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Dual RAS blockade—unresolved controversy?

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We read with interest the News & Views commentary by Piero Ruggenenti and Giuseppe Remuzzi (Ruggenenti, P. & Remuzzi, G. Meta-analyses can misdirect decisions on treatment. *Nat. Rev. Nephrol.* **9**, 311–312; 2013),[1] which was written in response to our meta-analysis that compared the efficacy and safety outcomes of dual renin–angiotensin system (RAS) blockade with that of monotherapy in 68,405 patients with hypertension, diabetes or proteinuria.[2] RAS inhibition using angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) versus other antihypertensive agents has unequivocally been shown to reduce renal outcomes in patients with proteinuria.[3,4] Many researchers, including ourselves and Remuzzi's team, have hypothesized that more intense RAS inhibition using more than one RAS blocker versus a single agent would offer more benefit in patients with proteinuric renal disease. However, our meta-analysis showed that dual RAS blockade compared with monotherapy failed to reduce mortality and was associated with an excessive risk of adverse events.[2]

Ruggenenti and Remuzzi suggest that the lack of benefit of dual versus single RAS blockade in our meta-analysis could be due to the inclusion of the ALTITUDE trial,[5] which evaluated an aliskiren-based regimen. However, even after excluding ALTITUDE we found no difference in all-cause mortality ($P = 0.35$) and cardiovascular mortality ($P = 0.15$) between the dual RAS blockade and monotherapy groups. Despite a significant fall in blood pressure, aliskiren conferred no benefit in terms of risk of stroke in the ALTITUDE[5] trial and no such benefit has been shown with ACE inhibitor plus ARB combinations.[6] Thus we disagree with the authors that aliskiren-based combinations are associated with an increased stroke risk.

Ruggenenti and Remuzzi also emphasized that a 23% reduction in heart failure hospitalizations and cardiovascular mortality was reported in patients with heart failure who were treated with dual RAS blockade compared with monotherapy in the CHARM-Added trial.[7] However, at least two studies (VALIANT[8] and Val-HeFT[9]) failed to show any benefit of dual RAS blockade with respect to all-cause mortality and cardiovascular mortality in patients with heart failure.

The criticism that we included heterogeneous trials in our meta-analysis is pertinent to any such analysis and is inevitable; short-term studies with small sample sizes have to be included in meta-analyses to address safety aspects. However, the few hard outcomes in the small trials that we included would not materially alter our summary data on major outcomes from large randomized controlled trials. Ruggenenti and Remuzzi suggest that safety outcomes were worse in the dual RAS blockade group only because patients with renal failure and nephropathy were included in our analysis. To answer this question, we analyzed published data on the risk of hyperkalaemia, hypotension and renal failure in patients treated with dual RAS blockade after excluding all studies that included patients with renal failure, diabetic nephropathy or microalbuminuria at baseline. We also excluded studies that used aliskiren-based combinations to further show that these therapies have similar event rates to ACE inhibitor and ARB combinations. We found that the relative risk of adverse events associated with dual RAS blockade significantly increased after patients with nephropathy were excluded, and increased further after those who received aliskiren-based therapies were excluded (Table 1).

We are surprised that Ruggenenti and Remuzzi state that "compared with single-drug RAS blockade, dual therapy more effectively reduced … proteinuria in patients

Table 1 | Risk of adverse events in patients receiving dual versus single-agent RAS blockade

Safety outcome	No. of studies	Total no. of patients	Relative risk of outcome (95% CI)	*P* value
Hyperkalaemia				
Overall	23	60,638	1.55 (1.32–1.82)	<0.0001
After excluding studies that included patients with nephropathy at baseline	17	50,760	1.64 (1.30–2.08)	<0.0001
After excluding studies that included patients with nephropathy at baseline and studies of aliskiren-based therapy	7	44,422	1.72 (1.12–2.63)	0.01
Hypotension				
Overall	18	61,252	1.66 (1.38–1.98)	<0.0001
After excluding studies that included patients with nephropathy at baseline	14	51,762	1.70 (1.33–2.16)	<0.0001
After excluding studies that included patients with nephropathy at baseline and studies of aliskiren-based therapy	10	49,359	1.83 (1.36–2.47)	<0.0001
Renal failure				
Overall	20	64,320	1.41 (1.09–1.84)	0.01
After excluding studies that included patients with nephropathy at baseline	12	52,335	1.83 (1.31–2.57)	0.0004
After excluding studies that included patients with nephropathy at baseline and studies that included patients with nephropathy	6	48,732	1.96 (1.31–2.94)	0.001

Abbreviation: RAS, renin–angiotensin system.

with renal disease, an effect that translated into almost complete protection against progression to ESRD [end-stage renal disease]." Such a general statement (that is, "renal disease" and "almost complete protection") is not supported by controlled data and is contradicted by our meta-analysis and by major trials with renal outcomes, including ORIENT,[10] ONTARGET,[11] ALTITUDE,[5] and VA-NEPHRON-D.[12] The VA-NEPHRON-D trial was stopped prematurely because of a lack of efficacy and increased incidence of adverse events in the ACE inhibitor plus ARB group,[12] which was consistent with the results of the other three outcome trials listed above. Reference of Ruggenenti and Remuzzi to their finding that dual therapy resulted in almost complete protection against progression to ESRD[13] seems to be contradicted by the ever increasing number of patients who present with ESRD despite increasing use of dual RAS blockade. We are also puzzled by the co-mingling in their arguments of hard outcomes and surrogate end points, such as proteinuria. When hard outcomes are available—as was the case in the data we analyzed—therapeutic decisions should no longer be based on surrogate end points.

Ruggenenti and Remuzzi also imply that hyperkalaemia should be redefined in people with renal disease such that serum potassium concentrations ≥5.5 mM are not considered abnormal. We are unaware of data that support this notion. The risks associated with hyperkalaemia are evident from population-wide data from Ontario, which showed that an increase in the prescription of spironolactone for heart failure resulted in a marked increase in hyperkalaemia-associated morbidity and mortality.[14]

In summary, although proteinuria is an outstanding marker for renal risk, reduction of proteinuria by various measures, short of bilateral nephrectomy, does not unequivocally lead to renal protection. Inhibition of the RAS using an ACE inhibitor or an ARB does offer such protection but dual RAS blockade does not seem to result in additional benefit. We invite Ruggenenti, Remuzzi and colleagues to initiate randomized controlled trials to determine in which, if any, clinical situation the beneficial effects of dual RAS blockade on hard renal outcomes might outstrip the well-documented risk of adverse events.

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Competing interests
F. H. Messerli has consulted for Abbott, Bayer, Daiichi Sankyo, Gilead, Ipca Laboratories Ltd, Medtronic, Novartis, Pfizer, PharmApprove, Servier and Takeda. S. Bangalore is a member of the advisory boards of Boehringer Ingelheim, Daiichi Sankyo and Pfizer. J. F. E. Mann has received honoraria or research funding from Abbott, Actelion, Amgen, Bayer, Boehringer-Ingelheim, Novo-Nordisk and Roche. H. Makani, K. A. Desouza and A. Shah declare no competing interests.

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