Canadian Society of Nephrology 2014 clinical practice guideline for timing the initiation of chronic dialysis

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Initiating chronic dialysis has major implications for patients and health care systems. Within the spectrum of severity of chronic kidney disease, there is a need to identify a threshold before which starting dialysis offers no benefit to the patient but beyond which there may be some measurable risk.

Identifying this threshold remains a challenge because of the inaccuracy of creatinine-based measures of kidney function;[1–3] a body of evidence composed of potentially biased observational data; and reliance on poorly validated nutritional surrogate markers,[4] with an underemphasis on patient-important outcomes such as hospital admission and quality of life. Collectively, these factors may account in part for the recent increase in earlier (i.e., at a higher level of kidney function) initiation of dialysis in Canada and the United States.[5] Considering the enormous burden imposed by dialysis on patients and health care systems, there is a need for a judicious approach to dialysis initiation.

The Initiating Dialysis Early and Late (IDEAL) study,[6] builds on the prior observational experience with timing of dialysis initiation and has prompted us to revisit the previous guidelines by the Canadian Society of Nephrology.[7,8]

Key points

- Traditional criteria for initiation of dialysis have limitations because they are based on creatinine-based measures of kidney function.
- Early initiation of dialysis does not improve survival, quality of life or hospital admission rates compared with late or deferred initiation of dialysis.
- We recommend an "intent-to-defer" strategy, whereby patients with an estimated glomerular filtration rate (eGFR) below 15 mL/min per 1.73 m^2 are closely monitored by a nephrologist, with dialysis initiated when clinical indications emerge or the eGFR is 6 mL/min per 1.73m^2 or less, whichever of these should occur first.
- Our recommendation places a high value on the avoidance of a burdensome and resource-intensive therapy that does not provide measurable benefit when started before the development of a clinical indication, such as uremic symptoms.

Scope

Our target audience includes Canadian nephrologists, primary care physicians, general internists, and other internal medicine subspecialists and nursing specialists who care for patients with chronic kidney disease and play a critical role in referring patients and comanaging their treatment.

The target population includes adults (aged > 18 yr) with stage 5 chronic kidney disease (i.e., estimated glomerular filtration rate [eGFR] < 15 mL/min per 1.73 m^2) for whom initiation of elective dialysis is planned. This guideline pertains to all forms of dialysis for chronic kidney disease in adults but does not consider timing of preemptive transplantation, dialysis for acute kidney injury, pediatric populations or patients choosing conservative management without dialysis.

Methods

Guideline panel composition

This guideline was developed by the Canadian Kidney Knowledge Translation and Generation Network (CANN-NET) Ad-Hoc Guidelines Working Group on Timing of Dialysis Start. Cochairs were nominated by the Canadian Society of Nephrology Clinical Practice Guidelines Committee. We assembled a nationally representative panel consisting of practising nephrologists from academic and community dialysis programs. Panel members had expertise in one or more of guideline development, knowledge translation, clinical nephrology and research methods.

Guideline development methods

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system for guideline development (Box 1).[9–16] We first formulated a clinical management question as follows: "Among adult patients with stage 5 chronic kidney disease for whom chronic dialysis is anticipated, is 'early,'

as compared with 'late,' initiation of dialysis associated with improved patient-important outcomes?" We conducted a systematic review and summarized pooled estimates of treatment effect for each of the important and critical outcomes for decision-making in GRADE evidence profile tables. The evidence profiles, systematic review protocol and search strategy are in Appendices 1, 4 and 5, respectively, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130363/-/DC1.

Our review focused on patient-important outcomes. Based on a prioritization exercise, survival and quality of life were rated critical, hospital admission was important but not critical, and nutritional surrogate markers were of interest, but not important for decision-making. All outcomes related to resource use were rated important, but not critical for decision-making. These included costs associated with travel for dialysis, hospital admission, clinic visits and the dialysis procedure itself. Where possible, we applied Canadian micro-costing data to units of resource use reported in the Australian IDEAL trial.[17,18] We assumed that days spent in hospital and time on dialysis in an Australian population would apply to a Canadian population, but we recognized that costs associated with travel, hospital admission and outpatient clinic visits could not be directly converted from Australian to Canadian dollars. The quality of evidence was therefore rated down for these outcomes.

Prior guidelines were based on observational studies that were prone to confounding by indication (i.e., patients who had earlier initiation of dialysis may have been in poorer health with a worse prognosis than those who started dialysis later) and cannot provide accurate estimates of the benefits and harms associated with starting dialysis early versus late. The IDEAL study compared early versus late initiation of dialysis, based on estimated creatinine clearance (eCrCl) thresholds (10–14 v. 5–7 mL/min per 1.73 m^2) as estimated by the Cockroft–Gault formula.[6] Patients randomly assigned to the group receiving late initiation of dialysis could cross over to an earlier initiation based on clinical symptoms and other complications of advanced chronic kidney disease. For the purposes of this guideline, we defined this as an "intent-to-defer" approach to dialysis initiation. Similarly, patients randomly assigned to an early start could cross over to a later start; this was termed an "intent-to-start-early" strategy.

In Canada, the eGFR, as estimated by the Modification of Diet in Renal Disease (MDRD) equation, is routinely reported with the creatinine level and is used in clinical decision-making. 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 per 1.73 m^2) eCrCl threshold used in the intent-to-defer strategy of the IDEAL study. To do this, we obtained data from the Canadian Organ Replacement Register, which records physical data and laboratory values of all patients starting chronic dialysis in Canada. We identified 2434 patients who initiated dialysis between 2006 and 2011, who had an eCrCl rate of 5–7 mL/min per 1.73 m^2. The corresponding eGFR was 5.2 ± 1.3 (median 5.1, range 1.8–10.8) mL/min per 1.73 m^2.

Recommendation

For adults (aged > 18 yr) with an eGFR of less than 15 mL/min per 1.73 m^2, we recommend an intent-to-defer over an intent-to-start-early approach for the initiation of chronic dialysis. (Strong recommendation; moderate-quality evidence.) A summary of the recommendation is found in Box 2.

Summary of findings

In our systematic review, we identified 26 reports of 23 studies, as well as one systematic review,

Box 1: Notes on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework for guideline development

This guideline was informed by a systematic review and was developed in accordance with the methods proposed by the GRADE Working Group:[9]

- We focused our review and recommendations on patient-important outcomes and resource use. Outcomes were proposed by the guideline panel, rated using a nine-point unipolar scale, and then prioritized based on mean score tertiles as critical, important but not critical, and not important for decision-making.
- Results of the systematic review were summarized on an outcome-by-outcome basis (Appendices 1–3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130363/-/DC1) in GRADE evidence profile tables. Quality of evidence ratings reflected our confidence in estimates of effect, and was rated as high, moderate, low or very low. Randomized trials started with a high quality rating, but could be rated down by limitations in any of five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias.[10–14] The same criteria were applied to observational studies, which began with a low quality rating, but could be rated up for very large treatment effects, for dose–response gradients, or when plausible biases would reduce apparent effects or create spurious effects when none were apparent.[15]
- We then considered benefits and harms, quality of evidence, patient values and preferences, and resource use in formulating a final judgment regarding the strength and direction of the recommendation.[16]
- The strength of the recommendation was based on the panel's confidence that adherence to the recommendation would provide more benefit than harm. A strong recommendation (phrased as "we recommend ...") implies that all or virtually all patients in the given situation would choose the recommended course of action, and only a very small proportion would not. A weak recommendation (phrased as "we suggest ...") implies that most patients would wish to follow the recommendation, but some patients would not. In such cases, clinicians should engage patients in shared decision-making, which takes into consideration the patients' unique values and preferences.

which reported a pooled estimate for survival with early versus late initiation of dialysis.[19] We identified a single clinical trial (IDEAL), which was published in three reports.[6,17,20] We identified five studies reporting survival outcomes that were not included in the previously published systematic review (Appendix 5). These studies were of low methodologic quality and were deemed unlikely to alter our conclusions. The panel therefore elected to use the previously published survival effect estimate to inform the guideline.[19] We identified two studies that reported quality of life, six that reported hospital admissions and one that described nutritional status as measured by total body nitrogen. Following the completion of our review, we identified two secondary analyses of the IDEAL study that reported echocardiographic findings and selection of peritoneal dialysis;[21,22] these outcomes were not relevant to this guideline and were not considered further. Details and key findings of these studies are summarized in Appendix 1.

Box 2: Recommendation

For adults (aged > 18 yr) with an estimated glomerular filtration rate (eGFR) of less than 15 mL/min per 1.73 m^2, we recommend an "intent-to-defer" over an "intent-to-start-early" approach for the initiation of chronic dialysis. (Strong recommendation; moderate-quality evidence.)

Underlying values and preferences

This recommendation places a high value on quality of life, by avoiding the burden associated with earlier initiation of dialysis without clinical indications, while avoiding complications of uremia. This recommendation also places a high value on resource use, which increases with earlier initiation of dialysis. This recommendation places a low value on surrogate markers, including serum albumin and body nitrogen levels, and eGFR, in the absence of symptoms.

Remarks

- With the intent-to-defer strategy, patients with an eGFR of less than 15 mL/min per 1.73 m^2 are monitored closely by a nephrologist, and dialysis is initiated with the first onset of a clinical indication or a decline in the eGFR to 6 mL/min per 1.73 m^2 or less, whichever of these should occur first.
- Clinical indications for the initiation of dialysis include the following: symptoms of uremia, fluid overload, refractory hyperkalemia or acidemia, or other conditions or symptoms that are likely to be ameliorated by dialysis. In the absence of these factors, the eGFR should not serve as a sole criterion for the initiation of dialysis unless it is 6 mL/min per 1.73 m^2 or less.
- Additional factors that may affect the timing of dialysis initiation include the following: patient education and modality selection; trajectory and severity of existing uremic symptoms; rate of decline in renal function; local wait times for vascular access creation or peritoneal dialysis catheter insertion; arteriovenous access maturation; access to diagnostic imaging and interventional radiology services; and availability of staff, physical space, equipment or other resources required for training or provision of a chosen dialysis modality.
- Adherence to this recommendation requires timely follow-up with a nephrologist to closely monitor clinical indications for dialysis initiation.
- This guideline pertains to patients with chronic kidney disease initiating either chronic hemodialysis or peritoneal dialysis, and does not address the timing of dialysis for acute kidney injury, patients choosing conservative management without dialysis, or preemptive transplantation.
- The intent-to-defer strategy pertains specifically to dialysis initiation, and does not imply that patients should be referred to nephrologists at a lower level of kidney function. Patients should be referred according to previously published guidelines.[7]

In the IDEAL study, the researchers found a difference in eCrCl of 2.2 mL/min between the intent-to-defer and intent-to-start-early groups. The intent-to-defer strategy resulted in a crossover rate of 75%, and a mean eCrCl of 9.8 mL/min (MDRD eGFR 7.2 mL/min) at dialysis initiation. There was also a 19% crossover rate among patients in the intent-to-start-early group, resulting in a mean eCrCl of 12.0 mL/min (MDRD eGFR 9.0 mL/min) at dialysis initiation.[17] Despite adequate power, there was no statistically significant difference in survival (hazard ratio [HR] 1.04, 95% confidence interval [CI] 0.83–1.30) with the intent-to-start-early versus intent-to-defer groups, using intent-to-treat analysis.[6] The recently published systematic review of survival outcomes found a similar result in the pooled analysis of 15 observational studies (HR 1.04, 95% CI 1.03–1.05).[19]

Between-group quality-of-life scores did not differ in either the IDEAL trial[17] or in two observational studies identified in our review. The rate of hospital admission and total days of hospital admission did not differ between groups in the IDEAL trial. Observational studies reporting rates of hospital admission showed conflicting results, and heterogeneity in study design, exposure and outcome definitions precluded pooling.

The IDEAL trial examined resource use. After randomization, the median time to start was 1.90 months in the intent-to-start-early group and 7.30 months in the intent-to-defer group (HR 1.96, 95% CI 1.67–2.30; $p < 0.001$)].[6] This was associated with higher dialysis costs (Can$10 777, 95% CI $313–$22 801, higher per patient) and transportation costs ($3610, 95% CI $1111–$9959, higher per patient). The costs and number of hospital admissions and outpatient visits were not significantly different between groups. All economic outcomes suggested cost savings with an intent-to-defer strategy, but the overall quality of evidence for economic outcomes was rated down one level for imprecision (wide CIs for some estimates). Nevertheless, we concluded that, on average, an intent-to-defer dialysis strategy would likely result in substantial cost savings, especially when applied across a health care system or population.

We found no evidence or rationale to support separate recommendations for patients initiating peritoneal versus hemodialysis, or for patients with or without diabetes (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130363/-/DC1). The IDEAL trial 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.[5] Given the concordant signals of comparable outcomes with an intent-to-defer strategy across all patient subgroups, we elected to issue a single recommendation, applicable to all subgroups.

Quality of evidence

The risk of bias among all observational studies was substantial, primarily owing to confounding by indication, because no study accounted for reasons for starting dialysis. Therefore, 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 deemed lower. Ratings of quality of evidence are summarized in Appendix 1. Given the considerable weight given to the results of the IDEAL study, we explicitly considered the generalizability (i.e., directness of evidence) to the Canadian population. Given similarities in health care delivery models and case-mix, the panel did not feel that the quality of evidence should be rated down for indirectness. The quality of evidence for observational studies evaluating critical outcomes (i.e., mortality and quality of life) was very low, whereas the quality of evidence for outcomes reported in the single randomized controlled trial (RCT) was moderate (the mortality outcome was rated down for imprecision). We therefore considered the overall quality of evidence to be moderate. The concordance in the direction of effect in the observational studies and the RCT further increases our confidence in the overall estimate of effect.

Balance of benefits and harms

There was no detectable evidence of benefit with intent-to-start-early as compared with intent-to-defer dialysis for mortality, quality of life or hospital admission in either the RCT or the observational studies. Time on dialysis and associated resource use were significantly greater in the intent-to-start-early group. For an asymptomatic patient, an intent-to-defer approach avoids the burden and inconvenience of an early start. Simultaneously, it allows for timely initiation of dialysis in patients with symptoms or other clinical indications.

Importantly, however, no published clinical trials have studied the effects of deferring dialysis beyond the threshold of 5–7 mL/min per 1.73 m^2 (eGFR ≤ 6 mL/min per 1.73 m^2). In the IDEAL study, all patients who remained in the intent-to-defer group initiated dialysis when the eCrCl reached 5–7 mL/min, regardless of whether they had symptoms. We therefore consider an MDRD eGFR range of 6 mL/min per 1.73 m^2 or less 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.

Values and preferences

We were unable to identify direct measures of patient preferences. Based on the clinical experience of our panel, we concurred that patients place a high value on ameliorating symptoms associated with uremia and hypervolemia, and 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.

Implementation

The Canadian Kidney Knowledge Translation and Generation Network (CANN-NET) will develop an integrated knowledge translation and communication strategy for this guideline, based on the priorities of and with input from CANN-NET knowledge users (i.e., heads of renal programs across Canada), patients and patient advocacy foundations (e.g., The Kidney Foundation of Canada). (For infographics designed to help clinicians and patients, see Appendix 6, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130363/-/DC1, and www.knowingkidneys.ca.)

Drawing on prospectively collected data in the Canadian Organ Replacement Register 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, rates of hospital admission, unplanned dialysis initiations and dialysis-related costs. More information about CANN-NET initiatives can be found at 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 published in 2008[8] and the European Renal

Association–European Dialysis and Transplant Association published in 2012[23] 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.[7] Our recommendation to initiate dialysis in the absence of symptoms in patients with an eGFR of 6 mL/min per 1.73 m^2 or less is consistent with the guidelines of Caring for Australians with Renal Impairment published in 2005[24] and the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative published in 2006.[25]

In contrast with the 2008 guidelines of the Canadian Society of Nephrology, 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[26]). Our recommendation differs from the recommendation of the Kidney Disease Outcomes Quality Initiative that "[w]hen patients reach stage 5 CKD [chronic kidney disease] (estimated GFR < 15 mL/min/1.73 m^2), nephrologists should evaluate the benefits, risks, and disadvantages of beginning kidney replacement therapy,"[25] and the recommendation of Caring for Australians with Renal Impairment to initiate dialysis at a GFR of less than 10 mL/min per 1.73 m^2 if uremic symptoms or signs of malnutrition arise.[24] Finally, unlike the European Renal Association–European Dialysis and Transplant Association, we do not recommend earlier initiation of dialysis in higher-risk subgroups, such as patients with diabetes.[23]

Gaps in knowledge

The optimal management of patients with an eGFR of 6 mL/min per 1.73 m^2 or less is based on limited data, because these patients 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

The panel agreed unanimously in favour of a strong recommendation for an intent-to-defer approach to dialysis (Box 2). An intent-to-start-early strategy is not justified given the lack of compelling benefit, along with the additional burden to patients and the health care system. An intent-to-defer strategy requires that patients be closely monitored for uremic symptoms or other complications, or a decline in eGFR to 6 mL/min per 1.73 m^2 or less, which would serve as indications for starting dialysis.

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Contributors: Louise Moist and William Clark cochaired the panel. Gihad Nesrallah and Louise Moist drafted and revised the manuscript. Lianne Barnieh and Adam Bass performed the systematic review. Gihad Nesrallah and Reem Mustafa provided guidance regarding the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methods. Scott Klarenbach conducted the economic evaluation and GRADE evidence profiles for outcomes related to resource use. All of the authors contributed to the content and interpretation of the results, the methodologic quality appraisal and the formulation of the recommendations, and approved the final version of the manuscript submitted for publication.

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Resources for clinicians and patients

Appendix 3: Detailed guideline and systematic review, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130363/-/DC1

Appendix 6: Infographic for clinicians, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130363/-/DC1 and www.informedkidneycare.ca

Infographic for patients and families, available at www.knowingkidneys.ca