Appendix 4: Clinical practice guideline systematic review protocol (as supplied by the authors)

CANN•NET
Canadian Kidney
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The effect of early versus late initiation of dialysis on mortality in patients with severe chronic kidney disease: A systematic review and meta-analysis

Canadian Society of Nephrology Clinical Practice Guidelines Committee and The Canadian Knowledge Translation and Generation Network (CANN-NET) Clinical Practice ad hoc Guidelines Working Group

Background

- Dialysis is being initiated for patients with increasingly higher levels of eGFR
- Initiating dialysis earlier may give major advantages or disadvantages in terms of outcomes
- There is a need to develop consensus guidelines based on evidence from randomized controlled trials and observational studies

Focused question

Primary: "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 outcomes?"

Eligibility criteria

Types of studies

- Randomized trials or cohort studies (retrospective or prospective)

Appendix to: Nesrallah GE, Mustafa RA, Clark WF, et al. Canadian Society of Nephrology 2014 clinical practice guideline for timing the initiation of chronic dialysis. *CMAJ* 2014. DOI:10.1503/cmaj.130363.

- Systematic reviews or meta-analyses addressing the same question (will only be used to identify studies contacting original data)

Population

Adult patients (mean participant age > 18 years) with Stage 5 chronic kidney disease (CKD) initiating either hemodialysis or peritoneal dialysis

Intervention

Earlier-start dialysis, as defined in the studies

Comparator

Later-start dialysis, as defined in the studies

Outcome:

Primary: all-cause mortality and health-related quality of life; secondary: as noted in abstract forms

Design

Observational cohort studies; RCTs with a minimum of 50 patients recruited

Types of participants

Adult patients with chronic kidney disease initiating either hemodialysis or peritoneal dialysis

Types of interventions

Early versus late start of renal replacement therapy (as defined by studies)

Types of outcomes

Primary

- All-cause mortality
- Health-related quality of life

Secondary

- Hospitalization
- Cost
- Nutritional markers

Information sources

The online databases to be searched are Medline, PubMed, EMBASE (Excerpta Medica Database), and CENTRAL (Cochrane Central Registry of Controlled Trials).

Search strategy

Two reviewers (LB, AB) will search the reference lists of all identified relevant publications, including all abstracts of major nephrology meetings (American Society of Nephrology, Canadian Society of Nephrology) between 2009 and 2011. Experts in the field will be contacted for information about other potential ongoing or unpublished studies. These experts will be identified from the review process. Authors of original studies may be asked to provide additional information where required.

Five clinical trial registries will be also be consulted to identify ongoing trials (clinical trials.gov, isrctn.com, vacsp.gov, CENTRAL, and www.controlled-trials.com/mrct).

The search of online databases will include all languages. The first Boolean search will be done by using the term "OR" to explode (search by subject heading) and map (search by keyword) terms for renal insufficiency and dialysis (see Appendix 3 for full search strategy). The second Boolean search will be done again using the term "OR" to explode and map terms for timing and initiation. The 2 Boolean searches will be combined by using the Boolean term "AND." The search will not be limited to RCT's to allow a systematic review of all studies (including observational trials) reporting outcomes related to initiation of dialysis.

Study selection

Title and abstract screen

Duplicates will be identified and removed. Two reviewers will independently screen all titles and abstracts (LB and AB) to determine articles eligible for further review.

Full-text screening

Articles will be separated into 2 groups of studies: group A (RCTs) and group B (observational trials). Observational studies will be handled separately in the data synthesis stage of the study. Agreement between reviewers will be quantified. Any disagreement between reviewers will be resolved by consensus.

The full papers of relevant citations will be retrieved and independently screened by the same 2 reviewers using the criteria noted previously.

Reports appearing as abstracts and subsequently as full-text articles will be grouped and will be considered a single study for data extraction purposes. A flow diagram depicting study exclusion at the aforementioned stages will be created.

Data collection process

Data extraction forms will be used to collate information from each identified study. Data will be extracted separately for group A (RCT) and group B (observational) studies.

Data items

We will collect data describing:

- Study design (RCT vs. observational)
- Methodology (method of randomization, allocation concealment, blinding, analysis)
- Study participants (inclusion/exclusion criteria, demographics, comorbidities)
- Study interventions (definition of early vs. late start)
- Outcomes
- Risk of bias (see following section)

Risk of bias in individual studies

We will use the criteria developed by Higgins at al. to evaluate risk of bias in clinical trials.[1]

For observational studies, we will apply the Newcastle Ottawa criteria for cohort studies.[2]

Risk of bias across studies

Where appropriate, we will construct funnel plots to assess the risk of publication bias.

Summary measures

We will use adjusted estimates of relative treatment effects (e.g., adjusted hazard ratio or relative risk), and will also compute absolute treatment effects (absolute rate or risk reduction) where possible. Where required, count data will be converted into rates using reported follow-up times.

Data from clinical trials and observational studies will be pooled separately.

Synthesis of results

If possible, data will be pooled. The generic inverse variance method will be used to pool data relative to treatment effect measures. Continuous variables will be pooled using inverse variance. We will use a random effects model, unless there are only 2 studies available for pooling, in which case we will use a fixed-effects model.

If pooling is not feasible, we will perform a narrative synthesis based on the previously specified outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to assess heterogeneity, and will consider pooled analyses with $I^2 >$ 50% as having significant heterogeneity. Heterogeneity will be further explored with subgroup analyses.

Subgroup analyses

If possible, subgroup analyses will include:

- Peritoneal versus hemodialysis
- Study definition of early versus late start
- Short-term versus long-term follow-up (90-day cut point)
- Diabetic versus non-diabetic
- Age effect
- By date of publication

Sensitivity analyses

If possible, we will examine the effect of excluding studies with high or uncertain risk of bias.

References

1. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
2. Guyatt G, Busse J. Tool to Assess Risk of Bias in Cohort Studies. Accessed June 21, 2012; http://www.evidencepartners.com/resources/. Accessed June 21, 2012, June 21, 2012.