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Range and Consistency of Cardiovascular Outcomes Reported by Clinical Trials in Kidney Transplant Recipients: A Systematic Review

Gregory J. Wilson, MBBS,[1,2,3] Kim Van, MBBS,[4] Emma O'Lone, PhD,[4] Allison Tong, PhD,[4] Jonathan C. Craig, PhD,[5] Benedicte Sautenet, PhD,[6] Klemens Budde, MD,[7] Derek Forfang,[8] John Gill, MD,[9] William G. Herrington, MD,[10] Tazeen H. Jafar, MPH,[11] David W. Johnson, PhD,[1,3] Vera Krane, MD,[12] Adeera Levin, MD,[13] Jolanta Malyszko, PhD,[14] Patrick Rossignol, PhD,[15] Deirdre Sawinski, MD,[16] Nicole Scholes-Robertons, PhD,[17] Giovanni Strippoli, PhD,[18] Angela Wang, PhD,[19] Wolfgang C. Winkelmayer, MD,[20] Carmel M. Hawley, MMedSci,[1,3] and Andrea K. Viecelli, PhD[1,3]

Background. Cardiovascular disease is a major cause of morbidity and mortality in kidney transplant recipients. Trial evidence to improve cardiovascular outcomes is limited by inconsistent reporting of outcomes, which may also lack patient-relevance. This study aimed to assess the range and consistency of cardiovascular outcomes reported by contemporary trials in kidney transplant recipients. **Methods.** A systematic review of all randomized controlled trials involving adult kidney transplant recipients that reported at least 1 cardiovascular outcome from January 2012 to December 2019 was performed, including Embase, MEDLINE, Cochrane, and ClinicalTrials.gov electronic databases. Trial characteristics were extracted and all levels of specification of the cardiovascular outcome measures reported were analyzed (the measure definition, metric, and method of aggregation). Measures assessing a similar aspect of cardiovascular disease were categorized into outcomes. **Results.** From 93 eligible trials involving 27 609 participants, 490 outcome measures were identified. The outcome measures were grouped into 38 outcomes. A cardiovascular composite was the most common outcome reported (40 trials, 43%) followed by cardiovascular mortality (42%) and acute coronary syndrome (31%). Cardiovascular composite was also the most heterogeneous outcome with 77 measures reported followed by cardiovascular mortality (n = 58) and inflammatory biomarkers (n = 51). The most common cardiovascular composite outcome components reported were major cardiovascular events (18 trials), stroke unspecified (11 trials), and myocardial infarction unspecified (10 trials). **Conclusions.** There is substantial heterogeneity in cardiovascular outcome reporting in kidney transplant trials.

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[1] *Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia.*

[2] *Department of Nephrology, Mater Health Services, Brisbane, QLD, Australia.*

[3] *Department of Nephrology, Princess Alexandra Hospital, Brisbane, QLD, Australia.*

[4] *Sydney School of Public Health, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia.*

[5] *College of Medicine and Public Health, Flinders University, Bedford Park, SA, Australia.*

[6] *Service de Nephrologie-Hypertension, Dialyses, Transplantation Rénale, Hopital Bretonneau, Université de Tours, Université de Nantes, INSERM SPHERE U 1246, Tours, France.*

[7] *Charité Universitätsmedizin Berlin, Berlin, Germany.*

[8] *National Kidney Foundation, New York, NY.*

[9] *University of British Columbia, Vancouver, BC, Canada.*

[10] *Nuffield Department of Population Health, Medical Research Council Population Health Research Unit at the University of Oxford, Oxford, United Kingdom.*

[11] *Duke – NUS Medical School, Singapore, Singapore.*

[12] *University of Würzburg, Würzburg, Germany.*

[13] *University of British Columbia, Vancouver, BC, Canada.*

[14] *Department of Medicine, Division of Nephrology, University of Wurzburg, Wurzburg, Germany.*

[15] *Université de Lorraine & FCRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists) Network, Nancy, France.*

[16] *Weill Cornell Medical College, New York, NY.*

[17] *The University of Sydney, Sydney, NSW, Australia.*

[18] *University of Bari, Bari, Italy.*

[19] *The University of Hong Kong, Pok Fu Lam, Hong Kong.*

[20] *Baylor College of Medicine, Houston, TX.*

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Correspondence: Gregory Wilson, MBBS, Faculty of Medicine, University of Queensland, Herston, Brisbane, QLD 4006, Australia. (gregory.wilson@uqconnect.edu.au).

INTRODUCTION

Kidney transplantation is the treatment of choice for most patients with kidney failure.[1] When successful, kidney transplantation is associated with significantly improved recipient survival and quality of life compared with maintenance dialysis.[1,2] However, cardiovascular disease remains a major cause of morbidity and mortality in transplant recipients.[3,4] Kidney transplant recipients have a 3–5 times increased risk of cardiovascular disease compared with age-matched peers and registry data have consistently shown that cardiovascular disease remains the leading cause of death in these patients.[3,4] Pre-existing risk factors for cardiovascular disease can be amplified posttransplantation by the metabolic effects of immune suppression, hypertension, dyslipidemia, and allograft dysfunction.[5] Significant research effort has focused on improving cardiovascular outcomes in kidney transplant recipients.[4]

However, it has been difficult to fully capitalize on research performed to date because of heterogeneity in cardiovascular outcome reporting.[6–9] This marked heterogeneity in reported outcomes has been well described in both nephrology and cardiology research.[10,11] Surrogate and composite outcomes (when 2 or more measurable outcomes are combined into a single measure) are widely utilized and there is currently no standardization of how metrics and methods of aggregation should be applied to outcome reporting.[10,12,13] Heterogeneity in cardiovascular outcome reporting is a significant issue as it limits the ability to compare outcomes between trials, leads to the loss of important clinical information, and results in trials being duplicated to reassess treatment effect or excluded from meta-analyses, all contributing to research waste.[14]

A core outcome set of standardized clinical outcomes of critical importance can help address these shortcomings by facilitating comparisons of outcomes across trials and improving research transparency, quality, and relevance.[6,7] The Standardized Outcomes in Nephrology Initiative is a global initiative developing core outcomes for clinical trials in nephrology including kidney transplantation based on the shared priorities of patients, caregivers, health professionals, and researchers.[8] Cardiovascular disease has been identified as a core outcome domain of critical importance in kidney transplantation.[9] This systematic review of all contemporary randomized controlled trials in kidney transplantation aimed to identify all reported cardiovascular outcome measures with a view to better informing the process to establish a core cardiovascular outcome measure in all future kidney transplant trials.

MATERIALS AND METHODS

Search Strategy and Selection

A systematic search was conducted in the Embase, MEDLINE, Cochrane, and ClinicalTrials.gov electronic databases for randomized controlled trials published or registered between the January 1, 2012, and December 31, 2019 (Table S1, SDC, http://links.lww.com/TXD/A468). This period was chosen to provide an assessment of outcome measures currently in use in contemporary trials. Trials of adult (18 y and older) kidney transplant recipients that measured and reported at least 1 cardiovascular outcome were included. The cardiovascular outcome reported was not required to be prespecified in a trial protocol to be included in the study. Both mechanistic and clinical cardiovascular outcomes were included. Trials that included pediatric subjects, were abstracts or conference proceedings only, did not contain a cardiovascular outcome, were registered but had not started recruitment, or had an unknown recruiting status, were excluded from the review.

Data Extraction

All citations identified by this search were screened by title and abstract by 2 independent reviewers (G.W. and K.V.) to assess if they met the inclusion criteria. Full-text articles or trial protocols (for ClinicalTrials.gov) of these citations were then assessed to confirm that all inclusion criteria were met. Cohort size, year of publication, country, continent, trial duration, trial intervention, donor type, kidney transplant age at trial commencement, and funding source were extracted from the identified trials. When a trial was identified through both ClinicalTrials.gov and a full-text article, the full-text article was used primarily for data extraction to provide the most contemporaneous and detailed information.

All cardiovascular outcome measures reported were identified by 2 reviewers (G.W. and K.V.). All levels of specification for each reported outcome measure were extracted. Specifically, the outcome measure definition (eg, nonfatal myocardial infarction, fatal myocardial infarction, ST-elevation myocardial infarction, non–ST-elevation myocardial infarction), metric (eg, change from baseline, total number of events), method of aggregation (eg, mean, median), and time points of measurement were recorded. When the full-text article did not provide the specific details required for the outcome measure, supplementary files, and trial protocols (both published and registered on ClinicalTrials.gov) were reviewed for additional information and clarification to allow outcome measures to be defined as accurately as possible. Despite this, some trials did not report all levels of specification for all outcome measures. These outcome measures were still included in this study but with the absent specification recorded as not available.

Data Analysis

Two reviewers (G.W. and K.V.) grouped individual outcome measures assessing a similar aspect of cardiovascular

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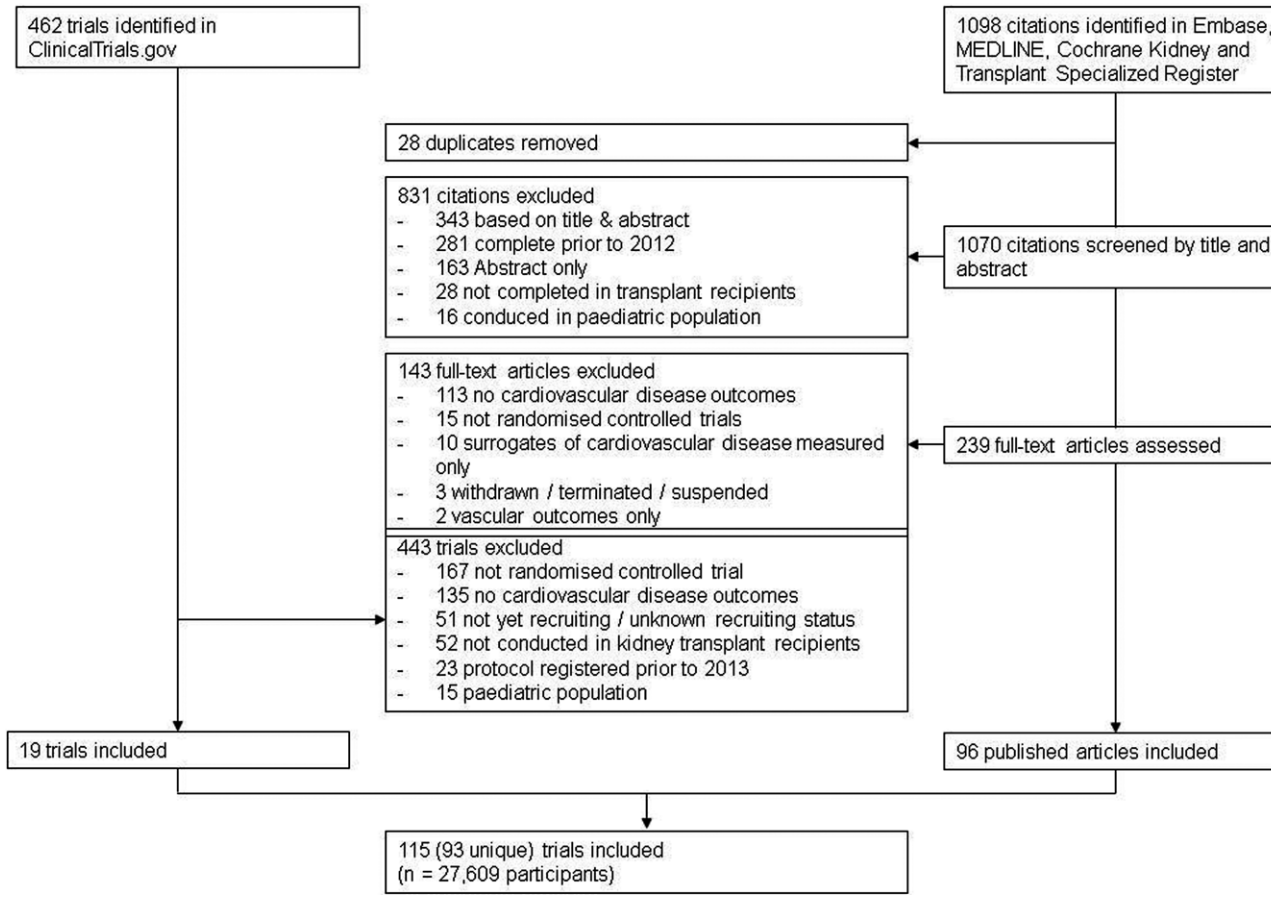

FIGURE 1. Flow diagram of systematic review search algorithm and results.

complications into unique outcomes (eg, outcome measures such as myocardial infarction, unstable angina, and presumed myocardial infarction were grouped into the outcome "acute coronary syndrome"; Figure S1, SDC, http://links.lww.com/TXD/A468). Two reviewers (G.W. and K.V.) then assigned all outcomes to 3 categories: clinical (a medical outcome that was based on a clinical assessment, surrogate (a laboratory, imaging or physical sign that was used as a substitute for a clinical endpoint), and patient reported (an outcome directly reported by a patient typically relating to quality of life or symptoms). The list of outcomes and their categorizations were reviewed and agreed upon by 4 additional reviewers (A.T., E.O., J.C., C.H.). A seventh reviewer (A.V.) assessed all outcome measure categorizations for accuracy and resolved any disagreements. Data analysis was performed in R (R Foundation for Statistical Computing, 2020, Vienna, Austria).

RESULTS

Trial Characteristics

A total of 115 published studies covering 93 trials and 27 609 participants were included in the review (Figure 1). Trial characteristics are described in Table 1. Thirty-six trials were conducted in new (incident) kidney transplant recipients (ie, trial enrollment was on the day of kidney transplantation) and 57 trials involved patients who already had a functioning kidney transplant in situ at the time of enrollment into the trial (prevalent). The median transplant duration at time of enrollment in prevalent trials was 3.75 y (IQR 0.9–6.6 y). Pharmacological therapies were the most common intervention studied (78%), particularly in incident transplant recipients (92%). Funding was most commonly from industry sources (49%). The median trial follow-up duration was 12 mo (interquartile range 10–24 mo) and the median trial size was 150 participants (interquartile range 70–510 participants). Europe was the most common World Health Organization region where trials had been conducted. Most (71%) trials were performed in a single country, whereas the remaining 29% were multinational.

Trial Outcomes and Measures

From the 93 trials included in this analysis, 490 cardiovascular outcome measures (based on the combination of measure definition, metrics, and methods of aggregation) were identified. Nineteen different metrics and 32 different methods of aggregation were identified. There were 335 cardiovascular outcome measure definitions identified. Of the 490 cardiovascular outcome measures identified, 266 (54%) were clinical outcome measures, 220 (45%) were surrogate outcome measures, and 4 (1%) were patient-reported cardiovascular outcome measures. In 28% of trials (50% of trials in incident transplant recipient and 14% of trials in prevalent transplant recipients), a cardiovascular outcome measure was only reported as part of serious adverse event reporting. The median number of cardiovascular outcome measures reported by each trial was 3 (range 1–32; Figure S2, SDC, http://links.lww.com/TXD/A468).

TABLE 1.
Characteristics of all included trials

	All trials (n = 93)
Participants	
0–49	15 (16%)
50–99	25 (27%)
100–499	38 (41%)
500–999	10 (11%)
1000–4999	4 (4%)
Not reported	1 (1%)
Year	
2012–2013	21 (23%)
2014–2015	23 (25%)
2016–2017	25 (27%)
2018–2019	6 (6%)
Not published	18 (19%)
WHO region	
Australia/New Zealand	2 (5%)
Europe	50 (54%)
International	17 (18%)
Middle East	2 (2%)
North America	17 (18%)
South America	2 (2%)
Duration (mo)	
1–3	7 (8%)
4–6	11 (12%)
7–12	35 (38%)
13–24	19 (20%)
25–48	6 (6%)
>48	15 (16%)
Intervention type	
Behavioral	9 (10%)
Device	1 (1%)
Lifestyle	3 (3%)
Pharmacological	72 (78%)
Surgical	3 (3%)
Other	5 (5%)
Funding source	
Government	11 (12%)
Hospital	13 (14%)
Industry	46 (49%)
University	17 (18%)
Not declared/other source	6 (7%)

Outcome measures were grouped into 38 unique outcomes (Figure 2). The most common outcome reported in included trials was a cardiovascular composite (43%) followed by cardiovascular mortality (42%), acute coronary syndrome (33%), and vascular function (18%). Cardiovascular composites had the largest number of unique outcome measures reported (n = 77) followed by cardiovascular mortality (n = 58) and inflammatory biomarkers (n = 51) as shown in Figure 3. Nineteen (50%) of the outcomes consisted of 5 or more different outcome measures. Even without considering the different metrics and methods of aggregations used to define the outcome measure, the number of unique outcome measure definitions remained high (36 for cardiovascular composites, 18 for cardiovascular mortality, and 29 for inflammatory markers) as shown in Figure S3 (SDC, http://links.lww.com/TXD/A468).

Outcomes were also compared across the 5 trial intervention categories (Table S2, SDC, http://links.lww.com/TXD/A468). In pharmacological trials (the most common intervention category), cardiovascular mortality (53%) was the most common outcome reported followed by cardiovascular composite (47%) and acute coronary syndrome (42%). In behavioral trials (the second most common trial intervention category), functional assessment was the most common outcome reported (44%) followed by heart rate (33%), inflammatory biomarkers (33%), and cardiac function (33%). Surrogate outcomes were more commonly reported in nonpharmacological trials (90%) compared with pharmacological trials (44%).

Cardiovascular Composite Outcome

Forty trials reported a cardiovascular composite outcome. The most common outcome components were major cardiovascular events (18 trials, 45%), stroke unspecified (11, 28%), and myocardial infarction unspecified (10, 25%) (Figure S4, SDC, http://links.lww.com/TXD/A468). For the 39 trials that reported a cardiovascular mortality outcome, the most common measures reported for this outcome were patient survival (n = 17), cardiovascular death (n = 12), and sudden circulatory death (n = 3). Of the 29 trials that reported an acute coronary syndrome outcome, the most common measures included myocardial infarction (n = 18), acute myocardial infarction (n = 4), and acute coronary syndrome (n = 2). Eighteen trials reported at least 1 cardiac or inflammatory biomarker. The most common biomarker reported was C-reactive protein (n = 8).

The individual components of each cardiovascular composite outcome are summarized in Figure 4. Of the 40 trials that reported a cardiovascular composite outcome, 29 (73%) had at least 1 element that was not specifically defined (eg, cardiovascular death, major cardiovascular event) and 19 trials (48%) did not specifically define any component of their cardiovascular composite outcome. For trials that reported all components of their composite outcome measure, only 3 trials shared the same components. The most common reported component of the specifically defined cardiovascular composites was stroke (type not further specified) followed by myocardial infarction (type not further specified). The average number of defined individual components was 5 (range 1–8). Only 11 (12%) trials included at least 1 mortality-related component in the composite. Industry-sponsored trials were more likely to include a cardiovascular composite outcome (24 trials, 52%) compared with trials funded by other sources (16 trials, 34%).

Trial Metrics, Methods of Aggregation, and Time Points

The most common metrics were the change from baseline (n = 502; 44%) followed by the end value (n = 396; 35%). The most common methods of aggregation were the total (n = 340; 30%) followed by the mean (n = 322; 28%). Outcomes were most commonly reported at 6 mo (24 trials), 12 mo (44 trials), and 24 mo (18 trials), but the range of different time points over which outcomes were reported was large (median 12 mo; range 1–180 mo; Table S3, SDC, http://links.lww.com/TXD/A468). Outcomes beyond 12 mo were more likely to be reported by pharmacological trials (49%) than nonpharmacological intervention (5%).

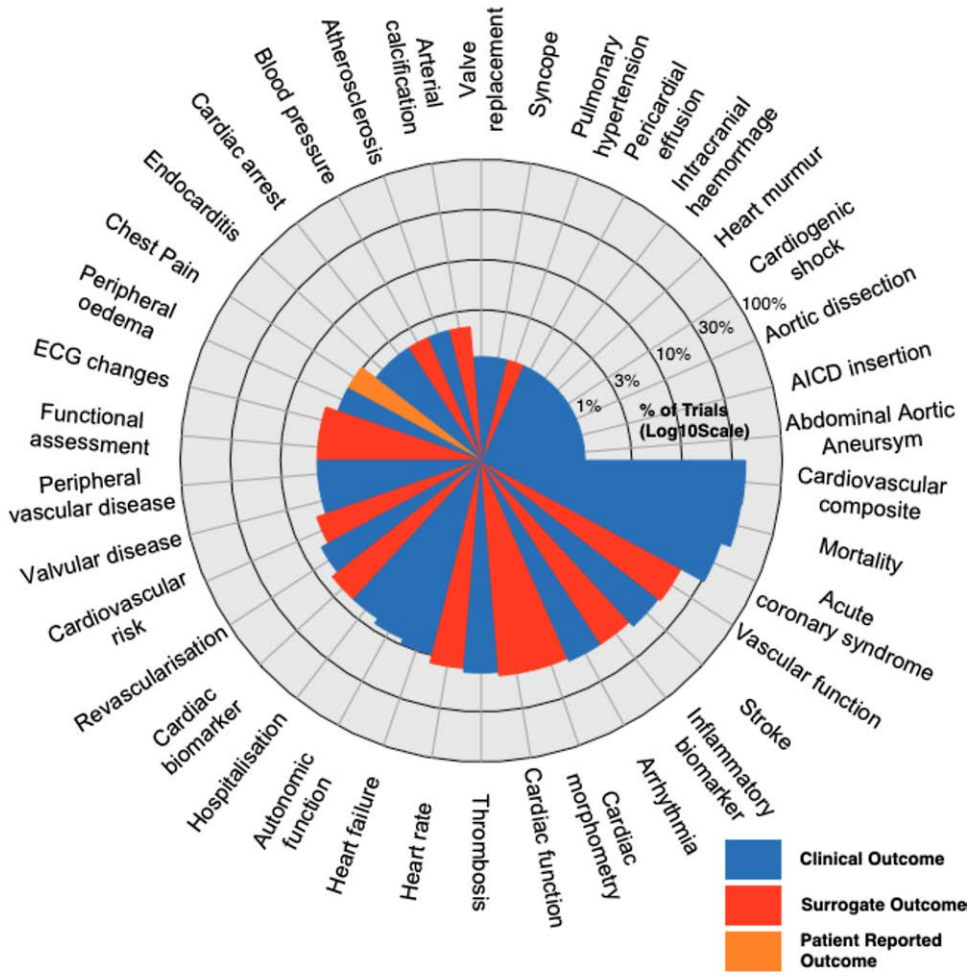

FIGURE 2. Proportion of trials reporting each of the 38 unique cardiovascular outcomes identified. Proportions are expressed in log10 scale. AICD, automatic implantable cardioverter defibrillator; ECG, electrocardiogram.

Forty-nine percent of pharmacological trials had a trial duration of 12 mo or greater compared with only 17% of nonpharmacological trials (Table S4, SDC, http://links.lww.com/TXD/A468).

DISCUSSION

This review demonstrates the substantial heterogeneity in cardiovascular outcome reporting in kidney transplant trials. There were 490 outcome measures reported corresponding to 38 different cardiovascular outcomes. Reported outcomes were mostly clinical and surrogates of varying significance. There was only 1 patient-reported outcome identified (chest pain). Cardiovascular composites and cardiovascular mortality were the most frequently reported outcomes as well as the most diverse with each consisting of >50 different outcome measures. Cardiovascular composites and cardiovascular mortality were predominantly reported in pharmacological trials. Cardiovascular composites were heterogenous combining outcome components of varying severity (eg, cardiovascular death and unstable angina). Most composites lacked adequate specification of the outcome components, compromising reproducibility, interpretation, and comparability of trial outcomes. The large number of different metrics and methods of aggregation used to report these outcome measures and the wide range of time points when outcomes were measured added further complexity to cardiovascular outcome reporting.

Cardiovascular composites were the most frequent (43%) and most heterogenous cardiovascular outcome reported. Composite outcomes are widely used in cardiovascular disease and kidney transplantation. They increase the event rate, reduce the sample size for a study, and can capture the overall impact of a therapeutic intervention, thereby increasing the statistical power of the study.[13,15] However, composite outcomes may overstate a treatment effect or understate a harmful effect by including components that have dissimilar clinical importance.[13,15] If they are to be a valid outcome measure, they must be carefully designed utilizing a prespecified combination of individual components of similar importance and standardized definitions to avoid reporting a biased result.

Surrogate outcome measures were frequently reported across many trials and vascular function was the most common surrogate outcome. Surrogate markers are utilized to increase trial event rates, increasing the likelihood of a significant finding and allowing for a shorter trial duration.[16] However, inappropriate use of surrogate outcomes can lead to inaccurate outcome reporting. Furthermore, different methods may be used to measure surrogate markers, increasing the heterogeneity of these outcomes.[17] Clinically focused trials should prioritize reporting clinical outcomes

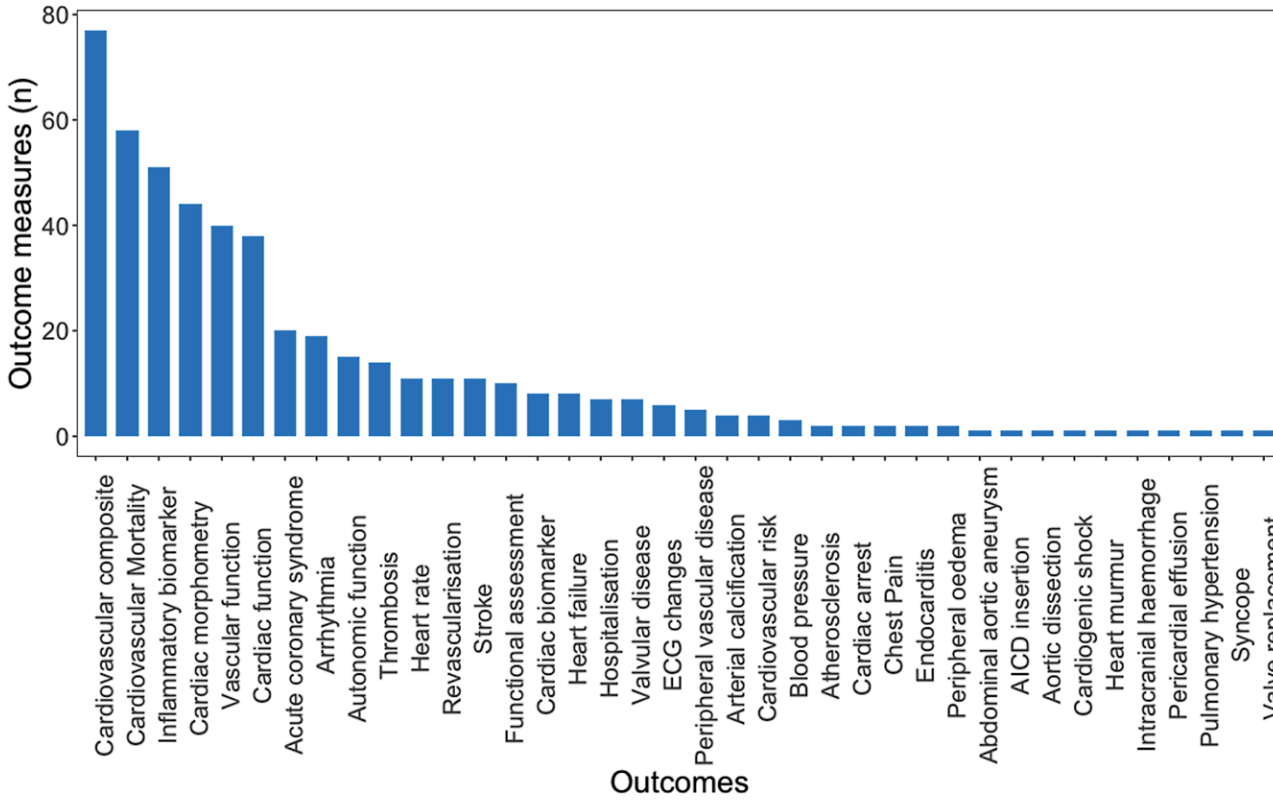

FIGURE 3. Number of different outcome measures reported for each cardiovascular outcome. Each outcome measure reported was a unique combination of the outcome measure definition, metric, and method of aggregation. AICD, automatic implantable cardioverter defibrillator; ECG, electrocardiogram.

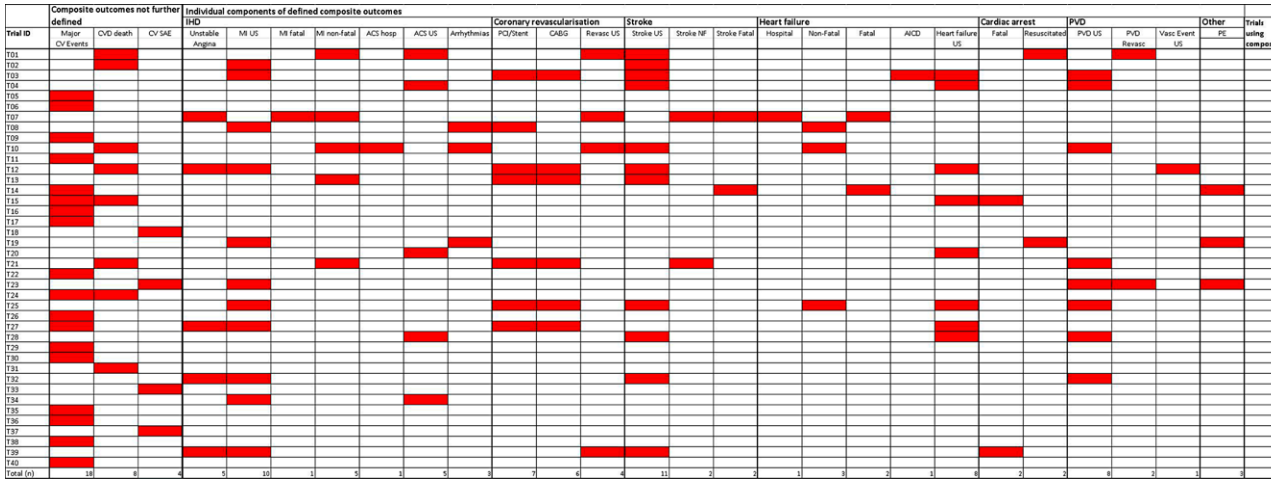

FIGURE 4. Matrix displaying the individual outcome components of 40 different cardiovascular composite outcome measures reported across 93 included trials. The bottom row tallies the number of times the individual component was used and the far right row tallies the number of trials using the composite. ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; hosp, hospitalization; MI, myocardial infarction; NF, nonfatal; PCI, percutaneous intervention; PE, pulmonary embolus; PVD, peripheral vascular disease; revasc, revascularization; US, unspecified (outcome was not further defined); vasc, vascular.

over surrogate outcomes when possible and only use well-validated surrogate measures when measuring a clinical outcome is not feasible.

The majority of trials included in our review were of small size with an average patient population of 150, which may be explained due to the small population of transplant recipients in contrast to the large scale cardiovascular trials using the general population.[18,19] The trial duration for most studies also was <1 y. Although cardiac events such as myocardial infarction can occur in the perioperative period following kidney transplantation, cardiovascular disease risk generally accumulates over several years following the onset of chronic kidney disease.[4] It may be that in some trials, cardiovascular measures were only reported as a secondary outcome and a shorter trial duration was therefore appropriate. However, longer follow-up is often required in cardiovascular trials as the cardiovascular benefits of an intervention may take several years to emerge.[20]

There were significant differences in trial durations and how outcomes were reported depending on the trial intervention type. Pharmacological trials were more likely to report clinical outcomes and have a longer follow-up compared with nonpharmacological trials. Pharmacological trials have been the mainstay of drug development for many decades and there is a well-defined and structured framework for pharmacological interventions.[21] However, trial designs for nonpharmacological interventions (especially behavioral or lifestyle interventions) have additional methodological complexities that affect how outcomes are measured,[21] such that it is unsurprising that there are differences in outcome reporting and duration between different trial types.

Only 1 patient-reported outcome was identified in this review, although patient-reported outcomes measure a key aspect of disease burden[22] and well-designed patient-reported outcomes can be of value to clinicians and researchers and complement other clinical and surrogate endpoints. These outcomes are now increasingly reported in cardiology[22] and nephrology trials[23] and their increased adoption would enhance the relevance of clinical research.

Core outcome sets represent a standardized group of outcomes that should be reported as a minimum in clinical trials.[6] They help reduce heterogeneity among study outcomes and ensure that meaningful endpoints are measured.[6] The Standardized Outcomes in Nephrology Initiative was established in 2014 and is in the process of developing core outcome sets across the spectrum of kidney disease including kidney transplantation.[8] They have identified cardiovascular disease as 1 of 6 critically important outcome domains.[9] Based on this and the finding of significant heterogeneity in cardiovascular disease outcome reporting in kidney transplantation, a core outcome measure is required.

For a core outcome measure to be effective, it must be directly relevant to patients, clinicians, and researchers and thereby contribute to patient care.[8] Based on the findings of this review, there are several possible outcome measures that could be included in a core outcome set. These include acute coronary syndrome, cardiovascular mortality death, and stroke. These outcomes were all frequently reported in trials included in the survey, have standardized definitions, can be ascertained simply and reliably form patient reports or medical notes (with or without adjudication), are serious conditions with associated morbidity and mortality, and are of direct relevance to patients and their treating clinicians. However, further research is required to determine which of these is the most appropriate outcome measure to include in a core outcome set for cardiovascular disease in kidney transplantation.

There is significant heterogeneity in the reporting of cardiovascular outcomes in kidney transplant clinical trials limiting the ability to compare trials in this area. In particular, the heterogeneity of cardiovascular composites is of concern as they are the most frequently reported outcome. A cardiovascular core outcome measure considered most critically important by patients and healthcare professionals would help improve the quality of research in kidney transplantation to better inform patient-centered care.

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