Appendix 3: Detailed guideline and systematic review (as supplied by the authors)

Canadian Society of Nephrology 2013 Clinical Practice Guideline for Timing the Initiation of Dialysis

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Introduction

Patients with kidney failure require renal replacement therapy as a life-sustaining treatment either in the form of dialysis (i.e., hemodialysis or peritoneal dialysis) or a kidney transplant. Whether provided at home or in-centre, the burden and morbidity imposed by dialysis mandates careful consideration for the optimal timing of its initiation. Since the inception of dialysis, clinicians and guideline developers have struggled to balance the trade-offs inherent to this decision-making process, recognizing the risks, costs, and inconvenience associated with the procedure itself, while concurrently seeking to avoid the deleterious effects of the uremic milieu.

To date, the development of clinical practice guidelines for timing the initiation of dialysis has been limited by methodological challenges and a lack of high-quality evidence. First, creatinine-based measures estimating kidney function, such as Modification of Diet in Renal Disease (MDRD) [1] estimated glomerular filtration rate (eGFR) and Cockroft–Gault estimated creatinine clearance (eCrCl), have historically served as criteria for initiation of dialysis.[2–4] However, both measures have limitations in their accuracy at lower levels of kidney function.[5] Second, the reliance on observational studies comparing "early" (at a higher level of residual kidney function, e.g., 10–15 mL/min) versus "late" (lower level of residual kidney function, e.g., < 10 mL/min) initiation of dialysis, has introduced many forms of bias inherent to these studies. Further, nutritional markers, such as subjective global assessment scores, serum albumin levels, and measures of body nitrogen, were previously considered important variables in decision making for timing of dialysis initiation.[6] More recent studies have suggested that these

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surrogate markers have limited associations with patient survival, and are not considered to be valid predictors of hard outcomes.[7] Moreover, treatment recommendations should be based on patient-important outcomes — those that align with patient values and preferences rather than physiological measures, surrogate or otherwise.[8]

The level of kidney function at dialysis initiation has been increasing in Canada and the United States over the past 2 decades.[9] Factors contributing to this phenomenon may include increasing reliance on eGFR and nutritional surrogate markers, as well as an increasing burden of comorbidity and frailty among patients with chronic kidney disease.[8] Additionally, it is well recognized that the human and financial resources required to care for the growing end-stage kidney disease population are substantial. Therefore, early initiation of dialysis, without specific indications or established benefit, may have implications for resource use.

With these considerations in mind, we build on previous iterations of the Canadian Society of Nephrology Clinical Practice Guidelines for Timing of the Initiation of Dialysis.[10,11] In this guideline, we introduce the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (www.gradeworkinggroup.org),[12] which provides a transparent and rigorous framework that considers the balance of benefits and harms based on patient-important outcomes, quality of evidence, patient values and preferences, and resource implications in formulating recommendations.

Purpose and scope of this guideline

Our objective was to develop a clinically useful and broadly generalizable guideline to assist healthcare providers in guiding their patients through decisions regarding the timing of initiation of dialysis. We assumed a Canadian societal perspective, and primarily considered Canadian practices and values in the development of this guideline. However, we believe our guidelines are generalizable to other jurisdictions. We provide detailed and explicit summaries and explanations of the factors considered in formulating our recommendations so that our guideline can be adopted and adapted by different end users nationally and internationally.

Definition of the "intent-to-defer" treatment strategy

While desirable, an unbiased and direct comparison of patient outcomes between 'early' (at higher eGFR) and 'late' (at lower eGFR) initiation of dialysis is not feasible. Prior to the completion of the Initiating Dialysis Early and Late (IDEAL) trial,[13] studies addressing the timing of initiation of dialysis were observational in design. These studies allowed for naturalistic observation of patients who started dialysis early versus late, but under a wide range of unmeasured clinical circumstances, allowing for potential residual confounding. Although these studies directly compared outcomes between early- and late-start dialysis, they were prone to serious risk of bias, which can only be overcome by random treatment allocation. In the controlled clinical trial setting, however, it is not feasible (or ethical) to directly study the effects of late versus early initiation of dialysis. Clinical circumstances must override treatment group allocation. Therefore, one would not attempt to delay the start of dialysis in patients with relatively preserved eGFR (e.g., 10–15 mL/min) who have significant uremic symptoms or other

complications likely to benefit from dialysis therapy. The IDEAL clinical trial protocol specified, appropriately, that patients could crossover to the other treatment arm at the discretion of the treating physician, thereby allowing for the direct evaluation of the following clinical question: Do patient outcomes vary if we aim to start dialysis earlier ("intent-to-start-early") versus later ("intent-to-start-late" or "intent-to-defer"). We considered these 2 treatment strategies (intent-to-start-early vs. intent-to-defer) when reviewing evidence and formulating recommendations.

Target population

This guideline is intended to address management decisions for adult patients (age >18 years) with Stage 5 chronic kidney disease (eGFR < 15 mL/min/1.73 m^2) for whom an elective start to dialysis is anticipated. This guideline applies to patients planning to use either home or in-centre hemodialysis, or peritoneal dialysis. We do not consider preemptive transplantation, urgent initiation of dialysis for acute kidney failure, conservative management without dialysis, or pediatric populations.

Guideline panel composition

Co-chairs for the guideline workgroup were selected by the Canadian Society of Nephrology Clinical Practice Guideline Committee based on their content and methodological expertise. Members of the Canadian Society of Nephrology were invited to participate in the guideline development, with select members invited based on their expertise in guideline development. The panel included a nationally representative group of nephrologists drawn from a mix of academic and community-based practices, many of whom had prior experience with guideline development, research methodology, knowledge translation, and the GRADE framework, as well as in the knowledge translation activities.

Guideline development methods

The GRADE process began with developing clinical management questions pertinent to the guideline, using the PICO (population, intervention, comparison, outcome) format.[14] This focused guideline addressed a single critical clinical management question: Among adult patients with Stage 5 chronic kidney disease for whom an elective start to dialysis is anticipated, is early (as compared to late) initiation of dialysis (as defined by eGFR thresholds in included studies) associated with improved patient-important outcomes?

Initially, the panel specified survival, quality of life, and hospitalization as relevant patient-important outcomes for the guideline. We then identified a number of outcomes related to resource use. The panel then performed a formal rating exercise (using a 9-point unipolar adjectival scale) rating importance of outcomes in decision-making. The panel assumed the patient perspective when rating outcomes. Critically important (score 7–9) and important (score 4–6) outcomes for decision-making were then considered in developing the recommendation. Survival and quality of life were rated critical, hospitalization was rated important but not critical, and nutritional surrogate markers were rated of interest but not

important for decision making. All outcomes related to resource use were rated important but not critical for decision making.

We conducted a systematic review to address the question and its related outcomes. A detailed systematic review protocol is presented in Appendix 2. We summarized pooled effects where possible, and used narrative synthesis when necessary. The evidence and quality judgments were summarized in evidence profile tables using the GRADE Profiler software application.[15] We converted relative treatment effects into absolute treatment effects using the baseline event rate in the control group and pooled relative treatment effects, where possible. We summarized and rated the quality of evidence on an outcome-by-outcome basis (across studies), based on 5 domains specified in GRADE: risk of bias, imprecision, indirectness, inconsistency, and publication bias.[16] Quality appraisal and pooled effect estimates were presented separately for observational studies and clinical trials. Levels of evidence quality were reported as high, moderate, low, and very low. In the GRADE system, evidence from randomized clinical trials begins with a high-quality rating, and is rated down for serious (1 level) or very serious (2 levels) limitations in any of the 5 domains. Evidence from observational studies begins with a low quality rating, but can be rated up for large treatment effects, dose–response relationships, or antagonistic bias (removing an existing bias would further strengthen the conclusions of the study).[17] Finally, we summarized our review findings and appraisal within 4 key domains as specified by GRADE for moving from evidence to recommendations: 1) the overall quality of the body of evidence, 2) the balance between benefits and harms, 3) patient values and preferences, and 4) resource implications. Considering this information, the panel members were asked to make a final qualitative judgment regarding the overall direction and strength of the recommendation. Panel members agreed unanimously in favour of the final stated recommendation.

After approval by the guideline panel, the document was submitted to the Canadian Society of Nephrology Clinical Practice Guidelines Committee for peer review by content and methodological experts, followed by a public review before final approval of the guideline.

Systematic review methods

We constructed search strategies (Appendix 3) in Medline, PubMed, EMBASE, and CENTRAL, in consultation with a health information specialist at Western University, London, Ontario, Canada. We included clinical trials, observational studies, and systematic reviews reporting on mortality, quality of life, hospitalization, and nutritional status as measured by total body nitrogen (studies reporting albumin or subjective global assessment scores were not included), with no language restrictions. Title and abstract screening, full-text screening, and data abstraction were performed independently and in duplicate (LB and AB), using pre-piloted forms. We hand-searched reference lists of identified studies and major nephrology conference abstracts published between 2009 and 2011. We collected information about methodological characteristics (including risk of bias assessment criteria), description of study participants, definitions of study interventions, and outcomes. Risk of bias for clinical trials was assessed

using the criteria developed by Higgins et al;[15] risk of bias for observational studies was assessed by applying a modified Newcastle Ottawa scale.[18]

A priori, we planned to examine observed heterogeneity by considering the following subgroups: peritoneal dialysis versus hemodialysis, study definition of early versus late, short-term (< 90 days) versus long-term (≥ 90 days) follow-up, and diabetes versus no diabetes.

Economic evaluation methods and quality appraisal

We considered differences in healthcare resource utilization and costs associated with time on dialysis, hospitalization, distance travelled for dialysis, and outpatient visits. Mean differences were calculated (intent-to-start-early–intent-to-start-late) and, where possible, Canadian microcosting data[19] were applied to units of resource use derived from the IDEAL trial.[20] We assumed that hospital days and time on dialysis in the Australian population would be applicable to a Canadian population and, therefore, did not rate-down the quality of evidence for these outcomes. However, travel, hospitalization, and outpatient visit costs could not be converted from Australian (A$) to Canadian (CA$) dollars; therefore, we rated-down the quality of evidence by one level because of indirectness (lack of directly applicable data).[21]

Implications of strength of recommendation

Within the GRADE framework, a strong recommendation implies that most patients would choose the recommended course of action, and that less deliberation and weighing of benefits and harms is required. A strong recommendation also implies that government agencies may consider adopting a recommendation as policy. A conditional recommendation, on the other hand, implies that while many informed patients would choose in favour of an intervention, many others would not. Thus a conditional recommendation requires that health care providers engage patients in shared decision-making, and acknowledge the likelihood that varying patient circumstances, values, and preferences will result in differing decisions regarding an intervention.

Adaptation of the Cockroft–Gault eCrCl to the MDRD eGFR in a Canadian Population

In Canada the eGFR, as estimated by the MDRD equation, is routinely reported with the creatinine level and is used in clinical decision making. In order to apply the findings of the IDEAL study in the Canadian population, we derived the range of eGFR values that correspond to the lower (5–7 mL/min/1.73 m^2) eCrCl threshold used in the IDEAL study intent-to-defer strategy. We obtained data from the Canadian Organ Replacement Register (CORR) which records physical data and laboratory values on all patients starting chronic dialysis in Canada. We identified 2434 patients who initiated dialysis between 2006 and 2011, with a CrCl between 5–7 mL/min/1.73 m^2. The corresponding eGFR was 5.2 mL/min/1.73 m^2 (standard deviation [SD] 1.3, median 5.1, range 1.8–10.8 mL/min/1.73 m^2).

Results

Study selection and study characteristics

Figure 1 in Appendix 3 details the search results and the reasons for study exclusion. We identified a total of 26 reports of 23 studies, and one systematic review by Susantitaphong et al., which reported a pooled estimate for the mortality outcome.[13] We found 3 reports from a single clinical trial (the IDEAL trial),[22] one of which was also included in the previous systematic review.[13] Among the additional reports, one described the hemodialysis-treated subgroup[23] and the second, the effect of dialysis initiation on quality of life.[20] The remaining 23 studies were observational in design. Sample sizes ranged from 100 to over 900,000 patients (large registry-based study). Five studies included only patients initiating hemodialysis,[24–28] 3 included patients initiating peritoneal dialysis,[29–31] and 14 included both hemodialysis and peritoneal dialysis patients[32–45]; in 1 study, modality was not specified.[46]

As already stated, a previous systematic review examined only mortality as an outcome. We identified an additional 5 studies that reported mortality,[23,32–35] which were not included in this systematic review.[13] The panel reviewed these studies in detail to determine if a *de novo* meta-analysis was warranted. One study did not provide data that could be used for pooling,[34] one presented unadjusted analyses resulting in a high risk of bias,[33] one did not present patient characteristics of the study population,[35] one [32] reported on a study population described in another included study,[45] and one was a subgroup analysis of the IDEAL trial.[23] In light of these observations, the panel decided to use the effect estimate for mortality provided by Susantitaphong et al.; this decision was based on the high quality of the analysis and report, and the low likelihood that including these additional studies would provide a more reliable estimate of effect.

For the other outcomes of interest, we identified 2 studies that reported quality of life,[20,36] 6 that reported hospitalizations,[20,24,29–31,33] and 1 that reported nutritional status as measured by total body nitrogen.[46] A narrative synthesis of these studies is provided in Appendix 4.

Synthesis of results

The single randomized controlled trial (RCT) that informed this guideline allowed for symptomatic patients randomized to the intent-to-defer arm (Cockroft–Gault eCrCl 5–7 mL/min) to begin dialysis earlier if they had symptoms of uremia or hypervolemia. This resulted in a crossover rate of 75% and an average eCrCl of 9.8 mL/min (MDRD eGFR 7.2 mL/min) at dialysis initiation in the late-start group. There was also a 19% crossover rate among those in the intent-to-start-early group, who deferred dialysis to a lower GFR, resulting in an average eCrCl of 12.0 mL/min (MDRD eGFR 9.0 mL/min) at dialysis initiation in the early start group.[20] Of note, all patients remaining in the intent-to-defer group started dialysis when the eCrCl reached 5–7 mL/min/m^2, regardless of the presence of symptoms.

Survival

The RCT demonstrated no effect with the intent-to-defer versus intent-to-start-early strategies (hazard ratio [HR]=1.04), but with a wide confidence interval (CI) (95% CI 0.83 to 1.30), which lowered our confidence in the estimate of effect. The pooled effect estimate from 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. However, residual confounding was likely severe in this body of evidence. Considering results of both the RCT and the observational evidence, we considered the overall quality of evidence for survival to be moderate.

Quality of life

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.[20] In addition, neither of the 2 observational studies that reported quality of life found an association between timing the start of dialysis and quality of life. One observational study found no significant difference in SF-36 health survey scores at 12-month follow-up, despite higher baseline health-related quality of life among those who initiated dialysis earlier.[36]

Hospitalization

We identified a total of 6 studies (5 observational [24,29–31,33] and 1 randomized trial[20]) that assessed the effect of earlier versus later initiation of dialysis on risk of hospitalization. The single randomized trial that examined this outcome found no significant difference in hospitalization days between early and late start of dialysis.[20] Measures and reporting of hospitalization varied across observational studies, and precluded pooling for this outcome. Three studies found no significant difference in the number of days spent in hospital in the early versus late initiation of dialysis groups.[24,31,33] However, Shiao et al.[30] found that late initiation of dialysis was associated with a reduced risk of all-cause hospitalization, although indication bias and residual confounding may have been present. Tang et al.[29] reported fewer hospitalizations per person-year among “elective starters” (intent-to-start-early), mean 2.13 (SD 1.13) as compared with “initial refusers” (intent-to-start-late) mean 3.14 (SD 1.17, $p = 0.05$); initial refusers may have had better health status, although this is a matter of speculation.

Nutritional status

One included study examined the effect of early versus late initiation of dialysis on nutritional status.[46] The study quality was limited by a serious risk of bias because of large unadjusted baseline differences between groups, and the form of dialysis provided was not specified. The study suggested that nitrogen index was higher in early versus late starters. Given the uncertainty surrounding the measurement, reporting, and clinical significance of this outcome, it was not considered in formulating the recommendations.

Resource use

One report from the IDEAL trial examined resource use. The intent-to-start-early group initiated dialysis a mean of 3.8 months (median 5.6 months) earlier from the time of randomization, compared with the intent-to-defer group [median start time 1.90 months in the intent-to-start-early group and 7.30 months in the intent-to-defer group (hazard ratio=1.96; 95% CI 1.67 to 2.30; $p < 0.001$)].[47] This was associated with higher dialysis costs (CA$10 777). Costs of transport to dialysis were also greater. The number and costs of hospitalizations and outpatient visits were not significantly different between groups (Table 3).

Risk of bias within studies

Susantitaphong et al.[13] rated study quality as fair with respect to risk of bias for the majority of the 17 studies included in their review (Newcastle–Ottawa Scale score range 3–7; mean 5, SD 1 for observational studies; Jadad scale score for the IDEAL trial=3/5). However, we considered the risk of indication bias a major limitation in this entire body of evidence because none of these studies could adjust or account for reasons for starting dialysis. Indications for late dialysis initiation may have ranged from late presentation (e.g., late referral), patient refusal, or lack of symptoms, whereas early initiation may have been due to intractable symptoms or physician discretion. Outcomes for patients with this diverse range of clinical presentations would be expected to vary significantly, yet none of these factors can be adequately addressed using observational designs. Therefore, we considered the risk of bias in this body of evidence to be serious. Accordingly, the majority (9/10) of observational studies that our group reviewed had serious to very serious risk of bias due to confounding by indication, selection bias, loss to follow-up, and suboptimal adjustment for important prognostic factors. We summarized the overall risk of bias across all outcomes in GRADE Evidence Profile tables (Appendix 4, Tables 1 and 2), with detailed explanations in footnotes.

Risk of bias across studies

Outcomes in the RCT were reported as per the published protocol; hence, there was no evidence of selective outcome reporting. Using funnel plots and the Egger test, Susantitaphong et al.[13] found no evidence of publication bias for studies reporting mortality.

Subgroup analyses

We found no evidence to support a subgroup effect or rationale to develop separate recommendations for patients initiating peritoneal dialysis or hemodialysis, or patients with or without diabetes. Specifically, the single RCT did not detect significant interactions between these factors and treatment effect. We made a post-hoc decision to consider studies that examined the association between high versus low levels of comorbidity and outcome with early versus late initiation of dialysis. One such observational study suggested potential harm with early initiation of dialysis in younger patients with lower levels of comorbidity.[35] Given the concordant signals of comparable or favourable outcomes with an intent-to-defer dialysis strategy across all patient subgroups, we elected to issue a single recommendation applicable to all subgroups.

Moving from evidence to recommendations

Balance of benefits and harms

Overall, we were unable to find any evidence of benefit with intent-to-start-early (or early) as compared with intent-to-defer (or late) dialysis for mortality, quality of life, or hospitalization in either the RCT or the observational studies. However, the time on dialysis and dialysis-associated health care resource use were significantly greater in the intent-to-start-early group. An intent-to-defer approach avoids the burden and inconvenience of an early start in an asymptomatic patient. Simultaneously, it avoids the morbidity associated with delaying dialysis in a symptomatic patient.

Importantly, however, no published clinical trials have studied the effects of deferring dialysis beyond 5–7 mL/min/1.73 m^2 (eGFR ≤ 6 mL/min/1.73 m^2). In the IDEAL study, all patients remaining in the intent-to-defer group initiated dialysis when the eCrCl reached 5–7 mL/min regardless of whether they had symptoms. Therefore, we consider an MDRD eGFR range of ≤ 6 mL/min/1.73 m^2 a reasonable lower threshold for the intent-to-defer strategy in a Canadian population. Hence, it seems prudent to initiate dialysis once this threshold is reached, based on this uncertainty and to reduce the risk of emergent dialysis.

Quality of evidence across studies

Quality of evidence ratings are summarized in Appendix 4, Tables 1 and 2. The quality of evidence for observational studies evaluating critical outcomes (mortality and quality of life) was very low, whereas the quality of evidence for outcomes reported in the single RCT was moderate (mortality outcome rated down for imprecision). The concordance in the direction of effect across the observational and RCT evidence increases our confidence in the overall estimate of effect.

Values and preferences

We were unable to identify direct measures of patient preferences as they pertain to the timing of initiation of dialysis. Based on our collective clinical experience, however, we 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 burden and inconvenience associated with initiating dialysis. Therefore, we assumed that patients without clinical indications for dialysis would favour deferring initiation of dialysis until a clear indication emerged. Although no published studies characterized values and preferences in this population, it is reasonable to assume they are uniform across the target population, particularly because there are no trade-offs between benefits and harms.

Implications for resource use

The quality of evidence for resource use ranged between low to high, but it was concluded that, on average, an intent-to-defer dialysis strategy would likely result in significant cost savings, especially when applied across a health care system or population.

Implementation

The CANN-NET Knowledge Translation Committee will develop an integrated knowledge translation (KT) and communication strategy for this guideline based on the priorities of and with input from CANN-NET knowledge users (heads of renal programs across Canada), patients, and a patient advocacy foundation (The Kidney Foundation of Canada).

Drawing on prospectively collected data in the CORR and other administrative databases, CANN-NET will also develop and implement a strategy to monitor outcomes outlined in this guideline. This will include a prospective evaluation of the impact of the adoption of this guideline on timing of dialysis initiation in patients with progressive chronic kidney disease, patient survival, hospitalization rates, unplanned dialysis starts, and dialysis-related costs. More information about CANN-NET KT initiatives can be found at http://www.cann-net.ca. This guideline will be updated as new relevant information becomes available.

Other guidelines

This guideline agrees with the recommendations from the Canadian Society of Nephrology (CSN) 2008 chronic kidney disease (CKD) guideline group,[4] and the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA; 2012)[48] that creatinine-based estimates of GFR alone should generally not be used to guide the start of dialysis in the absence of complications related to chronic kidney disease.[11] Our recommendation to initiate dialysis in the absence of symptoms in patients with eGFR ≤ 6 mL/min/1.73 m^2 is consistent with the Caring for Australians with Renal Disease (CARI) guidelines[49] (2005) and the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (2006).[50]

In contrast with the CSN 2008 guidelines, we no longer recommend that dialysis be initiated based only on a decline in nutritional status (as measured by serum albumin, lean body mass, or subjective global assessment). Our recommendation differs from the KDOQI recommendation that "When patients reach stage 5 CKD (estimated GFR<15 mL/min/1.73m2), nephrologists should evaluate the benefits, risks, and disadvantages of beginning kidney replacement therapy"[50] and the CARI recommendation to initiate dialysis at GFR < 10 mL/min/1.73 m^2 if uremic symptoms or signs of malnutrition arise.[49] Finally, unlike the ERA-EDTA, we do not recommend earlier initiation of dialysis in higher-risk subgroups, such as patients with diabetes.[48]

Gaps in knowledge

The optimal management of patients with eGFR ≤ 6 mL/min/1.73 m^2 is based on limited data because they represented a limited subset of the IDEAL study participants (25% of the intent-to-defer arm). Unfortunately, observational studies comparing these very late starts with other eGFR thresholds will likely be prone to indication bias, and clinical trials addressing this small population may not be feasible.

Conclusion

Given the overall quality of evidence, net balance of benefits and harms, values and preferences, and implications for resource use as described in detail here, the panel voted unanimously in favour of a strong recommendation for an intent-to-defer dialysis strategy. An intent-to-start-early approach to dialysis is not justified given the lack of compelling benefit, along with the additional burden to patients and the healthcare system. An intent-to-defer strategy requires that patients be closely monitored for the emergence of uremic symptoms or other complications, or a decline in eGFR to ≤ 6 mL/min/1.73 m^2, which would serve as indications for starting dialysis.

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