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Balancing the Evidence: How to Reconcile the Results of Observational Studies vs. Randomized Clinical Trials in Dialysis

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Abstract

Because large randomized clinical trials (RCTs) in dialysis have been relatively scarce, evidence-based dialysis care has depended heavily on the results of observational studies. However, when results from RCTs appear to contradict the findings of observational studies, nephrologists are left to wonder which type of study they should believe. In this editorial we explore the key differences between observational studies and RCTs in the context of such seemingly conflicting studies in dialysis. Confounding is the major limitation of observational studies, while low statistical power and problems with external validity are more likely to limit the findings of RCTs. Differences in the specification of the population, exposure, and outcomes can also contribute to different results among RCTs and observational studies. Rigorous methods are required regardless of what type of study is conducted, and readers should not automatically assume that one type of study design is superior to the other. Ultimately, dialysis care requires both well-designed, well-conducted observational studies and RCTs to move the field forward.

With the adoption of electronic medical records and the computing ability to crunch through millions of billing claims in seconds, medical research has entered the era of “Big Data.” With it has come a sharp increase in the number of large observational studies for outcomes research.[1, 2] At the same time, increasingly limited funding for clinical research has meant that large randomized controlled trials (RCTs) continue to be few and far between. If we were to wait for RCT results to confirm the findings of observational studies before changing clinical practice, the field of nephrology would move at a glacial pace. Yet, we have been burned before by putting our faith in observational studies that were later contradicted by RCTs. What’s a nephrologist to do?

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The purpose of this editorial is to provide a critical examination of the differences between observational studies and RCTs in dialysis research to help readers understand how to correctly interpret and understand the limitations of both types of studies.

Confounding: the Achilles' heel of observational studies

The Achilles' heel of observational studies is confounding – factors that are associated with both the exposure (*i.e.*, the treatment) and the outcome. Failing to account for confounders can lead researchers to find a spurious association between the exposure and the outcome, or to overestimate, underestimate, or even find the opposite of the actual association.

Although researchers can adjust for observed confounding factors, it is impossible to eliminate residual confounding from *unobserved* factors. Thus, observational studies can state that two things are related, but cannot prove that one caused the other. For this reason, we typically proceed to RCTs to confirm observational findings. RCTs minimize confounding because patients are exposed to an intervention based on the flip of a coin rather than pre-existing, and potentially confounding, conditions.

One area of dialysis care which may have seen conflicting results between RCTs and observational studies due to confounding is in anemia treatment. For example, an observational cohort study of 432 patients on maintenance dialysis found that higher hemoglobin concentrations were associated with a lower risk of death (relative risk 0.88 per 1g/dL higher hemoglobin, p=0.02).[3] Two years later, a landmark RCT that randomized 1233 patients on dialysis with cardiac disease to treatment with epoetin to reach a goal hematocrit of 42% or 30% was stopped early due to a *higher* rate of mortality in the higher target hemoglobin group.[4]

One explanation for the discordant results between the observational study and the RCT is that patients who are ill tend to have lower hemoglobin levels at baseline, and that these underlying conditions, rather the anemia itself, are putting the patient at an increased risk of death. After all, although the observational study adjusted for age, diabetes, and ischemic heart disease, it did not have data on (and thus could not adjust for) heart failure, residual renal function, frailty, non-adherence, and other potential unobserved confounding factors.

Another important confounder is the treatment needed to achieve higher hematocrit levels. There is a difference between naturally having a higher hemoglobin concentration and achieving higher hemoglobin levels with the aid of epoetin and iron supplementation. It is possible that the increased mortality in the higher hematocrit group of the RCT was due to the higher doses of epoetin and iron that group received.[4] The observational study, on the other hand, did not account for such treatments.[3]

Importantly, randomization is not a panacea against all confounding. Imbalance between groups can still arise by chance. This was recently demonstrated in the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, which randomized 3883 patients with secondary hyperparathyroidism who were undergoing dialysis to receive either cinacalcet or placebo.[5] Despite the large sample size, the patients in the cinacalcet group were still an average of 0.8 years older at baseline than those in the

placebo group—an important difference when examining an outcome like death and cardiovascular events. While an unadjusted intention-to-treat analysis found no significant reduction in the risk of death or cardiovascular events with cinacalcet (HR 0.93 95% CI: 0.85–1.02), the age-adjusted analysis was nominally significant (HR 0.88, 95% CI: 0.80–0.98). This demonstrates the importance of evaluating and adjusting for imbalances in baseline characteristics between groups, even in RCTs. Moreover, a well-designed RCT should anticipate possible imbalances in baseline characteristics and stratify patients at the time of randomization on these variables to ensure an even distribution.[6]

Specifying the population, exposure, and outcome: are we comparing apples to oranges?

When observational studies and RCTs come to different conclusions, lack of randomization isn't always, or only, to blame. Other aspects of the study designs may have differed, leading to a comparison of apples to oranges.

Population

Observational studies and RCTs commonly focus on different populations. Due to cost and time restraints, RCTs tend to recruit patients who will be adherent to therapy and able to follow-up, limiting the generalizability of the results to actual clinic populations.[7] Observational studies, on the other hand, typically include a more representative sample of patients.

Returning to the anemia studies discussed above, the study populations were different: the RCT was restricted to those with clinical evidence of congestive heart failure or ischemic heart disease and had hematocrit values of 27–33% while receiving epoetin, while the observational study included all patients with end-stage kidney disease who had undergone maintenance dialysis for at least 6 months at three Canadian centers, regardless of comorbidity or hematocrit level.[3, 4] Interestingly, a systematic review of the literature from 1980 to 2004 that included 5 RCTs and 13 observational studies found that RCTs that included a more general dialysis population showed a trend of either no difference or a benefit to higher hemoglobin levels, consistent with the results seen in observational studies.[8] Notably, though, none of these trends was statistically significant, and the authors could not definitively conclude that targeting hemoglobin levels above 11–12 g/dL was beneficial or harmful for the very reason that the study populations were too heterogeneous.

The take home point is that when observational studies and RCTs come up with different answers, one is not necessarily wrong; the question may just have been asked in two different sets of patients.

Exposure or Treatment

Changing how an exposure is defined can also affect its measured association with the outcome. The literature on dialysis dosing is a prime example. The National Cooperative Dialysis Study (NCDS) was the first RCT of dialysis dose and linked higher urea clearance to better outcomes.[9] Based on this study, a Kt/V of about 1.0 was established as adequate

dialysis.[10] As the average dose of dialysis in clinical practice rose, observational studies suggested that more was even better.[11–15] So, it came as a surprise when the hemodialysis (HEMO) Study showed that patients randomly assigned to a higher vs. a standard dose of dialysis (equilibrated Kt/V of 1.53 vs. 1.16) did not have lower rates of death or cardiovascular outcomes.[16] Part of the discrepancy among these studies lies in the definition of the exposure, dialysis dose. The HEMO trial considered a mean Kt/V of 1.16 to be a standard dose, whereas at least one observational study analyzed Kt/V in the range of 0.6–1.6.[11] When the range was narrowed to 0.9–1.6 in the observational study, the association between dose and mortality was attenuated and more consistent with the RCT result. In short, when comparing across studies, it is important to examine whether the exposure was defined in the same manner.

Exposures should also be defined in a way that minimizes misclassification. A potential source of bias in observational studies of drugs is the inclusion of prevalent rather than of incident ("new") users.[17] Prevalent users have tolerated and adhered to the medication and thus tend to be healthier than those who may have stopped taking the drug shortly after initiation. This "healthy user, sick stopper" phenomenon tends to bias the result towards a beneficial effect of the drug because the "sick stoppers" are misclassified as unexposed, or non-users. This may account for the lower mortality rate of prevalent statin users observed in a cohort of patients initiating dialysis.[18] By contrast, multiple RCTs have consistently found that initiating statin use in patients on dialysis does not lead to significant reductions in death or cardiovascular outcomes.[19–21] The observational study may well have been consistent with the RCTs had it minimized misclassification of the exposure by studying a new user cohort.

Randomization in an RCT, though, does not guarantee that two treatment groups will differ in their actual exposure to treatment. Crossing over between treatment groups can make it just as difficult for RCTs to make a valid conclusion about the efficacy of an intervention as it is for an observational trial. For instance, in the EVOLVE trial, many patients randomized to receive cinacalcet stopped using the drug while patients randomized to the placebo group started active treatment anyway, thereby contaminating actual exposure to treatment in both arms of the trial and reducing the power to detect the pre-specified outcomes of interest.[5]

Furthermore, for some exposures or treatments, RCTs simply cannot be performed because they are not feasible. For instance, an RCT meant to compare outcomes between patients who initiated hemodialysis and those who started on peritoneal dialysis was terminated early after only 38 patients had been randomized over three years; recruitment of the estimated 100 patients needed to power a clinically meaningful trial would have required an additional 5–6 years.[22] The recruitment goal was unfeasible because 95% of the eligible patients screened declined participation because they already had a strong preference for one of the modalities. In such cases we must depend on well-designed observational studies to guide clinical practice.

Outcome

Outcomes can potentially be misclassified in any type of study. RCTs tend to minimize misclassification by having multiple researchers adjudicate outcomes using specific,

predefined criteria, as they did in the 4D statin trial.[19] Observational studies can classify outcomes in a similarly rigorous fashion. However, this typically requires access to the medical record, making it prohibitively time-consuming in large studies or simply impossible in cases where such access is not available. Misclassification of the cause of death may be part of the reason that the observational study of statins detected a difference in non-cardiovascular deaths that the RCTs did not, since the study determined cause of death from a form submitted by the patient's physician, an instrument that has not been validated.[18]

The more salient difference between outcomes in observational studies and RCTs is that observational studies of existing databases allow researchers to study longer-term outcomes in a much shorter period of time. These retrospective cohort studies can examine populations that have been exposed long enough in the past that outcomes have already occurred, saving researchers the time to wait for events to happen.[23] Researchers must be careful, though, to treat the data in a prospective manner by setting a study start date and assessing baseline characteristics using only information available before or on that date. For instance, a patient with no known history of malignancy on the study start date may be diagnosed with metastatic cancer a month later. Even though researchers in the present know that he must have had the malignancy on the start date, he would still be counted as being cancer-free at baseline because the information was not available at the time of the study date. Allowing future information to inform past events would otherwise bias the study.[24]

Are RCTs powerful enough?

The advantages of RCTs come at the price of reduced power to detect a statistically significant difference between treatment or exposure groups. Small samples, short follow-up, low event rates, and small effect sizes can all lead to an under-powered study.[25]

The NCDS is perhaps the most well-known example in dialysis of an underpowered RCT. It randomized 151 patients to two treatment times, 3 hours and 4.5 hours.[9] Shorter treatment time was associated with a higher risk of hospitalization, but at a p-value of 0.06.[26] While many equated the statistical insignificance ($p>0.05$) of the study with clinical insignificance, the marginal p-value actually suggests that the study may have reached statistical significance had the sample size been just a bit bigger. Multiple large observational studies since then support the finding that longer treatment length is associated with better outcomes.[27–32]

More recently, the Frequent Hemodialysis Network (FHN) Nocturnal Trial randomized patients to three times per week conventional hemodialysis or six times a week nocturnal dialysis.[33] Motivated by observational studies that linked frequent nocturnal hemodialysis to better outcomes, the RCT did not find a statistically significant reduction in death or left ventricular mass with frequent dialysis.[34–38] This was in contrast to the primary FHN trial which demonstrated improved outcomes with six times a week daytime dialysis.[39] The discordance between FHN nocturnal and the other studies is likely due to the small sample size-only 87 patients were randomized, compared to 125 in the primary FHN trial.

Even EVOLVE, the largest RCT involving patients on dialysis to date, was underpowered. Crossing over of the groups, a lower than expected event rate, and use of the co-interventions of parathyroidectomy and kidney transplant all reduced the power of the study.[6] Clearly it is not possible to turn to RCTs to answer all of our questions in dialysis care.

Maximizing the potential of observational studies and RCTs

RCTs and observational studies each have their strengths and limitations. Observational studies can test a number of hypotheses at low cost in a relatively short period of time in a large sample of patients representative of the general population. RCTs, on the other hand, minimize confounding and can prove causation in a select sample of patients when they are well-designed and adequately powered. When results from the two types of study appear to conflict, it is not always due to confounding in the observational study, and an RCT should not be automatically assumed to be more valid than an observational study. Careful comparison of how the population, exposure, and outcome were specified may reveal flaws in the design of either (or both) types of studies, or that the studies simply address different questions.

In cases where an RCT is not feasible, the associations from observational studies may still be relied on to guide clinical practice. First, the effect estimate should be large enough to be clinically meaningful. Findings are more likely to be valid if they have biological plausibility and have been replicated in multiple well-designed studies. A well-conducted observational study will not only have adjusted for measured confounders, but also will have checked for modification of the association in relevant subgroups. Findings should also be consistent across sensitivity analyses that address potential biases. While residual confounding will always be a threat to the validity of an observational study, it should not automatically invalidate the findings.

In conclusion, when well-designed and well-conducted, observational studies and RCTs together can provide the field of nephrology with clinically meaningful answers about dialysis management.

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