Published in final edited form as:

JAMA Intern Med. 2016 January 1; 176(1): 124–125. doi:10.1001/jamainternmed.2015.6403.

Exclusion of Patients With Kidney Disease From Cardiovascular Trials

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Despite a high prevalence of kidney disease (KD)—ranging from 30% to 60%—among patients with cardiovascular disease (CVD)¹ and the association of KD with worse cardiovascular outcomes,² two previous systematic reviews observed underrepresentation of patients with KD in randomized clinical trials of cardiovascular interventions published from 1985 through 2005.^{1,2} 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 al³ 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,^{1,2} 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.³ Outcomes of treatment were statistically significantly different among participants with KD in 13.2% of trials in which the possibility was considered.

Even though about 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

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Conflict of Interest Disclosures: Dr Ishida reported receiving research funding from Genentech/Roche. Dr Johansen serves on the Steering Committee for the Prolyl Hydroxylase Inhibitor Program in Chronic Kidney Disease With Anemia for GlaxoSmithKline. No other disclosures were reported.

Role of the Funder/Sponsor: The NIDDK had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

that of the prior study conducted by Coca et al.¹ 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.⁴ 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.² 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.¹

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%.¹ 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,² 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.³ 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 therapies⁵ 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.

Acknowledgments

Funding/Support: This work was supported by a Midcareer Investigator Award in Patient-Oriented Research (K24DK085153) from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (Dr Johansen) and by a Mentored Patient-Oriented Research Career Development Award (K23DK103963) from the NIDDK (Dr Ishida).

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