An Updated Systematic Review of Trials of Cardiovascular Interventions: Letters

Letters

Representation of Patients With Kidney Disease in Trials of Cardiovascular Interventions: An Updated Systematic Review

be based as much on patients’ experience after discharge as during a hospital stay.

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The prevalence of kidney disease (KD) among the general population and in patients with cardiovascular disease (CVD) is high and growing.1 Also, standard therapeutic strategies may act differently in patients with KD, making extrapolation of trial data from patients without KD unreliable.2 In addition, trials in nephrology are more likely to be smaller and unblinded, leading to poorer-quality evidence.3 Despite the need for high-quality evidence for CVD interventions, 2 systematic reviews using data from 1985-2005 and 1998-2005 showed that patients with KD are underrepresented in randomized clinical trials of CVD interventions.4,5 We aimed to update the estimates of the representation of patients with KD in major randomized clinical trials of CVD interventions.

Methods | We performed a systematic search of MEDLINE between January 1, 2006, and December 31, 2014. Analysis was conducted from November 1, 2014, to August 31, 2015. We restricted the search to the top 10 medical journals ranked by impact factor from 2006 to 2013 to obtain 2350 citations and 2 of us (I.K. and G.N.N.) reviewed each full article. We included trials if they were randomized or controlled, treated heart failure or acute coronary syndrome, and randomized 100 participants or more. We excluded trials that did not report mortality or were subgroup analyses. We extracted the following data: trial characteristics, whether interventions were class I or II recommendations, exclusion of patients with KD, exclusion threshold of patients with KD (based on laboratory test results, renal replacement therapy, or nonspecific terms), reported indices of baseline renal function, proportion of patients with KD in each arm, and number of subgroup analyses by any nonrenal or renal characteristics. We evaluated differences in exclusion of patients with KD by each trial characteristic. Institutional review board approval was not sought because this is a systematic review of published data.

Results | A total of 371 trials randomizing 590 040 participants were included for analysis. Overall, 212 trials (57.1%) excluded patients with KD. Patients with KD were more likely than patients without KD to be excluded from North American and Canadian trials vs European trials (84 of 129 [65.1%] vs 107 of 206 [51.9%]), were more likely to be included in trials that tested medications vs those that tested procedures (142 of 200 [71.0%] vs 32 of 94 [34.1%]), were more likely than patients without KD to be included in industry-funded trials vs government-funded trials (111 of 172 [64.5%] vs 49 of 101 [48.5%]), and were more likely than patients without KD to be included in trials of patients with heart failure vs trials of patients with acute coronary syndrome (91 of 144 [63.2%] vs 120 of 244 [53.6%]). The Figure shows the exclusion of patients with KD by specific categories of treatment and diagnosis. There were no significant differences in representation of patients with KD in trials testing an intervention that was a class I or II recommendation vs representation of patients with KD in all trials (Table).

Of 212 trials excluding patients with KD, 111 (52.4%) used serum creatinine levels as the exclusion threshold, 21 (9.5%) used estimated glomerular filtration rate, 22 (10.4%) used creatinine clearance thresholds, 60 (28.3%) used renal replacement therapy of any form, and 36 (17.0%) used nonspecific qualitative exclusion criteria. Only 156 (42.0%) and 84 (22.6%) trials, respectively, reported at least 1 measure of
baseline renal function or proportion of patients with KD in each arm. Although 197 trials (53.1%) reported subgroup analyses by nonrenal baseline characteristics, only 60 (16.2%) reported subgroup analyses by renal characteristics (Table). In trials reporting renal subgroup analysis, 38 of 60 (63.3%) reported a test for interaction between renal function and outcome and, of those, 5 of 38 (13.2%) reported a significant interaction.

Discussion | In this systematic review, we found continued underrepresentation of patients with KD in trials of CVD interventions despite previously highlighted underrepresentation of these patients in such trials. This finding is troubling since KD and CVD are independent risk factors leading to increased prevalence of KD in patients with CVD and vice versa.1 Exclusion of patients with KD in trials of CVD interventions may be owing to cautiousness in certain conditions (eg, anticoagulation) but not in lower-risk interventions or when KD is a major confounder. However, we found that only 13.2% of trials assessing effect by KD subgroup had any interaction and thus, concerns of harm may be overstated.

Most trials excluded patients by serum creatinine levels instead of estimated glomerular filtration rate. Given the availability of superior methods to estimate renal function and the inaccurateness of serum creatinine measurements,6 use of serum creatinine levels for exclusion is inappropriate. Finally, trials did not report baseline renal function or outcomes by renal function, leading to poor understanding of the response to interventions of patients with KD.

In summary, we urge trialists to include patients with KD in trials of CVD interventions and to both report and analyze outcomes by renal function to improve the understanding of the risks and benefits of interventions in this vulnerable population.

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Figure. Frequency of Exclusion of Patients With Kidney Disease From Trials of Cardiovascular Interventions

A Exclusion by intervention category

β-Blocker (n = 7)
PVI (n = 13)
Thrombectomy (n = 15)
Device (n = 35)
Exercise (n = 5)
Remote ischemic postconditioning (n = 5)
Management plans (n = 56)
Antiplatelet agent (n = 45)
Fibrinolysis (n = 9)
Cell therapy (n = 8)
Supplement (n = 20)
Other* (n = 74)
Statin (n = 13)
RAAS antagonist (n = 20)
Anticoagulant (n = 17)
Diuretics (n = 7)
Calcium channel blockers (n = 2)

Trials Excluding Patients With Kidney Disease, %

B Exclusion by diagnostic category

Myocardial infarction and heart failure (n = 3)
Myocardial infarction (mixed only) (n = 19)
NSTEMI and STEMI (n = 14)
HFrEF (n = 72)
STEMI (n = 124)
UA, NSTEMI, and STEMI (n = 31)
UA and NSTEMI (n = 25)
NSTEMI (n = 11)
HFpEF (n = 11)
Heart failure (mixed only) (n = 61)

Trials Excluding Patients With Kidney Disease, %

Percentage of trials excluding patients with kidney disease based on specific intervention categories (A) and specific diagnostic categories (B). The bar graphs represent the percentage of trials out of the total that evaluate a particular intervention or a particular diagnostic category. HFrEF indicates heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone system; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

* Includes management, exercise, oxygen therapy, and systems-wide quality improvement initiatives.
Table. Exclusion of Patients With Kidney Disease From and Reporting of Renal Function in Cardiovascular Trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trials, Value*</th>
<th>Intervention Was Class I or II Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>371/371 (100)</td>
<td>118/371 (31.8)</td>
</tr>
<tr>
<td>Excluded patients with kidney disease based on the index report, methods report, or registered protocol</td>
<td>212/371 (57.1)</td>
<td>64/118 (54.2)</td>
</tr>
<tr>
<td>Threshold for exclusion†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine level, mg/dL</td>
<td>111/212 (52.4)</td>
<td>38/64 (59.4)</td>
</tr>
<tr>
<td>&gt;1.3-2.0</td>
<td>3/212 (1.4)</td>
<td>1/64 (1.6)</td>
</tr>
<tr>
<td>≥2.0-3.0</td>
<td>67/212 (31.6)</td>
<td>27/64 (42.2)</td>
</tr>
<tr>
<td>≥3.0</td>
<td>41/212 (19.3)</td>
<td>10/64 (15.6)</td>
</tr>
<tr>
<td>eGFR and/or creatinine clearance, mL/min/1.73 m²</td>
<td>48/212 (22.6)</td>
<td>13/64 (20.3)</td>
</tr>
<tr>
<td>eGFR and/or creatinine clearance ≤30</td>
<td>21/212 (9.9)</td>
<td>4/64 (6.3)</td>
</tr>
<tr>
<td>Creatinine clearance ≤30</td>
<td>22/212 (10.4)</td>
<td>8/64 (12.5)</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>60/212 (28.3)</td>
<td>14/64 (21.9)</td>
</tr>
<tr>
<td>Nonspecific exclusion‡</td>
<td>36/212 (17.0)</td>
<td>11/64 (17.2)</td>
</tr>
<tr>
<td>No. of trials reporting baseline renal characteristics for each group in index report</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine level, eGFR, or creatinine clearance*</td>
<td>156/371 (42.0)</td>
<td>47/118 (39.8)</td>
</tr>
<tr>
<td>Serum creatinine level</td>
<td>105/371 (28.3)</td>
<td>30/118 (25.4)</td>
</tr>
<tr>
<td>eGFR</td>
<td>65/371 (17.5)</td>
<td>14/118 (11.9)</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>29/371 (7.8)</td>
<td>10/118 (8.5)</td>
</tr>
<tr>
<td>Proportion of patients with kidney disease</td>
<td>84/212 (39.7)</td>
<td>26/118 (22.0)</td>
</tr>
<tr>
<td>Trials reporting subgroup analyses in index report</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 subgroup analysis by nonrenal characteristics</td>
<td>197/371 (53.1)</td>
<td>55/118 (46.6)</td>
</tr>
<tr>
<td>No. of nonrenal subgroup analyses, mean (SD)</td>
<td>3.9 (5.2)</td>
<td>3.5 (4.8)</td>
</tr>
<tr>
<td>At least 1 subgroup analysis by renal characteristics</td>
<td>60/371 (16.2)</td>
<td>17/118 (14.4)</td>
</tr>
</tbody>
</table>

Abbreviation: eGFR, estimated glomerular filtration rate.

Si conversion factors: To convert serum creatinine to micromoles per liter, multiply by 88.4; creatinine clearance to milliliters per second per meter squared, multiply by 0.0167.

* Data are presented as number/total number (percentage) of patients unless otherwise indicated.

† Class I refers to conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective. Class II indicates conditions for which there is conflicting evidence or a divergence of opinion about the usefulness and/or efficacy of a procedure or treatment. These recommendations were derived from the current American College of Cardiology/American Heart Association guidelines on the management of heart failure in adults, management of patients with ST-segment elevation myocardial infarction, or management of patients with unstable angina and non-ST-segment elevation myocardial infarction (unstable angina, non-ST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction, myocardial infarction, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, or heart failure, alone or in any combination).

‡ The sum of the number of trials reporting each baseline renal parameter (serum creatinine level, eGFR, and creatinine clearance) is greater than the total number of trials that reported baseline renal function because several trials reported multiple renal parameters (eg, serum creatinine level and eGFR) and thus were counted for each category. The sum of the percentages is greater than 100% for this reason.

§ Nonspecific exclusion terms such as: “anticipated to start dialysis within 1 year,” “severe renal dysfunction,” “severe kidney failure,” “severe renal failure,” “known renal insufficiency,” “severe renal impairment,” “clinically significant renal disease,” “known renal failure,” “known prior history of renal insufficiency,” and “known severe kidney disease” without a qualifying eGFR or serum creatinine value.

§ The sum of the number of trials for each category of exclusion criteria (serum creatinine level, eGFR, creatinine clearance, renal replacement therapy, and nonspecific exclusion) is greater than the total number of trials that excluded patients with kidney disease because several trials used multiple concurrent criteria for exclusion of patients with kidney disease (eg, serum creatinine level and renal replacement therapy) and thus were counted for each category. The sum of the percentages is greater than 100% for this reason.

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Invited Commentary

Exclusion of Patients With Kidney Disease From Cardiovascular Trials

Despite a high prevalence of kidney disease (KD)—ranging from 30% to 60%—among patients with cardiovascular disease (CVD) and the association of KD with worse cardiovascular outcomes, two previous systematic reviews observed underrepresentation of patients with KD in randomized clinical trials of cardiovascular interventions published from 1985 through 2005. Eighty-six of 153 (56.2%) to 69 of 86 trials (80.2%) excluded patients with KD, and only 6 of 86 (7.0%) to 15 of 153 (9.8%) studies reported patients’ kidney function at the start of the trial.

In this issue of JAMA Internal Medicine, Konstantinidis et al report findings from an updated systematic review on the representation of patients with KD in randomized clinical trials of cardiovascular interventions published from 2006 through 2013. Of the 371 trials included in this study, 212 (57.1%) excluded patients with KD (defined based on varying thresholds of serum creatinine level, estimated glomerular filtration rate, and/or creatinine clearance; renal replacement therapy; or nonspecific qualitative criteria). Renal function and the proportion of patients with KD in each study group at baseline were reported in 156 (42.0%) and 84 (22.6%) trials, respectively. Although these percentages represent considerable progress since the previous studies, there is much room for improvement. Sixty trials (16.2%) examined and reported results among subgroups defined according to kidney function, of which 63.3% formally evaluated whether treatment effects differed among participants with and without evidence of KD. Outcomes of treatment were statistically significantly different among participants with KD in 13.2% of trials in which the possibility was considered.

Even though a decade has passed since this topic was last examined systematically and a strong recommendation was issued at that time for greater inclusion of patients with KD into cardiovascular trials, the underrepresentation of these patients in such trials remains a persistent problem; the proportion of patients excluded in this report was comparable with that of the prior study conducted by Coca et al. Why should that still be the case? Are there valid reasons why patients with KD should be excluded from cardiovascular trials? Features of KD that may contribute to CVD, such as altered salt and water handling, abnormal bone and mineral metabolism, hyperkalemia, and uremic toxemia, may not be modifiable with standard interventions geared toward the general population. Thus, it is possible that the pathophysiologic features of CVD are altered in patients with KD and that they may be resistant to conventional treatments. Therefore, investigators may fear that the inclusion of such patients in cardiovascular trials may shift the results toward the null. Concern for elevated risks of adverse effects may also contribute to the reluctance to enroll patients with KD in trials of cardiovascular interventions. For example, the potential for bleeding complications related to platelet dysfunction associated with KD and hyperkalemia with certain agents may raise concerns regarding enrolling patients with KD into some trials.

If patients with KD composed a rare subgroup, one could argue that it might be reasonable to exclude them from cardiovascular trials for these reasons. However, KD is highly prevalent among those with CVD, with estimates ranging from 30% to 60%. Thus, it is nearly inevitable that internists and nephrologists will face the need to manage CVD in patients with KD in clinical practice. Excluding patients with KD from cardiovascular trials may be viewed as the path of least resistance—or even greatest prudence—when designing cardiovascular trials because of concerns about the possibility of less benefit or greater risk. However, given that patients with KD are at higher risk of death and morbidity from CVD, they stand to garner the greatest absolute benefit from treatment if the relative benefit is similar among those with and without KD.

On the other hand, Konstantinidis et al note that outcomes differed among patients with and without KD in a subset of trials, so it cannot be assumed that the relative benefit of cardiovascular treatments will be the same in these subgroups. Notably, exclusion of patients with KD from many trials precluded assessment of whether outcomes differed according to kidney function, thus the extent of the modification of effect observed in this report may be an underestimate. In addition, this study did not include a report of rates of adverse events according to renal function (likely because most trials did not perform such analyses). Future research is required to inform how renal function modifies the safety of cardiovascular interventions. In the long term, a strategy of excluding patients with KD from large trials eliminates the opportunity to define the risk to benefit ratio for a sizeable subpopulation with a high burden of CVD and could put them at higher risk for subsequent underuse of beneficial therapies or overuse of therapies that are less effective or present higher risks among patients with KD.

The underrepresentation of patients with KD in cardiovascular trials is akin to the historically low representation of women in clinical trials, which prompted the National Institutes of Health and the US Food and Drug Administration to
issue guidelines on the inclusion of women in clinical trials. 6 Given that KD is highly prevalent and may modify relevant parameters of some medications or procedures (eg, efficacy, safety, and pharmacokinetics), patients with KD should be included in cardiovascular trials in the absence of absolute contraindications. Investigators’ goal should be to enroll a study population in which the prevalence and severity of KD match the prevalence and severity in the target population. Furthermore, investigators should consider stratifying treatment assignment based on kidney function to achieve balance and should report outcome and safety results stratified by level of baseline kidney function.

What does widespread exclusion of patients with KD from cardiovascular trials mean for the practicing internist or nephrologist who must manage CVD in patients with KD? Unfortunately, the currently available randomized clinical trial data on the efficacy and safety of cardiovascular interventions in patients with KD is insufficient to make recommendations on the optimal approach for many therapies. This report underscores the need for greater inclusion of patients with KD in cardiovascular trials or the design of trials specifically focused on this population to better characterize the risks and benefits of cardiovascular interventions in this highly prevalent and prognostically important subgroup of patients. The number of randomized clinical trials within the field of nephrology is low, and the trials are of poor quality and are unlikely to provide adequate data on the treatment of CVD in patients with KD. 2 Extrapolation of trial results conducted in the general population to patients with KD may or may not be appropriate, and a deeper understanding of the barriers to including patients with KD in cardiovascular trials and the development of strategies to overcome them is urgently needed.

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Association Between Clinician Computer Use and Communication With Patients in Safety-Net Clinics

Safety-net clinics serve populations with limited proficiency in English and limited health literacy who experience communication barriers that contribute to disparities in care and health. 1 Implementation of electronic health records in safety-net clinics may affect communication between patients and health care professionals. 2 We studied associations between clinician computer use and communication with patients with diverse chronic diseases in safety-net clinics.

Methods | This observational study took place from November 1, 2011, to November 30, 2013, at an academically affiliated public hospital with a basic electronic health record for reviewing test results, tracking health care maintenance, prescribing medications, and referring patients. Some clinics (internal medicine and diabetes) required typed visit documentation, which was optional in other clinics (family medicine, cardiology, and rheumatology).

Eligible adults who spoke English or Spanish had specific chronic conditions and received primary and subspecialty care (Table 1). Physicians, nurse practitioners, fellows, and residents could decline participation or designate patients as ineligible. Research assistants enrolled and interviewed patients by telephone before appointments, videotaped the subsequent visit, and interviewed patients after the visit. Clinician participants completed paper or online questionnaires. Data analysis was conducted from March 12, 2013, to September 11, 2015. All clinicians and patients provided written informed consent; patients provided verbal consent via telephone before the baseline interview. The University of California, San Francisco, Institutional Review Board approved this study.

The clinician computer use score summed the following 4 coder ratings (Cronbach α, .67): amount of review of computer data, typing or clicking the computer mouse, eye contact with patients, and noninteractive pauses. 2-4 With ratings for eye contact reversed, as more eye contact is indicative of less computer use, high total scores (range, 0-12) indicated more computer use. Interrater reliability was 0.90 (4 videos), and we validated the score calculating its correlation (0.66) with clinician and patient statements.