Cardiovascular outcomes reported in hemodialysis trials: consistent and important to patients?

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Abstract 261 words

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 less than 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 where a single trial is often insufficiently powered to fully assess clinical and economic impact of interventions, differences in outcome reporting across trials makes the task of meta-analysis and interpretation of all the available evidence challenging. Core outcomes sets are now being established across many specialties in healthcare to prevent these problems. Through the global Standardised Outcomes in Nephrology - Hemodialysis (SONG-HD) 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.

Condensed abstract (86 words)

Patients on long-term hemodialysis are at very high risk for cardiovascular disease. There are no universally agreed cardiovascular outcomes for trials conducted in the hemodialysis population. This review highlights the considerable heterogeneity in outcomes reported in cardiovascular trials in patients on hemodialysis as well as the extensive use of surrogate and composite outcomes. There is an urgent need for a "core outcome set" to be developed to improve consistency, patient-relevance, and transparency of outcomes measured and reported by clinical trials in this very high risk population.

Key words: cardiovascular, outcomes, hemodialysis, composites

“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* (1), Lewis Carrol could have been referring to cardiovascular outcomes reported in clinical trials, particularly among patients on hemodialysis.

Cardiovascular disease and hemodialysis

Worldwide, more than two million people have end stage kidney disease (ESKD), with this number increasing annually by 5-7% (2). Patients with ESKD who are treated with dialysis require a disproportionately high use of health-care resources. The prevalence of cardiovascular disease (CVD) in people on hemodialysis exceeds 60% (3,4) and accounts for over 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 people with ESKD 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, and 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 to improve confidence in the effects of interventions in the hemodialysis population, but would require that the outcomes are 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 areas of health or healthcare (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 (OMERACT) 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, OMERACT has improved the relevance of outcomes reported in rheumatology trials. More recently, the Core Outcome Measures in Effectiveness Trials (COMET) 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 events,' 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 between 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 is often used outside its original context with 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 cardiovascular diseases in specific populations including a set for the effectiveness of cardiac surgery (30), and a set for pregnant women with cardiovascular disease (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 one cardiovascular outcome. 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 (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 twenty-six 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 healthcare 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 (32%) trials were unpublished. The published trials were conducted across 28 countries, most frequently in Japan (8%) and the USA (8%), and 12 (7%) trials were multinational. The median (interquartile range [IQR]) trial duration was 15.0 months (IQR 5.5 to 42.0 months) and the median sample size was 83 participants (IQR 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 is small. The most common type of intervention was pharmacological (103 [60%] trials). In 48 (27%) trials, the intervention was a dialysate, dialysis membrane or modality of hemodialysis (such as hemodiafiltration or hemodialysis).

Outcomes and outcome measures

The 1743 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 one to six 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 two outcomes reported per trial (range 1 to 16). Of the 26 outcomes, 15 (58%) were clinical, 10 (38%) were surrogates and one (4%), was a patient-reported outcome – pain. (Figure 2) The top three most frequently reported outcomes were: *serum biomarker* (biomarkers excluding lipids and traditional cardiac biomarkers) (52 [30%] trials), *cardiovascular composite* (52 [30%] trials), and *serum lipid levels* (41 [23%] trials).

The number of measures for each outcome ranged from 1 to 61 (Figure 3). The *serum biomarker* outcome included 61 different biomarker measures; C-reactive protein was the most frequently reported biomarker (34 [20%] trials) followed by homocysteine (8[5%] trials). The outcome *cardiovascular composite* included 11 composite measures, the three most frequent being a "cardiovascular composite" measure (e.g. "the cumulate rate of non-fatal MI or acute coronary syndrome, hospitalization for heart failure, nonfatal stroke or CV death" (27 [16%] trials), a "cardiovascular event" (e.g. "rate of cardiovascular events" (24 [14%] trials) and "cardiovascular event non-fatal" (4 [2%] trials) (Figure 3). The outcome *serum lipid levels* had ten different measures, the three most frequently reported being "HDL" (26 trials [15%], "triglycerides" (26 [15%] trials and "total cholesterol" (21 [12%] trials.

Across the clinical outcomes, there were 13 different metrics used to report the original definitions and these included: 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 4. Fifty-one trials (29%) used a cardiovascular composite measure and each trial used a range of one to six different composite combinations. Within these 51 trials there were 50 unique composite combinations (Figure 4). The proportion of trials reporting each measure within the cardiovascular composite outcome is shown in Online Figure 2.

Mortality outcomes

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

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 one was patient-reported (pain). The use of surrogate outcomes is probably a function of the small

sample size 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 their 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 over 60 different serum biomarkers measured and over 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, over 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 (SONG) 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). Cardiovascular disease was identified as a core outcome domain (along with vascular access, fatigue and mortality). The next phase of the SONG 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 importantly, has the potential to improve interpretation of clinical trials data in the hope of reducing mortality and morbidity for people on hemodialysis.

PERSPECTIVES

Competency in Medical Knowledge: Cardiovascular disease is the leading cause of death in people on hemodialysis.

Competency in Patient Care: Establishing the wide heterogeneity of CVD outcomes to inform the development of core outcomes, which will improve clinicians' ability to compare the effect of interventions across trials for better informed decision-making.

Translational Outlook 1: This study will inform the SONG-HD initiative in establishing core outcome measures for cardiovascular disease to be reported in all hemodialysis trials.

Translational Outlook 2: Highlighting the problems with outcome reporting and developing a standardized set of outcomes and outcome measures should improve the quality, transparency and value of trial-based evidence to support decision-making and better patient outcomes.

References

1. Carroll L, Tenniel J. Alice through the looking-glass. Giant illustrated ed ed. London: Academy Editions etc., 1977.
2. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney Int 2011;80:1258-70.
3. Foley RN, Parfrey PS, Harnett JD et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int 1995;47:186-92.
4. Saran R, Li Y, Robinson B et al. US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis 2016;67:Svii, S1-305.
5. Cheung AK, Sarnak MJ, Yan G et al. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. Kidney Int 2004;65:2380-9.
6. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;9:S16-23.
7. Fellstrom BC, Jardine AG, Schmieder RE et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395-407.
8. Investigators ET, Chertow GM, Block GA et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med 2012;367:2482-94.
9. Baigent C, Landray MJ, Reith C et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377:2181-92.
10. Wanner C, Krane V, Marz W et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353:238-48.
11. Group FHNT, Chertow GM, Levin NW et al. In-center hemodialysis six times per week versus three times per week. N Engl J Med 2010;363:2287-300.

12. Maduell F, Moreso F, Pons M et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol 2013;24:487-97.
13. Grooteman MP, van den Dorpel MA, Bots ML et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol 2012;23:1087-96.
14. Williamson PR, Altman DG, Blazeby JM et al. Developing core outcome sets for clinical trials: issues to consider. Trials 2012;13:132.
15. McGauran N, Wieseler B, Kreis J, Schuler YB, Kolsch H, Kaiser T. Reporting bias in medical research - a narrative review. Trials 2010;11:37.
16. Chan AW, Song F, Vickers A et al. Increasing value and reducing waste: addressing inaccessible research. Lancet 2014;383:257-66.
17. Ferreira-Gonzalez I, Permanyer-Miralda G, Busse JW et al. Methodologic discussions for using and interpreting composite endpoints are limited, but still identify major concerns. J Clin Epidemiol 2007;60:651-7; discussion 658-62.
18. Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ 2007;334:786.
19. Ioannidis JP, Greenland S, Hlatky MA et al. Increasing value and reducing waste in research design, conduct, and analysis. Lancet 2014;383:166-75.
20. Yudkin JS, Lipska KJ, Montori VM. The idolatry of the surrogate. BMJ 2011;343:d7995.
21. Tunis SR, Clarke M, Gorst SL et al. Improving the relevance and consistency of outcomes in comparative effectiveness research. J Comp Eff Res 2016;5:193-205.
22. Kirkham JJ, Gorst S, Altman DG et al. Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. PLoS Med 2016;13:e1002148.

23. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. Trials 2007;8:38.

24. Sinha IP, Gallagher R, Williamson PR, Smyth RL. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. Trials 2012;13:103.

25. Hicks KA, Tcheng JE, Bozkurt B et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). J Am Coll Cardiol 2015;66:403-69.

26. American College of Cardiology/American Heart Association Task Force on Clinical Data S, Buxton AE, Calkins H et al. ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). Circulation 2006;114:2534-70.

27. Weintraub WS, Karlsberg RP, Tcheng JE et al. ACCF/AHA 2011 key data elements and definitions of a base cardiovascular vocabulary for electronic health records: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards. J Am Coll Cardiol 2011;58:202-22.

28. Hermans WR, Foley DP, Rensing BJ et al. Usefulness of quantitative and qualitative angiographic lesion morphology, and clinical characteristics in predicting major adverse cardiac events during and after native coronary balloon angioplasty. CARPORT and MERCATOR Study Groups. Am J Cardiol 1993;72:14-20.

29. Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. J Am Coll Cardiol 2008;51:701-7.

30. Moza A, Benstoem C, Autschbach R, Stoppe C, Goetzenich A. A core outcome set for all types of cardiac surgery effectiveness trials: a study protocol for an international eDelphi survey to achieve consensus on what to measure and the subsequent selection of measurement instruments. Trials 2015;16:545.

31. Developing a core outcome set for pregnant women with cardiac disease.http://www.comet-initiative.org/studies/details/834?result=true.

32. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database – update and key issues. N Engl J Med 2011;364.

33. Aronson JK. Biomarkers and surrogate endpoints. Br J Clin Pharmacol 2005;59:491-4.

34. Black N. Patient reported outcome measures could help transform healthcare. BMJ 2013;346:f167.

35. Whitehead L, Perkins GD, Clarey A, Haywood KL. A systematic review of the outcomes reported in cardiac arrest clinical trials: the need for a core outcome set. Resuscitation 2015;88:150-7.

36. Urquhart-Secord R, Craig JC, Hemmelgarn B et al. Patient and Caregiver Priorities for Outcomes in Hemodialysis: An International Nominal Group Technique Study. Am J Kidney Dis 2016;68:444-54.

37. Tong A, Manns B, Hemmelgarn B et al. Standardised outcomes in nephrology - Haemodialysis (SONG-HD): study protocol for establishing a core outcome set in haemodialysis. Trials 2015;16:364.

38. Prinsen CA, Vohra S, Rose MR et al. Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus

on how to select outcome measurement instruments for outcomes included in a 'core outcome set'. Trials 2014;15:247.

Figure titles and legends

Figure 1. Search results

Comprehensive literature 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 reporting at least one cardiovascular outcome.

HD = Hemodialysis, CVD = cardiovascular disease

Figure 2 and Central Illustration. Proportion of trials reporting each outcome (174 trials, 26 outcomes)

Chart to show the 26 outcome groups determined from the 174 trials and the proportion of trials which reported them. The most frequently reported outcomes were the surrogate outcome of *serum biomarker* and a *cardiovascular composite* outcome. Only one outcome was patient reported.

ACS - Acute coronary syndrome, ECG- Electrocardiogram

Figure 3. Number of unique measures within each outcome group

Bar chart to show how the number of different measures that 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 – electrocardiogram, MI – Myocardial infarction, PVD – Peripheral vascular disease

Figure 4 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 utilized each composite and the bottom row tallies the number of times each component was incorporated into a composite. Myocardial infarction was the most frequently utilized component in a composite and most composite combinations were only used in one or two trials.

US= unspecified, Dx=disease, Hosp=hospitalisation, MACE=Major adverse cardiovascular event, NF= non fatal, SAE= Serious adverse event, Morb=morbidity, DVT=deep vein thrombosis, PE=pulmonary embolism, VA=vascular access, throm=thrombosis, Embol=embolism, Ang=angina, ACS=acute coronary syndrome, CHD=coronary heart disease, cor=coronary, MI=myocardial infarction, TIA=transient ischaemic attack, CVA=cerebrovascular, haem=hemorrhagic, CA=cardiac arrest, cereb=cerebrovascular, VF=cardiac arrhythmia, AS= Atherosclerotic, morb= morbidity

Figure 5. Mortality Composite matrix

Matrix to show the individual components of the 12 composites after deconstruction.
The far right column tallies the number of trials that utilized 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, CHD=coronary heart disease, haem=hemorrhagic , MI=myocardial infarction, SCD=sudden cardiac death, US=unspecified

Table 1. Characteristics of included trials (total=174)

Characteristics		Number of trials	%
Participants (n)	0-49	64	38
	50-99	35	21
	100-499	49	29
	500-999	10	6
	1000-4999	9	5
	=>5000	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
	USA	13	7
	International	12	7
	Middle East	11	6
	South/Central America	4	2
	Australasia	4	2
Duration of trial (months)	1 to 3	8	7
	>3 to 6	24	20
	>6 to 12	11	9
	>12 to 24	28	23
	>24 to 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