Exclusion of Persons with Kidney Disease in Trials of Peripheral Artery Disease

A Systematic Review of Randomized Trials

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Patients with CKD are at higher risk of developing peripheral artery disease (PAD) and have worse outcomes than persons without CKD (1,2). Current PAD treatment strategies include exercise, medications, and revascularization techniques. However, it is likely that persons with advanced CKD are excluded from trials of these interventions as in trials of cardiovascular disease and cancer (3,4). We aimed to perform a systematic review to determine the representation or exclusion of patients with CKD in randomized controlled trials of PAD intervention.

We systematically searched the MEDLINE database from January 1, 2000 through October 31, 2018. The search strategy included articles indexed under the Medical Subject Headings of "intermittent claudication" or "peripheral artery disease," as well as "peripheral artery disease," "intermittent claudication," "critical limb ischemia," "randomized controlled trial," or "randomised controlled trial" under title/abstract. We included randomized trials of PAD treatment including critical limb ischemia and intermittent claudication, with at least 50 participants that reported clinical outcomes and were published in English. We extracted information on journal, publication year, study characteristics, country, funding source, intervention, whether the interventions were American Heart Association/American College of Cardiology Class (AHA/ACC) 1 or 2 recommendations, measures of kidney function used, and criteria for exclusion of patients with CKD. We reviewed methods reports and registered protocols of studies for completeness. For studies with multiple reports, the first published report was used. We assigned trials to four groups based on their publication year and sample size, and six groups based on the intervention studied. We grouped interventions into surgery, endovascular procedure, medication, exercise, other, and more than one intervention. We tested differences in exclusion by each characteristic with the chi-squared test and one-way ANOVA test.

We identified 1218 citations of which 900 (74%) did not meet inclusion criteria. After reviewing full texts of the remaining 318 trials, 237 trials randomizing 157,520 participants met inclusion criteria. Of these, 104 (44%) trials excluded patients with CKD based on various criteria including serum creatinine (n=48), eGFR (n=17), creatinine clearance (n=4), renal replacement therapy (n=19), and nonspecific description (n=28). Trials that evaluated interventions of class 1 or 2 recommendations in current guidelines—such as statin medication, antiplatelet therapy for general patients with PAD, or supervised exercise—were less likely to exclude patients with CKD (38% versus 53%, P=0.03). Industry-funded trials were more likely to exclude patients with CKD compared with academic- or government-funded ones (54% versus 38%, P=0.04). Trials evaluating endovascular procedures or medications were more likely to exclude patients with CKD compared with those evaluating surgical interventions (52% in endovascular procedures versus 57% in medications versus 21% in surgical interventions, P<0.001). Frequency of exclusion did not differ by time period of publication, trial size, number of centers, location, and diagnostic categories (Table 1).

The criteria for exclusion varied across trials. Of the 104 trials that excluded patients with kidney disease, 48 (46%) used serum creatinine, 17 (16%) used eGFR, 4 (4%) used creatinine clearance, 19 (18%) used KRT of any form, and 28 (27%) used nonspecific qualitative exclusion criteria (such as "significant renal impairment," "renal dysfunction," and "severe renal insufficiency"). Among the 48 studies using serum creatinine, the threshold for exclusion was 1.5–2 mg/dl in 20 studies, 2.1–2.9 mg/dl in 24 studies, and ≥3.0 mg/dl in four studies. Among 17 studies using eGFR, the threshold of exclusion was ≤30 ml/min per 1.73 m^2 in 13 studies, 31–60 ml/min per 1.73 m^2 in two studies, and 61–90 ml/min per 1.73 m^2 in one study. The trend of using serum creatinine or nonspecific thresholds did not change across years (P=0.82). Only 27 (11%) trials reported baseline kidney function, with serum creatinine being the most commonly used (n=23) followed by eGFR (n=4), and two trials used both measures.

In summary, trials of PAD therapies frequently exclude persons with CKD and use imprecise and inconsistent methods for reporting kidney function. The lower enrollment of patients with CKD in PAD-therapy trials impairs the quality of evidence available in this high-risk population. Frequent use

Table 1. Characteristics of peripheral artery disease trials

Characteristics	Trials	Patients	Explicit Exclusion of Kidney Disease Based on Index Report, Methods Report of Registered Protocol, Trials (% [*N*])	*P* Value
Overall	237	157,520	104 (44%)	
Publication year				0.16
2000–2004	43	12,848	20 (47%)	
2005–2009	45	12,140	15 (33%)	
2010–2014	86	78,728	35 (41%)	
2015–2018	63	53,804	34 (54%)	
Class 1/2 recommendation				0.03
Yes	144	62,294	55 (38%)	
No	93	95,226	49 (53%)	
Trial enrollment size				0.47
50–99	76	5164	34 (45%)	
100–499	136	27,671	61 (45%)	
500–999	12	8601	6 (50%)	
>1000	13	116,084	3 (23%)	
Sites				0.19
Single center	72	8261	27 (38%)	
Multicenter	165	149,259	77 (47%)	
Location				0.68
United States/Canada	82	128,373	39 (48%)	
Europe	132	25,412	56 (42%)	
Other (Asia, Australia, South America)	23	3735	9 (39%)	
Funding source				0.04
Academic grant/government	61	10,143	23 (38%)	
Industry	90	132,846	49 (54%)	
Both	20	3132	10 (50%)	
Not specified	66	11,399	22 (33%)	
Diagnostic category				0.57
Critical limb ischemia	31	5517	11 (36%)	
Intermittent claudication	114	29,406	55 (48%)	
All PAD	39	90,728	16 (41%)	
Other[a]	53	31,869	22 (42%)	
Specific therapeutic class				<0.001
Surgery	14	2844	3 (21%)	
Endovascular	65	10,356	34 (52%)	
Exercise	28	2947	8 (29%)	
Medication	90	134,385	51 (57%)	
Other[b]	30	4647	6 (20%)	
More than one intervention	10	2341	2 (20%)	

PAD, peripheral artery disease.
[a]Other: atherosclerotic disease including patients with PAD, patients with PAD who undergo procedure without specifying clinical presentation.
[b]Other: gene therapy, stem cell therapy, smoking cessation, ultrasound therapy, external beam radiation, phlebotomy, dressing, suture, pneumatic compression, psychologic intervention, remote ischemic preconditioning, brachytherapy, negative pressure wound therapy, ultrasound-guided stent delivery.

of creatinine rather than the guideline-recommended use of eGFR complicates the interpretation of true kidney function and thus patients with mild CKD may be excluded.

We acknowledge several limitations. First, we limited the search to studies published between 2000 and 2018. Given prior data showing that inclusion of persons with CKD in clinical trials has only modestly improved over time, inclusion of older data would only strengthen our case (5). Secondly, we limited our search to trials randomizing >50 patients. Smaller trials may have been more likely to include patients with CKD. However, our results showed consistent rates of exclusion across sample size.

Our findings emphasize the need for inclusion of patients with CKD in future PAD trials and the use of eGFR rather than serum creatinine as a method to quantify kidney function. We encourage future studies to include assessment of efficacy and safety related to therapy based on kidney function, and to evaluate the outcomes among patients with CKD. These recommendations will provide evidence to improve PAD care in CKD.

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