

## Is diabetes still a compelling indication for renin-angiotensin-aldosterone system inhibitors?

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**TO THE EDITOR:** The recent review by Momoniati et al, “ACE inhibitors and ARBs: Managing potassium and renal function,” provides a thorough overview of these important medication classes.<sup>1</sup> The authors state, “In general, a renin-angiotensin-aldosterone system inhibitor is recommended if the patient has diabetes; stage 1, 2, or 3 chronic kidney disease; or proteinuria.” The sentence suggests that patients with diabetes alone, even without nephropathy, are to receive renin-angiotensin-aldosterone system inhibitors.

We take issue with this statement. The current literature no longer supports the notion that diabetes mellitus is a compelling indication for use of renin-angiotensin-aldosterone system blockers in the absence of associated nephropathy. In a systematic review and meta-analysis of 19 randomized controlled trials that enrolled 25,414 participants with diabetes for a total of 95,910 patient-years of follow-up, we demonstrated that inhibitors of the renin-angiotensin-aldosterone system were not superior to other antihypertensive drug classes in patients with diabetes.<sup>2</sup> Specifically, renin-angiotensin-aldosterone system blockers were not superior to thiazides, calcium channel blockers, or beta-blockers at reducing the risk of hard cardiovascular and renal end points.<sup>2</sup> Current guidelines from the American Diabetes Association,<sup>3</sup> European Society of Cardiology,<sup>4</sup> and Joint National Committee<sup>5</sup> also do not give preference to these drug classes in patients with diabetes without nephropathy.

Perhaps the word “diabetes” could be removed in the above-referenced sentence. Furthermore, heart failure with reduced ejection fraction could be added to the list of conditions that are indications for inhibition of the renin-angiotensin-aldosterone system irrespective of initial blood pressure level.

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### REFERENCES

1. Momoniati T, Ilyas D, Bhandari S. ACE inhibitors and ARBs: Managing potassium and renal function. *Cleve Clin J Med* 2019; 86(9):601–607. doi:10.3949/ccjm.86a.18024
2. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin-angiotensin system blockers: systematic review and meta-analysis of randomized trials. *BMJ* 2016; 352:i438. doi:10.1136/bmj.i438
3. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care* 2017; 40(9):1273–1284. doi:10.2337/dci17-0026
4. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39(33):3021–3104. doi:10.1093/eurheartj/ehy339
5. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311(5):507–520. doi:10.1001/jama.2013.284427

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**IN REPLY:** We would like to thank Dr. Fakheri and colleagues for their extremely helpful comments on our recent review of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).<sup>1</sup> We agree entirely with their suggestion on the lack of current data on any superiority of ACE inhibitors or ARBs in patients with diabetes without proteinuria and diabetes with “normal” renal function.<sup>2,3</sup> As mentioned, the sentence perhaps lacks clarity.

In the United Kingdom, ACE inhibitors and ARBs are commonly prescribed for diabetic microalbuminuria, proteinuric renal disease, and hypertension, as well as after myocardial infarction and in heart failure.<sup>4</sup> We therefore also concur that heart failure with reduced ejection fraction could be added

to the list of conditions that are indications for inhibition of the renin-angiotensin-aldosterone system irrespective of the initial blood pressure level.

Interestingly, chronic kidney disease is associated with significantly increased risk of cardiovascular disease and cardiovascular death.<sup>5,6</sup> Studies of patients with chronic kidney disease have noted an increased relative risk of coronary heart disease, heart failure, and stroke compared with those without chronic kidney disease.<sup>7,8</sup> We recognize that additional randomized controlled studies and a better understanding of these differences in risk are required to guide optimal therapy and improve outcomes, and we wonder if ACE inhibitors and ARBs might be useful in this high-risk population even before proteinuria is established, as alluded in the heart failure group.

Finally, although the data are not available, we wonder if over a longer period of follow-up, one may in the future see a benefit from reduced intraglomerular hyperfiltration, but we concede this is mere speculation, and more recent data have challenged the hyperfiltration model of renal damage.

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#### REFERENCES

1. **Momoniat T, Ilyas D, Bhandari S.** ACE inhibitors and ARBs: managing potassium and renal function. *Cleve Clin J Med* 2019; 86(9):601–607. doi:10.3949/ccjm.86a.18024
2. **Palmer SC, Mavridis D, Navarese E, et al.** Comparative efficacy and safety of blood pressure lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet* 2015; 385(9982):2047–2056. doi:10.1016/S0140-6736(14)62459-4
3. **Bangalore S, Fakhri R, Toklu B, Messerli FH.** Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. *BMJ* 2016; 352:i438 doi:10.1136/bmj.i438.
4. **NICE guidelines (CG127).** Hypertension in adults: diagnosis and management. Available at: <http://www.nice.org.uk/guidance/cg127/chapter/1-recommendations#choosingantihypertensive-drug-treatment-2>. Accessed on October 18th, 2019.
5. **Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY.** Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351(13):1296–1305. doi:10.1056/NEJMoa041031
6. **Weiner DE, Tighiouart H, Amin MG, et al.** Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol* 2004; 15(5):1307–1315. doi:10.1097/01.asn.0000123691.46138.e2
7. **Meisinger C, Doring A, Lowel H; KORA Study Group.** Chronic kidney disease and risk of incident myocardial infarction and all-cause and cardiovascular disease mortality in middle-aged men and women from the general population. *Eur Heart J* 2006; 27:1245–1250. doi:10.1093/eurheartj/ehi880
8. **Muntner P, Judd SE, McClellan W, et al.** Incidence of stroke symptoms among adults with chronic kidney disease: results from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Nephrol Dial Transplant* 2012; 27(1):166–173. doi:10.1093/ndt/gfr218

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