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JACC REVIEW TOPIC OF THE WEEK

Cardiovascular Outcomes Reported in Hemodialysis Trials

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ABSTRACT

Patients on long-term hemodialysis are at very high risk for cardiovascular disease but are usually excluded from clinical trials conducted in the general population or in at-risk populations. There are no universally agreed cardiovascular outcomes for trials conducted specifically in the hemodialysis population. In this review, we highlight that trials reporting cardiovascular outcomes in hemodialysis patients are usually of short duration (median 3 to 6 months) and are small (59% of trials have <100 participants). Overall, the cardiovascular outcomes are very heterogeneous and may not reflect outcomes that are meaningful to patients and clinicians in supporting decision making, as they are often surrogates of uncertain clinical importance. Composite outcomes used in different trials rarely share the same components. In a field in which a single trial is often insufficiently powered to fully assess the clinical and economic impact of interventions, differences in outcome reporting across trials make the task of meta-analysis and interpretation of all the available evidence challenging. Core outcome sets are now being established across many specialties in health care to prevent these problems. Through the global Standardized Outcomes in Nephrology–Hemodialysis initiative, cardiovascular disease was identified as a critically important core domain to be reported in all trials in hemodialysis. Informed by the current state of reporting of cardiovascular outcomes, a core outcome measure for cardiovascular disease is currently being established with involvement of patients, caregivers, and health professionals. Consistent reporting of cardiovascular outcomes that are critically important to hemodialysis patients and clinicians will strengthen the evidence base to inform care in this very high-risk population. (J Am Coll Cardiol 2018;71:2802–10)

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"When I use a word,' Humpty Dumpty said, in rather a scornful tone, 'it means just what I choose it to mean—neither more nor less.' 'The question is,' said Alice, 'whether you can make words mean so many different things.'" In writing *Through the Looking Glass*, Lewis Carroll (1) could have been referring to cardiovascular outcomes reported in clinical trials, particularly among patients on hemodialysis.

CARDIOVASCULAR DISEASE AND HEMODIALYSIS

Worldwide, >2 million people have end-stage kidney disease, with this number increasing annually by 5% to 7% (2). Patients with end-stage kidney disease who are treated with dialysis require a disproportionately high amount of health care resources. The prevalence of cardiovascular disease (CVD) in people on hemodialysis exceeds 60% (3,4) and accounts for >50% of deaths (4–6). CVD mortality remains up to 30 times higher in people on dialysis than in the general population (6).

THE IMPORTANCE OF AN OUTCOME

Clinical trials of interventions designed to reduce CVD in patients with end-stage kidney disease have evaluated the use of medications (7–10) and the intensity and type of hemodialysis (11–13), but the results have generally not identified clear evidence of benefit. Such trials may have been less informative than possible because they were too small to identify modest but realistic treatment effects. Inconsistencies in how cardiovascular outcomes were measured and reported made it difficult to compare the effectiveness of interventions across different trials or to combine trial results in meta-analyses (14). Reporting bias, both in terms of selective outcome reporting and publication bias, also has the potential to cause misinterpretation of evidence (15). The value of trials to inform decision making among patients, clinicians, and policy makers may also be reduced if the outcomes are selected on the basis of feasibility rather than importance (16).

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

MACE = major adverse cardiac event(s)

The importance of choosing the right outcomes for clinical trials to inform decision making is widely accepted, but appropriate measurement of cardiovascular outcomes in trials can be challenging. In particular, the major cardiovascular outcomes occur only in a relatively small fraction of participants meaning, unless trials are very large, follow-up periods may need to be long in order to capture a sufficient number of specific events. This has led to an increasing use of composite outcomes to increase the number of events captured and to reduce sample size requirements (17,18). When using composite endpoints, it is difficult to estimate the true effect of an intervention on different components of the composite, particularly those that occur less frequently. Composites often combine outcomes with very different levels of importance to patients, making interpretation of the overall importance of the trial findings difficult (18,19). Similarly, a compounding problem is that inclusion of surrogates diverts attention from outcomes of more importance to patients and clinicians (20). Outcomes need to be relevant to all stakeholders, in particular the patients within the specific disease group (21).

The capacity to compare outcomes across trials and produce summary effect estimates through meta-analysis would help improve confidence in the effects of interventions in the hemodialysis population but would require that the outcomes be reported consistently.

THE NEED FOR CORE OUTCOME SETS

A core outcome set is an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials in the relevant

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