	
Wilson[35]	HD only	< 5.0 5.0–10.0 > 10.0	46 180 45	Reference 1.58 (0.54–4.65)¶ 1.68 (0.65–4.32)	Sex, age, months at CKD clinic, comorbidity (cardiac disease, PVD, diabetes, antihypertensive use)
Tang[15]	PD only	Per ↓ 1 mL/min/1.73 m^2	233	1.53 (1.20–3.99)	Age, gender, diabetic status
Shiao[17]	PD only	Per ↑ 1 mL/min/1.73 m^2	275	1.18 (1.02–1.37)	Age, sex, level of education, occupational activity, nephrology referral, implantation of catheters, initiation of dialysis, comorbidities (diabetes, CAD, congestive heart failure), lab data
Hwang[36]	HD only	Per ↑ 1 mL/min/1.73 m^2	23 551	1.15 (1.14–1.17)	Age, sex, diabetes, GN, HTN, chronic TIN, CAD, CHF CVD, malignancy, liver cirrhosis, TB, dialysis initiation year
Clark[37]	HD only	Per ↑ 1 mL/min/1.73 m^2	25 910	1.01 (1.01–1.02)	Age, sex, ethnicity, DM, GN, RVD, modified CMi score, CAD, CHR, HTN, CVD, PVD, lung disease, malignancy, albumin, vascular access, late referral

Studies examining mortality among subgroups					
Author	Subgroup	eGFR category	No. patients	HR (95% CI)	Adjustment variables
Note: BMI = body mass index; CAD = coronary artery disease; CHD: coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CMi= Charlson Comorbidity Index; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GN = glomerulonephritis; HD = hemodialysis; HR = hazard ratio; HTN = hypertension; M = model; PD = peritoneal dialysis; PVD = peripheral vascular disease; RVD = renal vascular disease; TB = tuberculosis; TIN = tubulointerstitial nephritis. *Without diabetes, congestive heart failure, or heart disease. †Not presenting unadjusted analyses. ‡Number of patients in each subgroup not detailed for each model. §Hazard ratio not written out (read off of table). ‖ Confidence intervals not presented. ¶ Odds ratio, year 2 mortality (year 1 mortality not presented).					

Appendix 2: Search Strategies and Results

Question: Among adult patients (age 18 years or older) with advanced (stage 5) chronic kidney disease, what are the effects of an intent-to-initiate dialysis early (eGFR 10-14 ml/min) strategy compared with an intent-to-defer dialysis (eGFR 5-7 ml/min) strategy?

B**enefits, Harms and Resource Use**

Database: **Embase and MEDLINE**	
Search strategy: Hemodialysis benefits and harm and resources	**Date of search: 11/2013**
1. (start$ or initiation or initiate$ or initiating or timing or commenc$).ti. 2. (((start$ or initiation or initiate$ or initiating or commenc$) and timing) or ((early$ or late$ or earlier or delay$) adj (start or initiation))).tw. 3. 1 or 2 4. exp Renal Dialysis/ or h?emodialy$.tw. or dialy$.ti. or peritoneal dialysis.mp. or dialysis patient$.tw. or ((end stage or endstage) adj (kidney or renal)).ti. or dialysis therapy.tw. or exp *Hemofiltration/ or *Renal Replacement Therapy/ or esrd.ti. or renal replacement.ti. or capd.tw. or ur?emic patient$.tw. or h?emofilt$.tw. or intradialy$.tw. or sevelamer.mp. or ur?emia.ti. or tenckhoff$.tw. or renal hyperparathyroidism.tw. or ccpd.tw. or nephrogenic systemic fibrosis.tw. or (((((kidney or renal) adj failure) or (chronic adj (kidney or renal))).tw. or Catheterization,Central Venous/ or Catheters, Indwelling/ or renal replacement.mp. or infection$.mp. or erythropoietin$.mp. or fistula$.tw. or hyperoxaluria.mp.) and dialysis.tw.) or (exp Renal Insufficiency/ and (Catheters, Indwelling/ or erythropoietin$.mp. or Catheterization,Central Venous/ or an?emi$.ti. or nephrogenic.tw. or amyloid$.mp.)) or ((chronic or end-stage).mp. and (renal replacement or azot?emia).tw.) or (((chronic adj (kidney or renal)) or ur?emi$ or ckd).ti. and (inflammation.tw. or erythropoietin$.mp. or renal osteodystrophy.mp. or hypertrophy.tw.)) or ((ur?emi$.ti. or *Uremia/) and (calcification.tw. or hyperparathyroidism secondary.mp. or pruritus.mp. or secondary hyperparathyroidism.tw.)) or (((kidney or renal) adj transplant$) and candidates).tw. or (encapsulating.tw. and sclerosis.mp.) 5. 3 and 4 6. ((early$ or earlier or late$ or delay$) adj (dialys$ or h?emodialys$ or renal replacement)).tw. 7. ((start$ or initiation or initiate$ or initiating or timing or commenc$) adj3 (chronic dialysis or dialy$ or h?emodialys$ or renal replacement)).tw. and ((eGFR or mGFR or (residual adj (renal or kidney)) or rGFR or GFR or glomerul$ filtration rate$ or cGFR or (ml$ adj min) or MDRD$).mp. or (serum albumin or serum creatinine).tw.) 8. (((start$ or initiation or initiate$ or initiating or timing or commenc$) adj2 (dialys$ or h?emodialys$)) and (mortality and survival)).mp. 9. (((start$ or initiation or initiate$ or initiating or timing or commenc$) adj2 (dialys$ or h?emodialys$)) and ((early$ or earlier or late or later or delay$) adj3 (dialysis or h?emodialysis))).tw. 10. (initiation adj5 (dialysis or h?emodialysis)).tw. and ((eGFR or mGFR or (residual adj (renal or kidney)) or rGFR or GFR or glomerul$ filtration rate$ or cGFR or (ml$ adj min) or MDRD$).tw. or Time Factors/ or Glomerular Filtration Rate/) 11. ((start$ or initiation or initiate$ or initiating or timing or commenc$) adj2 (dialys$ or h?emodialys$ or renal replacement)).tw. and ((mortality or morbidity or death or died or prolong$).tw. or mo.fs.) and (survival.tw. or time factors/ or risk factor$.tw.) 12. (peritoneal clearance$ and dialysis).ti. and ((mortality or morbidity or death or died or prolong$).tw. or mo.fs.) 13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 14. (aki or intensive care or icu or (acute adj (kidney or renal))).ti. or critical.jw. 15. *Acute Kidney Injury/ not *Kidney Failure,Chronic/ 16. ((transplant$ or donor$) not (dialys$ or h?emodialys$ or end-stage)).ti. 17. 13 not (14 or 15 or 16) 18. limit 17 to (case reports or editorial or letter or news) 19. 17 not 18 20. 19 not (animals/ not (humans/ or exp persons/)) 21. limit 20 to english language 22. limit 21 to yr="2012 - 2013"	

Date limit: 01/2012 - 11/2013 Study Types: All	
Records Retrieved	953

Database: **Additional papers suggested by Panel members**
1. https://scot.org.sa/en/images/stories/pdf/ANNUAL_REPORT_2012/annual_report_2012_en.pdf Accessed December 5th, 2013 2. Amal A. Hassanien, Fahdah Al-Shaikh, Eszter P. Vamos, Ghasem Yadegarfar, Azeem Majeed Epidemiology of end-stage renal disease in the countries of the Gulf Cooperation Council: a systematic review *JRSM Short Reports June 2012 3: 38, first published on June 1, 2012 doi:10.1258/shorts.2012.011150* 3. Al Wakeel J, Al Harbi A, Bayoumi M, Al-Suwaida K, Al Ghonaim M, Mishkiry A Quality of life in hemodialysis and peritoneal dialysis patients in Saudi Arabia. Journal Ann Saudi Med. 2012 Nov-Dec;32(6):570-4. doi: DOI: 10.5144/0256-4947.2012.570 4. Al Onazi M, Al Jondeby M, Azeem M, Al Sayyari A. Factors affecting Saudi hemodialysis patients' perception of healthcare providers' empathy. Journal Arab J Nephrol Transplant. 2011 May; 4(2):71-6. 5. Al Saran K, Sabry A. The cost of hemodialysis in a large hemodialysis center. Journal Saudi J Kidney Dis Transpl. 2012 Jan; 23(1):78-82.

Summary of Searches

Total No. Retrieved:	**958**
Cochrane:	0
Medline/Embase	953
Others:	5
Duplicates:	263
No. Total without duplicates**:**	**695**
Screening (Title and Abstract Review)	
No. Excluded:	684
Included for Full Text review:	11
Selection (Full Text Review)	
No. Excluded:	4
Reasons for exclusions:	
1. Review article 2. Do not compare early and late dialysis	

Search for Values and Preferences

Database: **Embase and MEDLINE**	
Search strategy: Hemodialysis values and preferences	**Date of search: 11/2013**

1. patient$ participation.mp. or exp patient participation/
2. patient$ satisfaction.mp. or exp patient satisfaction/
3. attitude to health.mp. or exp Attitude to health/
4. (patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or user$ view$ or patient$ view$ or patient$ value$).mp.
5. (patient$ utilit$ or health utilit$).mp.
6. health related quality of life.mp. or exp "quality of life"/
7. (health stat$ utilit$ or health stat$ indicator$ or (health stat$ adj 2 valu$)).mp. or exp Health Status Indicators/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Saudi Arab$.mp. or Saudi Arabia/
10. Riyadh.mp.
11. Jeddah.mp.
12. Kh*bar.mp.
13. Dammam.mp.
14. 9 or 10 or 11 or 12 or 13
15. Kuwait$.mp. or Kuwait/
16. United Arab Emirates.mp. or United Arab Emirates/
17. Qatar$.mp. or Qatar/
18. Oman$.mp. or Oman/
19. Yemen$.mp. or Yemen/
20. Bahr*in$.mp. or Bahrain/
21. 15 or 16 or 17 or 18 or 19 or 20
22. Middle East$.mp. or Middle East/
23. Jordan$.mp. or Jordan/
24. Libya$.mp. or Libya/
25. Egypt$.mp. or Egypt/
26. Syria$.mp. or Syria/
27. Iraq$/ or Iraq.mp.
28. Morocc$.mp. or Morocco/
29. Tunisia$.mp. or Tunisia/
30. Leban$.mp. or Lebanon/
31. West Bank.mp.
32. Iran$.mp. or Iran/
33. Turkey/ or (Turkey or Turkish).mp.
34. Algeria$.mp. or Algeria/
35. Arab$.mp. or Arabs/
36. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
37. 35 or 36
38. 14 or 21 or 37
39. (start$ or initiation or initiate$ or initiating or timing or commenc$).ti.
40. (((start$ or initiation or initiate$ or initiating or commenc$) and timing) or ((early$ or late$ or earlier or delay$) adj (start or initiation))).tw.
41. 39 or 40
42. exp Renal Dialysis/ or h?emodialy$.tw. or dialy$.ti. or peritoneal dialysis.mp. or dialysis patient$.tw. or ((end stage or endstage) adj (kidney or renal)).ti. or dialysis therapy.tw. or exp *Hemofiltration/ or *Renal Replacement Therapy/ or esrd.ti. or renal replacement.ti. or capd.tw. or ur?emic patient$.tw. or h?emofilt$.tw. or intradialy$.tw. or sevelamer.mp. or ur?emia.ti. or tenckhoff$.tw. or renal hyperparathyroidism.tw. or ccpd.tw. or nephrogenic systemic fibrosis.tw. or (((((kidney or renal) adj failure) or (chronic adj (kidney or renal))).tw. or Catheterization,Central Venous/ or Catheters, Indwelling/ or renal replacement.mp. or infection$.mp. or erythropoietin$.mp. or fistula$.tw. or hyperoxaluria.mp.) and dialysis.tw.) or (exp Renal Insufficiency/ and (Catheters, Indwelling/ or erythropoietin$.mp. or Catheterization,Central Venous/ or an?emi$.ti. or nephrogenic.tw. or amyloid$.mp.)) or ((chronic or end-stage).mp. and (renal replacement or azot?emia).tw.) or (((chronic adj (kidney or renal)) or ur?emi$ or ckd).ti. and (inflammation.tw. or erythropoietin$.mp. or renal osteodystrophy.mp. or hypertrophy.tw.)) or ((ur?emi$.ti. or

*Uremia/) and (calcification.tw. or hyperparathyroidism secondary.mp. or pruritus.mp. or secondary hyperparathyroidism.tw.)) or (((kidney or renal) adj transplant$) and candidates).tw. or (encapsulating.tw. and sclerosis.mp.) 43. 41 or 42 44. ((early$ or earlier or late$ or delay$) adj (dialys$ or h?emodialys$ or renal replacement)).tw. 45. ((start$ or initiation or initiate$ or initiating or timing or commenc$) adj3 (chronic dialysis or dialy$ or h?emodialys$ or renal replacement)).tw. and ((eGFR or mGFR or (residual adj (renal or kidney)) or rGFR or GFR or glomerul$ filtration rate$ or cGFR or (ml$ adj min) or MDRD$).mp. or (serum albumin or serum creatinine).tw.) 46. (((start$ or initiation or initiate$ or initiating or timing or commenc$) adj2 (dialys$ or h?emodialys$)) and (mortality and survival)).mp. 47. (((start$ or initiation or initiate$ or initiating or timing or commenc$) adj2 (dialys$ or h?emodialys$)) and ((early$ or earlier or late or later or delay$) adj3 (dialysis or h?emodialysis))).tw. 48. (initiation adj5 (dialysis or h?emodialysis)).tw. and ((eGFR or mGFR or (residual adj (renal or kidney)) or rGFR or GFR or glomerul$ filtration rate$ or cGFR or (ml$ adj min) or MDRD$).tw. or Time Factors/ or Glomerular Filtration Rate/) 49. ((start$ or initiation or initiate$ or initiating or timing or commenc$) adj2 (dialys$ or h?emodialys$ or renal replacement)).tw. and ((mortality or morbidity or death or died or prolong$).tw. or mo.fs.) and (survival.tw. or time factors/ or risk factor$.tw.) 50. (peritoneal clearance$ and dialysis).ti. and ((mortality or morbidity or death or died or prolong$).tw. or mo.fs.) 51. 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 52. (aki or intensive care or icu or (acute adj (kidney or renal))).ti. or critical.jw. 53. *Acute Kidney Injury/ not *Kidney Failure,Chronic/ 54. ((transplant$ or donor$) not (dialys$ or h?emodialys$ or end-stage)).ti. 55. 51 not (52 or 53 or 54) 56. 8 and 38 and 55 57. limit 56 to (humans and yr="2003 -Current" and (arabic or english)) 58. limit 57 to (case reports or editorial or letter or news) 59. 57 not 58 Study Types: All	
Records Retrieved	289

Summary of Searches

Total No. Retrieved::	**289**
Cochrane:	0
Medline/Embase:	289
Duplicates:	74
No. Total without duplicates**:**	**215**
Screening (Title and Abstract Review)	
No. Excluded:	214
Included for Full Text review:	1
Selection (Full Text Review)	
No. Excluded:	1
Reasons for exclusions:	
1. Does not inform values and preferences about early vs late dialysis	


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The Saudi Center for Evidence Based Health Care
وزارة الصحة
Ministry of Health