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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).

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

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

MACE = major adverse cardiac event(s)

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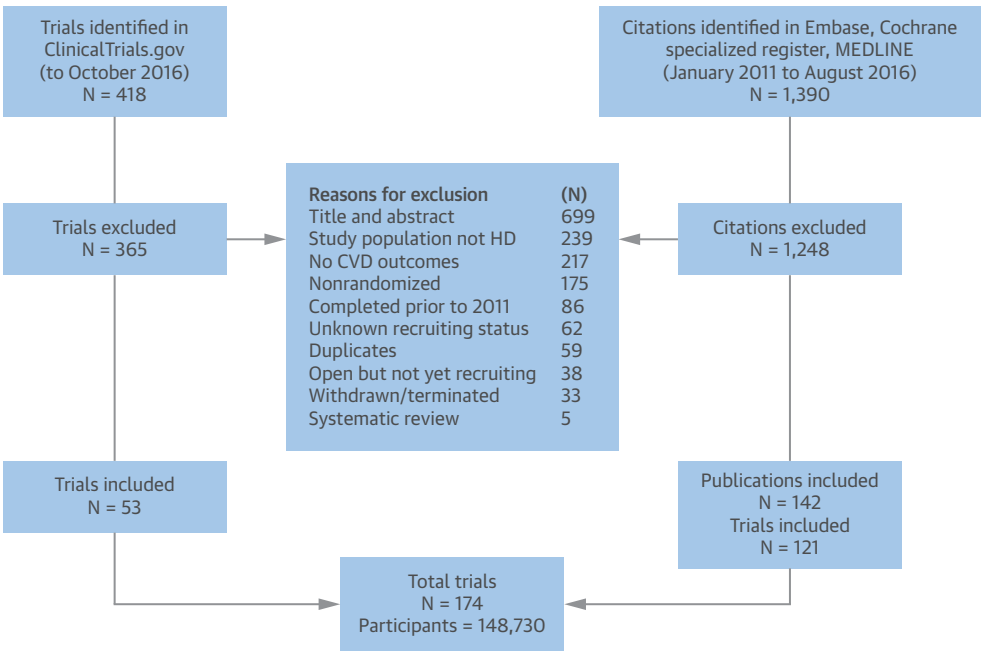
FIGURE 1 Search Results



Comprehensive search of MEDLINE, Embase, the Cochrane Kidney and Transplant Specialized Register, and ClinicalTrials.gov from 2011 to 2017 resulted in 174 randomized trials in patients on hemodialysis (HD) reporting at least 1 cardiovascular outcome. CVD = cardiovascular disease.

areas of health or health care (22). Recently, there has been a proliferation of discipline-specific and global initiatives to develop core outcome sets (23,24). The Outcome Measures in Rheumatology initiative was formed in 1992 and set the foundation for the development of core outcomes, specifically in rheumatology trials. With the involvement of patients, health care providers, and policy makers, Outcome Measures in Rheumatology has improved the relevance of outcomes reported in rheumatology trials. More recently, the Core Outcome Measures in Effectiveness Trials initiative was established to facilitate the development and collation of core outcome sets across all diseases internationally (23).

Among cardiovascular trialists, there have been concerted efforts to standardize cardiovascular outcome reporting (25–27). Early attempts include the introduction of the term MACE, defined as "major adverse cardiac event(s)," in the mid-1990s, with its use theoretically restricted to in-hospital complications related to percutaneous coronary interventions (28). However, the components of a MACE vary, even among trials of similar interventions. For example, a systematic review assessing the components of MACE used in studies comparing bare-metal versus drug-eluting stents found large-scale heterogeneity in the outcomes used (29). The use of "MACE" has become widespread, but the term is often used outside its original context with a large number of varied outcome measures used to make up the composite endpoint (29). More recently, a number of core outcome sets have been developed for CVDs in specific populations, including a set for the effectiveness of cardiac surgery (30) and a set for pregnant women with CVD (31).

CURRENT STATE OF REPORTING OF CVD OUTCOMES IN HEMODIALYSIS TRIALS

A systematic search was conducted in MEDLINE, Embase, the Cochrane Kidney and Transplant Specialized Register, and ClinicalTrials.gov for randomized controlled trials conducted in adults on hemodialysis (both published or in progress, from 2011 to 2017), which reported at least 1 cardiovascular outcome (Online Table 1). We extracted a number of trial characteristics as well as all cardiovascular outcome measures, including all levels of specification (if reported), and the specific metric (e.g., time to event, change from baseline), method of aggregation

TABLE 1 Characteristics of Included Trials (n = 174)

	Number of Trials	%
Participants		
0–49	64	38
50–99	35	21
100–499	49	29
500–999	10	6
1,000–4,999	9	5
≥5,000	2	1
Not stated	5	3
Year of publication		
2011–2012	50	29
2013–2014	52	30
2015–2016	16	9
Not published	56	32
Region/country		
Not stated	64	37
Europe	43	25
Asia	23	13
United States	13	7
International	12	7
Middle East	11	6
South/Central America	4	2
Australasia	4	2
Duration of trial (months)		
1–3	8	7
>3–6	24	20
>6–12	11	9
>12–24	28	23
>24–48	23	19
>48	27	22
Not stated	53	30
Intervention type		
Pharmacological/supplement	104	60
Dialysate	22	13
Mode of hemodialysis	26	15
Lifestyle	6	3
Other	5	3
Dialysis machine	9	5
Coronary intervention	3	2

(e.g., mean, median, proportion), and time point of measurement (32).

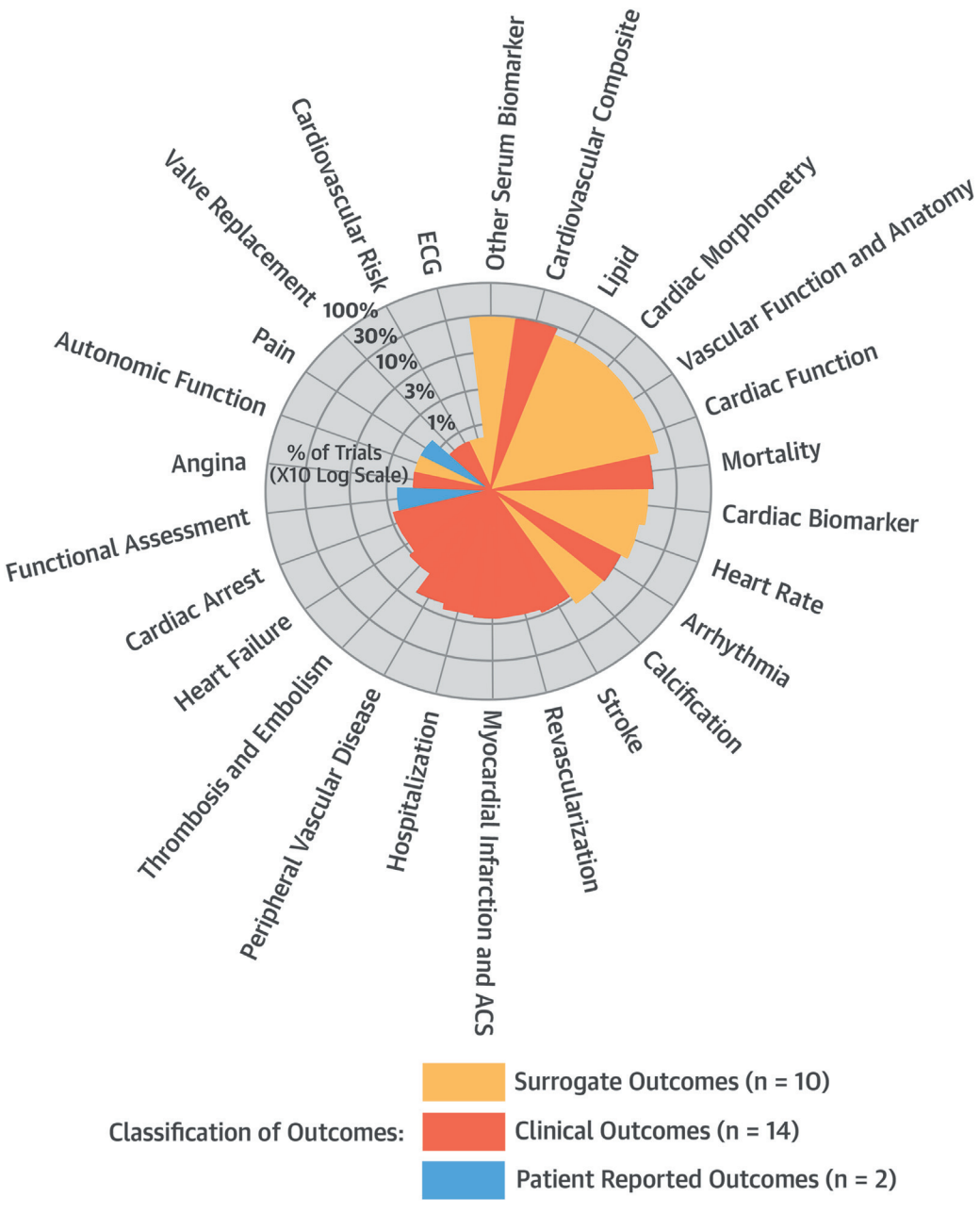
We classified the outcomes into 236 measures (e.g., troponin) and then again into 26 outcome groups (e.g., cardiac biomarker). A schema of the categorization is provided in Online Figure 1, with an example in Online Table 2. Outcomes were further classified as surrogate, clinical, or patient reported. A surrogate outcome was defined as a biochemical, imaging, or other marker used as a substitute for a clinical outcome (33). A clinical outcome was defined as a medical event or comorbidity (e.g., mortality, myocardial infarction, hospitalization) diagnosed by the clinician. Patient-reported outcomes were those reported directly by patients regarding how they function or feel in relation to a health condition and its therapy, without interpretation by a health care professional or anyone else (34).

TRIAL CHARACTERISTICS. We identified and included 174 trials involving 148,730 participants (**Figure 1**). Trial characteristics are presented in **Table 1**. Fifty-six trials (32%) were unpublished. The published trials were conducted across 28 countries, most frequently in Japan (8%) and the United States (8%), and 12 trials (7%) were multinational. The median trial duration was 15.0 months (interquartile range: 5.5 to 42.0 months), and the median sample size was 83 participants (interquartile range: 32 to 200 participants). It is of note that relative to many cardiovascular trials in the general population, both the trial duration and the sample size are small. The most common type of intervention was pharmacological (103 trials [60%]). In 48 trials (27%), the intervention was a dialysate, dialysis membrane, or modality of hemodialysis (such as hemodiafiltration or hemodialysis).

OUTCOMES AND OUTCOME MEASURES. The 1,743 definitions (including different time points of measurement) were categorized into 236 measures (e.g., troponin), with a median of 3.5 outcome measures reported per trial (range: 1 to 23). Across all trials, measures were assessed at 67 different time points with a range of 1 to 6 time points per trial. The number of measures was not associated with the sample size (Online Table 3). These measures were further grouped into 26 outcomes (e.g., cardiac biomarkers), with a median of 2 outcomes reported per trial (range: 1 to 16). Of the 26 outcomes, 15 (58%) were clinical, 10 (38%) were surrogates, and 1 (4%) was a patient-reported outcome: pain (**Central Illustration**). The top 3 most frequently reported outcomes were serum biomarkers (excluding lipids and traditional cardiac biomarkers; 52 trials [30%]), cardiovascular composite (52 trials [30%]), and serum lipid levels (41 trials [23%]).

The number of measures for each outcome ranged from 1 to 61 (**Figure 2**). The serum biomarker outcome included 61 different biomarker measures; C-reactive protein was the most frequently reported biomarker (34 trials [20%]), followed by homocysteine (8 trials [5%]). The outcome cardiovascular composite included 11 composite measures, the 3 most frequent being a "cardiovascular composite" measure (e.g., "the cumulative rate of non-fatal MI [myocardial infarction] or acute coronary syndrome, hospitalization for heart failure, nonfatal stroke or CV [cardiovascular] death"; 27 trials [16%]), a "cardiovascular event" (e.g., "rate of cardiovascular events";

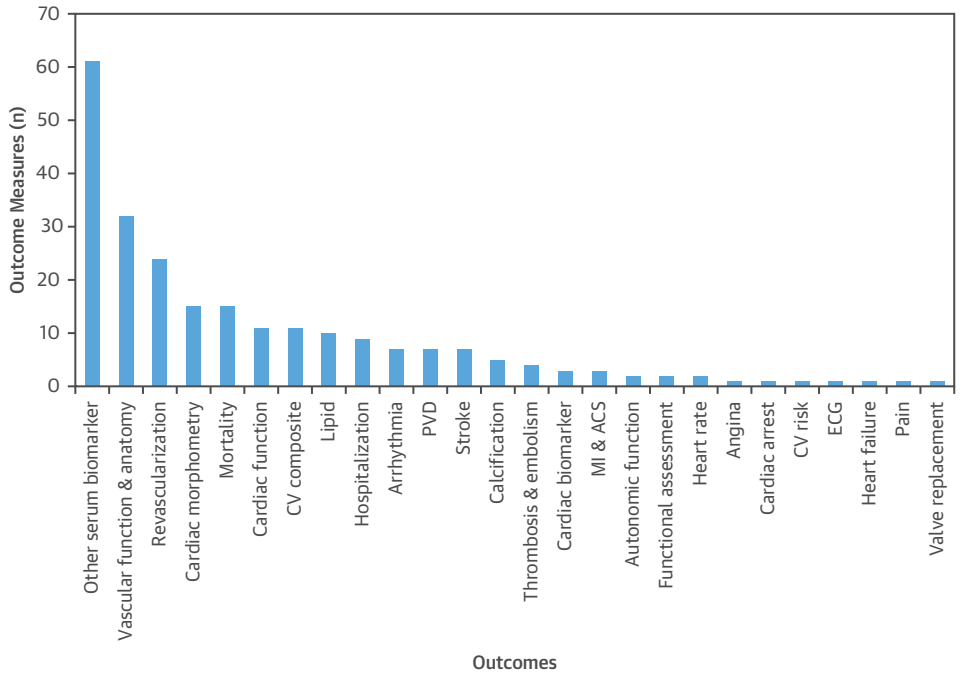
CENTRAL ILLUSTRATION **Cardiovascular Outcomes in Hemodialysis: Proportion of Trials Reporting Each Outcome (174 Trials, 26 Outcomes)**



O'Lone, E. et al. J Am Coll Cardiol. 2018;71(24):2802-10.

Chart to show the 26 outcome groups determined from the 174 trials and the proportion of trials that reported them. The most frequently reported outcomes were the surrogate outcome of serum biomarker and a cardiovascular composite outcome. Only 1 outcome was patient reported. ACS = acute coronary syndrome; ECG = electrocardiography.

FIGURE 2 Number of Unique Measures Within Each Outcome Group



Bar chart showing how the number of different measures contributed to each outcome excluding time points. There were 61 different biomarkers measured in the outcome group other serum biomarkers and 32 different ways of measuring vascular function and anatomy. ACS = acute coronary syndrome; CV = cardiovascular; ECG = electrocardiography; MI = myocardial infarction; PVD = peripheral vascular disease.

24 [14%] trials), and "cardiovascular event non-fatal" (4 trials [2%]) (Figure 2). The outcome serum lipid levels had 10 different measures, the 3 most frequently reported being high-density lipoprotein (26 trials [15%]), triglycerides (26 [15%] trials), and "total cholesterol" (21 [12%] trials).

Across the clinical outcomes, 13 different metrics were used to report the original definitions, including number of events, rate of event, event free survival, and time to event. The methods of aggregation for the clinical outcomes included mean, median, proportion, and proportional change.

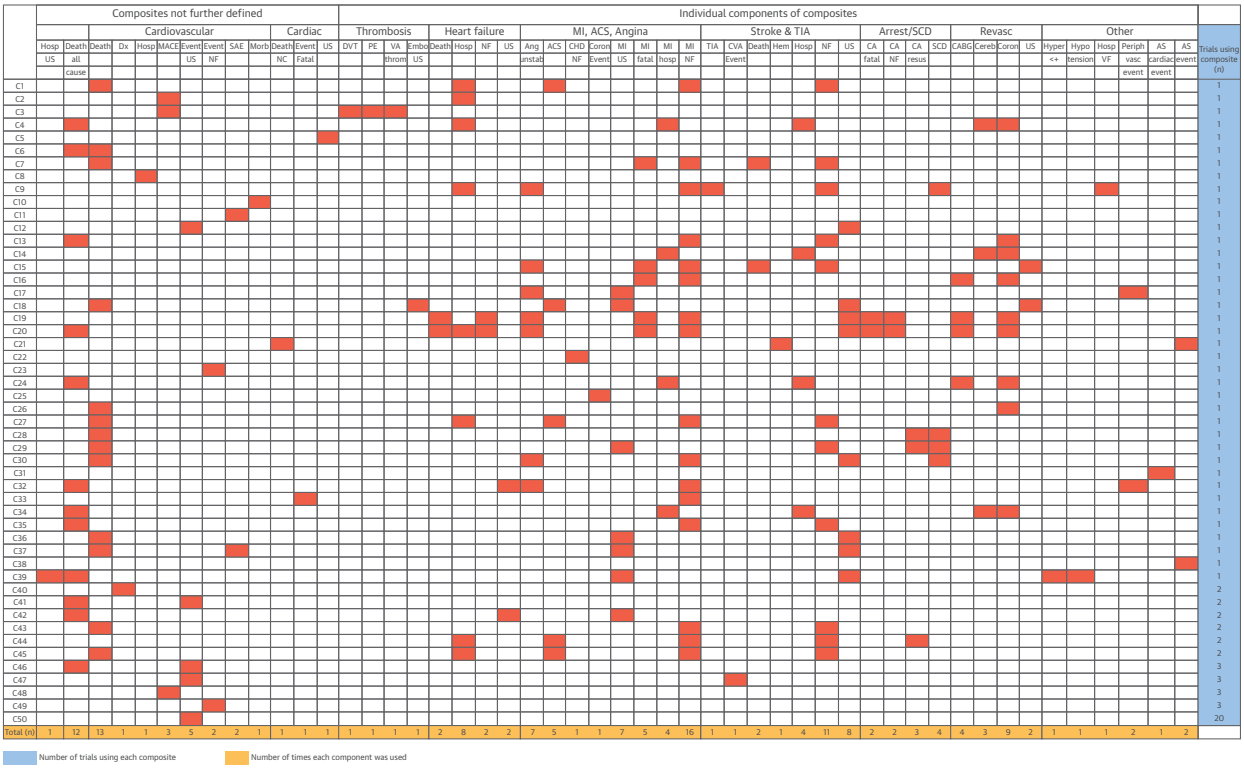
CARDIOVASCULAR COMPOSITE OUTCOME. Each composite measure was deconstructed into its components, and the number of trials using each component was analyzed as shown in Figure 3. Fifty-one trials (29%) used cardiovascular composite measures, and each trial used a range of 1 to 6 different composite combinations. Within these 51 trials, there were 50 unique composite combinations (Figure 3). The proportion of trials reporting each measure within the cardiovascular composite outcome is shown in Online Figure 2.

MORTALITY OUTCOMES. Cardiovascular mortality outcomes were reported in 25 (14%) trials. Included in the mortality outcome were 8 individual events, of which sudden cardiac death was the most frequently reported (7 trials [4%]) (Online Figure 3). Composite mortality measures were assessed in 14 trials (8%), and 12 composite combinations were used (Figure 4). Within the mortality outcome, the most frequently reported composite outcome measure was cardiovascular death, reported as a unique term in 16 trials (9%) and also used in 5 mortality composite combinations (42%) (Figure 4).

TIME FOR MORE CONFIDENCE IN OUTCOMES

In contemporary clinical trials conducted in patients on hemodialysis, a very large number of different cardiovascular outcomes have been reported. Over a third of these outcomes were classified as surrogates rather than outcomes that would be expected to be directly important to patients and clinicians (such as sudden cardiac death, myocardial infarction), and only 1 was patient reported (pain). The use of

FIGURE 3 Cardiovascular Composite Matrix



Matrix to display the individual components of the 51 composite outcomes after deconstruction. The far right column tallies the number of trials that used each composite, and the bottom row tallies the number of times each component was incorporated into a composite. Myocardial infarction was the most frequently used component in a composite, and most composite combinations were only used in 1 or 2 trials. ACS = acute coronary syndrome; Ang = angina; AS = atherosclerotic; CA = cardiac arrest; Cereb = cerebrovascular; CHD = coronary heart disease; Coron = coronary; CVA = cerebrovascular accident; DVT = deep vein thrombosis; Dx = disease; Embol = embolism; Hem = hemorrhagic; Hosp = hospitalization; MACE = major adverse cardiovascular event; MI = myocardial infarction; Morb = morbidity; NC = noncoronary; NF = nonfatal; PE = pulmonary embolism; Periph = peripheral; resus = resuscitation; Revasc = revascularization; SAE = serious adverse event; throm = thrombosis; TIA = transient ischemic attack; US = unspecified; VA = vascular access; vasc = vascular; VF = cardiac arrhythmia.

surrogate outcomes is probably a function of the small sample sizes of most of the trials identified. Use of composite outcomes was common, being used in a third of the trials, but each trial used different components to make up its composites, and they were often ill defined, making comparisons across studies problematic. This echoes the findings in other populations regarding the complexity and discord within composite outcomes (18,29). A review of composite outcomes within cardiovascular trials found that the components of composite endpoints varied widely in terms of their importance to patients and in the magnitude of their effect of the intervention. This can give rise to misleading interpretations regarding the impact of treatment (18).

The variety of measures used to assess each outcome was substantial, particularly among the surrogate outcomes, with more than 60 different serum biomarkers measured and more than 30 different ways to measure vascular function and anatomy. Heterogeneity was evident at multiple levels, including definition of the measurement, the metric, the method of aggregation, and the time point of measurement of the outcome measure. This heterogeneity is not unique to the hemodialysis population. In a review of outcomes in cardiac arrest trials, more than 160 individual outcomes were reported, including 39 different measures of survival (35).

This review highlights the urgent need to develop a core outcome set in hemodialysis trials. Recently, the Standardized Outcomes in Nephrology initiative was established, which has used validated consensus methodology to bring together patients and health care professionals to identify critically important outcomes in hemodialysis (36-38). CVD was identified as a core outcome domain (along with vascular

FIGURE 4 **Mortality Composite Matrix**

		Composites not further defined					Individual components							
		Vascular death	CV Death	CHD death	Cardiac death	Cardiac arrest	SCD	Cardiac arrhythmia	Acute MI	Heart failure	Stroke US	Stroke ischemic	Stroke hem	Trials using composite (n)
Composites	C1	■												2
	C2			■										2
	C3						■	■						2
	C4		■											16
	C5				■									4
	C6					■			■	■	■			1
	C7		■											1
	C8		■						■	■	■			1
	C9	■	■		■						■	■	■	1
	C10				■									1
	C11		■											1
	C12						■	■	■	■	■			1
Total (n)*		2	5	1	3	1	2	2	3	3	4	1	1	

■ Number of trials using each composite ■ *number of times each component is used

Matrix showing the individual components of the 12 composites after deconstruction. The far right column tallies the number of trials that used each composite, and the bottom row tallies the number of times each component was incorporated into a composite. The composite cardiovascular death was used in 16 trials but was not further defined. CV = cardiovascular; SCD = sudden cardiac death; other abbreviations as in Figures 2 and 3.

access, fatigue, and mortality). The next phase of the Standardized Outcomes in Nephrology initiative aims to establish these core measures with consensus on their definition. Moving forward, this effort will facilitate improvement in the quality, transparency, and value of cardiovascular trials in people on hemodialysis and, most important, has the potential to improve interpretation of clinical trials data in the hope of reducing mortality and morbidity for people on hemodialysis.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.