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CORRESPONDENCE

Optimal renin–angiotensin system blockade—wishful thinking?

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We read with interest the News & Views by Jürg Nussberger and Jürgen Bohlender (Optimal blockade of the renin–angiotensin–aldosterone system. *Nat. Rev. Cardiol.* 10, 183–184 (2013)[1] highlighting the role of dual renin–angiotensin system (RAS) blockers in the management of cardiovascular diseases. The News & Views article was written in response to our meta-analysis comparing the efficacy and safety outcomes of RAS blockade using monotherapy or combination therapy.[2] We agree with Nussberger and Bohlender that optimal, rather than complete, RAS blockade should be the goal of therapy regardless of whether RAS blockade is given for hypertension, heart failure, coronary heart disease, or other indications.

Nussberger and Bohlender define optimal RAS blockade as the maximal blockade achieved without causing hypotension, hyperkalaemia, or renal dysfunction. Our meta-analysis, which included data for >60,000 patients, documented no incremental benefit of dual RAS-blocker therapy compared with single RAS blockade.[2] To the contrary, we actually observed harm in the form of hypotension, hyperkalaemia, renal dysfunction, or a combination of these conditions in some patients. This finding simply indicates that dual RAS blockade does not fulfill the Nussberger and Bohlender criteria of optimal RAS blockade. Thus, by definition, dual RAS blockade cannot be considered 'optimal' RAS blockade.

So, how do we achieve 'optimal' RAS blockade? Nussberger and Bohlender should consider that, even for monotherapy, the upper range of the dose–response curve has not been satisfactorily defined. For instance, additional possible benefits are associated with supramaximal doses of angiotensin-receptor blockers, despite these seemingly excessive doses not causing further reductions in blood pressure. Several studies have shown that proteinuria that persisted despite treatment with the maximum recommended dose of a RAS blocker can be reduced by resorting to supramaximal doses.[3–5] Conversely, the 600 mg daily dose of aliskiren is known to have incremental antihypertensive efficacy, but also to significantly increase the incidence of gastrointestinal adverse events, compared with lower doses.

Some, but not all, studies have shown that patients with high plasma renin activity (PRA) have increased long-term mortality and rates of cardiovascular events; therefore, one suggestion is to treat patients with various antihypertensive agents on the basis of PRA.[6] However, we don't have an evidence-based answer to the simple question 'should patients with high PRA be treated with a high dose or a low dose of a RAS blocker?'. Fortunately, solid evidence from numerous randomized trials indicate that single RAS blockade reduces the risk of cardiovascular events in patients with hypertension and heart failure with adverse effect profile similar to other antihypertensive agents, regardless of the dose and baseline PRA level.

Clearly, optimal RAS blockade has not yet been defined for monotherapy, let alone for dual RAS blockade. On the basis of anecdotal evidence, even triple RAS blockade (angiotensin-converting-enzyme inhibitor + angiotensin-receptor blocker + aliskiren) has been suggested for the reduction of proteinuria.[7] However, as dual or triple RAS blockade has not shown any benefit—we do not consider a reduction in a surrogate end point, such as proteinuria, a clinically significant benefit—we are unwilling to tolerate any incremental harm. Nussberger and Bohlender seem to agree with us that, for a given patient, optimal RAS blockade is the way to go. Why not then define optimal RAS blockade for monotherapy first before embarking on dual or triple RAS blockade?

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Competing interests
S. Bangalore declares associations with the following companies: Boehringer Ingelheim, Daiichi Sankyo, and Pfizer. F. H. Messerli declares associations with the following companies: Abbott, Bayer, Daiichi Sankyo, Medtronic, Novartis, Pfizer, Servier, and Takeda. See the article online for full details of these relationships. H. Makani declares no competing interests.

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