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CORRESPONDENCE

Research Correspondence

Is Dual Renin-Angiotensin-System Blockade Associated With Increased Risk of Stroke?

To the Editor: Increased risk of stroke with dual renin-angiotensin system (RAS) blockade during the interim analysis coupled with the lack of benefit was 1 of the primary reasons for early termination of the ALTITUDE trial (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) (1). The authors of the ALTITUDE trial stated that the higher stroke rates with dual RAS blockers may be due to chance. In a recent post hoc analysis of the ONTARGET (Ongoing Telmisartan alone and in combination with Ramipril Global endpoint) trial (2) in high-risk diabetic patients, there was no difference in the stroke rates between dual RAS blockers and RAS blocker monotherapy despite greater reduction in blood pressure (BP) with combination therapy.

High BP is an independent risk factor for stroke, and the optimal target BP level is still open to debate. Stroke deaths increased progressively and linearly from 115 mm Hg systolic and 75 mm Hg diastolic, in a large meta-analysis of observational studies of over 1 million patients (3). In a secondary analysis of data from the INVEST trial (International Verapamil-Trandolapril study), a J-shaped curve was not observed for stroke, suggesting that lower BP did not lead to greater stroke rates, and if anything, was beneficial (4). However, in another study with elderly patients, a J-shaped curve was observed between treated hypertensive patients and risk of stroke (5). Data suggest that the reduction in both systolic and diastolic BP is greater with dual RAS blockade compared with monotherapy (1,2,6–13) (Table 1). It would be fair to assume that this greater BP reduction with dual RAS blocker would translate into a lower stroke rate. However, studies have shown conflicting data with respect to stroke and dual RAS blocker therapy.

In the present study, our objective was to evaluate the risk of stroke comparing dual RAS blockade (any 2 of angiotensin-converting enzyme inhibitor [ACEi], angiotensin receptor blocker [ARB], or aliskiren) with RAS blocker monotherapy.

A systematic search was made in PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (Cochrane Library Issue 6, June 2012) using the key terms "ACE inhibitors," "Angiotensin Receptor Blockers," and "Direct Renin Inhibitors," and with the names of individual medications. We restricted our search to randomized controlled trials in humans and peer-reviewed journals from 1990 to March 2013. We checked the reference lists of the reviewed articles and original studies to find other potentially eligible articles. No language restriction was applied.

Trials were screened for eligibility using the following criteria: 1) randomized clinical trials comparing individual RAS blocker with combination of RAS blockers (ACEi or ARB or DRI); 2) data on stroke rates; and 3) duration of trial at least 6 months. Two authors (H.M. and S.B.) searched the data independently and in duplicate. Disagreements were resolved by consensus. We extracted the publication year, baseline characteristics of the study population, baseline systolic and diastolic BP, sample size, type of the medication used, mean age, study duration, and stroke rates for this analysis. Stroke was defined in most studies as a combination of fatal or nonfatal stroke.

The statistical analysis was done in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (14) guidelines using Review Manager (RevMan), version 5.1.7 (the Cochrane Collaboration, Oxford, United Kingdom, 2012). Heterogeneity was assessed using the I^2 statistics. The random-effects model of DerSimonian and Laird (15) was used to calculate the effect sizes because of known clinical and methodological heterogeneity of the studies. Results were calculated by relative risk ratio and 95% confidence intervals with the use of the Mantel-Haenszel method. Head-to-head comparison was made between individual RAS blocker and the combination of RAS blockers for stroke rates. The criteria used for quality assessment of the studies (16) were sequence generation of allocation; allocation concealment; masking of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias, as recommended by the Cochrane Collaboration. Studies with high or unclear risk of bias for any of the first 3 components were classified as low quality. Publication bias was estimated visually by funnel plots (17) or by use of the Begg's test and the weighted regression test of Egger et al. (18).

We identified 2,220 articles, of which 61 abstracts were retrieved and reviewed for possible inclusion (Fig. 1). Nine trials (1,6–13) enrolling 54,355 patients (mean age 62 years; 72% men) and the mean follow-up duration of 2.2 years were included in the analysis. A combination of ACEi and ARB was used in 6 trials, ACEi and aliskiren combination in 1 trial, and 2 trials used a combination of either ACEi or ARB with aliskiren. On the basis of quality assessment, 7 were deemed as low bias risk trials and the rest as high bias risk.

A total of 778 of 20,397 (3.8%) patients had stroke on combination therapy compared with 1,362 of 33,930 (4.0%) patients on monotherapy. Dual RAS blockade was associated with a similar stroke rate as that of RAS monotherapy ($p = 0.98$; relative risk 1.00; 95% confidence interval 0.90 to 1.12; $I^2 = 12\%$) (Fig. 2). There was no evidence of publication bias among included studies (Egger's $p = 0.78$). Systolic pressure was lower by 0.1 to 4.6 mm Hg (Table 1) with dual RAS blockade when compared with RAS blocker monotherapy in the included trials.

In this meta-analysis of randomized clinical trials, dual RAS blockade was associated with similar risk of stroke when compared with RAS monotherapy, despite a lower systolic pressure. In the most recent meta-analysis of 59 trials (19) comparing the efficacy of dual RAS blockers compared with monotherapy in patients with chronic kidney disease, the absolute reduction in systolic, diastolic, and mean BP was 3.8 mm Hg, 2.2 mm Hg, and 1.7 mm Hg,

Table 1 Characteristics of the Included Trials

Trial/First Author (Ref. #), Year	Patient Population	Total Patients	Mean Age (yrs)	Follow-Up (Weeks)	Comparison Group	Dual RAS Blockers Baseline SBP/DBP	RAS Blocker Monotherapy Baseline SBP/DBP	Reduction in BP With Dual RAS Blockers Compared With Monotherapy	Risk of Bias
ALTITUDE (1) 2012	Diabetic nephropathy	8,561	65	139	Aliskiren+ACEi or ARB vs. ACEi or ARB alone	137.3/74.1	137.3/74.3	−1.3 mm Hg systolic −0.6 mm Hg diastolic	Low
ASPIRE (6) 2011	Post-MI with EF ≤45%	820	60	36	Aliskiren+ACEi vs. ACEi or ARB alone	121.6/75.2	121.7/75.4	−2.1 mm Hg systolic −2.4 mm Hg diastolic	Low
ASTRONAUT (7) 2013	Stable HHF pts	1,615	65	49	Aliskiren+ACEi or ARB vs. ACEi or ARB alone	123.4*	123.1*	−1.2 mm Hg systolic*	Low
CALM II (8) 2005	HTN and diabetes	75	55	52	Candesartan+lisinopril vs. lisinopril	139.1/83.8	142.6/82.8	−0.1 mm Hg systolic +1 mm Hg diastolic	High
CHARM Added (9) 2003	HF and EF ≤40%	2,548	64	178	Candesartan+any ACEi vs. ACEi alone	124.7/75	125.6/75.2	−4.6 mm Hg systolic −3.0 mm Hg diastolic	Low
Cice et al. (10) 2010	Hemodialysis pts with HF	332	63	156	Telmisartan+any ACEi vs. any ACEi	124.5/82.6	126.3/79.4	Not reported	Low
Mehdi et al. (11) 2009	Diabetes, HTN, albuminuria	81	50	48	Losartan+lisinopril vs. lisinopril	136/72	132/74	Not reported	High
ONTARGET (12) 2008	High-risk CVD	25,620	67	243	Telmisartan+ramipril vs. ramipril and telmisartan	141.9/82.1	141.8/82.1	−1.5 mm Hg systolic −0.8 mm Hg diastolic	Low
VALIANT (13) 2003	AMI complicated by HF	14,703	65	107	Valsartan+captopril vs. Valsartan and captopril	122.5/72.3	122.8/72.4	−2.2 mm Hg systolic −1.0 mm Hg diastolic	Low

*Diastolic blood pressure data not reported.

ACEi = angiotensin-converting enzyme inhibitor; ALTITUDE = the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; ASPIRE = Aliskiren Study in Post-MI Patients to Reduce Remodeling; ASTRONAUT = the Aliskiren Trial on Acute Heart Failure Outcomes; BP = blood pressure; CALM = Candesartan and Lisinopril Microalbuminuria; CHARM = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CVD = cardiovascular disease; DBP = diastolic blood pressure; DRI = direct renin inhibitor; EF = ejection fraction; HF = heart failure; HHF = hospitalizations for heart failure; HTN = hypertension; ONTARGET = the Ongoing Telmisartan alone and in combination with Ramipril Global endpoint trial; pts = patients; RAS = renin-angiotensin system; SBP = systolic blood pressure; VALIANT = Valsartan in Acute Myocardial Infarction Trial Investigators.

respectively. These data clearly show discordance between BP reduction and stroke reduction in that the dual RAS blockers, despite systolic pressure reduction, did not translate into reduction in stroke rates. The most likely explanation could be the result of adverse effects, including hypotension in patients on dual RAS blockers. The underlying mechanism is likely explained by sensitization of the Bezold-Jarisch reflex conditioned by the withdrawal of the effect of angiotensin II (20). Angiotensin II exerts its effect by a central mechanism that serves to ameliorate the vagally induced bradycardia and the withdrawal of sympathetic tone, consequent upon activation of the afferent pathways of this reflex. Indeed, severe hypotension and long-term bradycardia reported with blockade of the renin-angiotensin-aldosterone system by infusions of renin inhibitors has been attributed to an exaggeration of the Bezold-Jarisch reflex (21). Conversely, in patients with high plasma renin activity levels who exhibit evidence of sodium depletion, the elevated angiotensin levels help to avoid undue hypotension (22). Excess blockade of RAS with dual RAS blockers can interfere with this compensatory mechanism, causing hypotension, renal failure, and hyperkalemia. In our most recent meta-analysis (23), 18 trials comparing dual RAS blockers to RAS blocker monotherapy reported data on hypotension with a total of 61,252 patients. The risk of hypotension was 66% higher in patients on dual RAS blockers (8.7%) compared with RAS blocker monotherapy (5.9%), $p < 0.001$. In addition to hypotension, dual RAS blocker therapy was associated with significantly higher rate of hyperkalemia and renal failure without any benefit on all-cause mortality and cardiovascular mortality (23).

Clearly, the failure to prevent strokes despite lower BP in the presence of worse adverse events strongly argues against the routine use of dual RAS blocker therapy.

As with other meta-analyses, given the lack of data in each trial, we did not adjust our analysis for adherence to therapy. Also, the results are subject to limitations inherent to any meta-analysis based on pooling of data from different trials with different duration, doses of drugs, and patient groups.

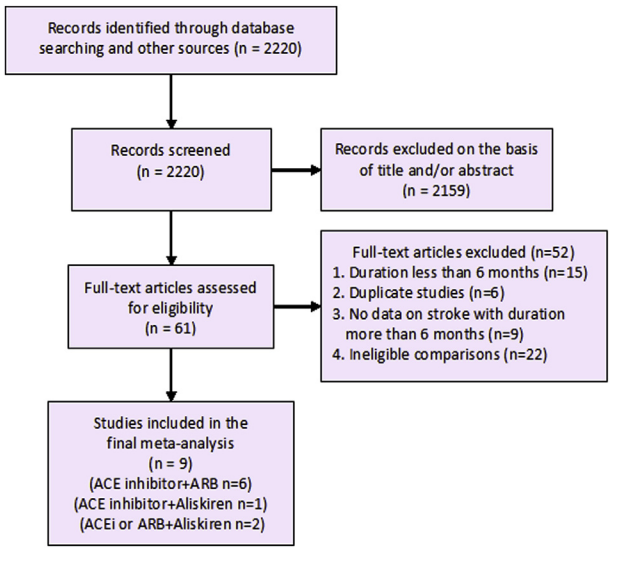

Figure 1 Selection of Studies

ACE = angiotensin-converting enzyme; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

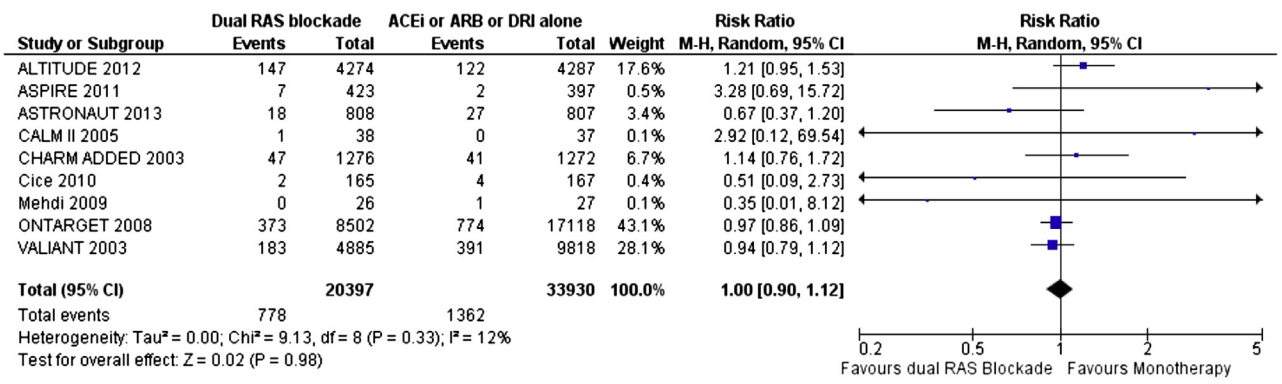

Figure 2 Comparison of Dual RAS Blockers to RAS Blocker Monotherapy for Stroke Rates

Error bars represent 95% CI; data marker sizes indicate the sample sizes of the cohorts. CI = confidence interval; DRI = direct renin inhibitor; M-H = Mantel-Haenszel test; RAS = renin-angiotensin system; other abbreviations as in Figure 1.

In this large meta-analysis of randomized trials, dual RAS blockade was associated with similar risk of stroke when compared with RAS blocker monotherapy.

Harikrishna Makani, MD†
Sripal Bangalore, MD, MHA‡
Peter Sever, MD§
***Franz H. Messerli, MD†**

*Division of Cardiology
St. Luke's–Roosevelt Hospital
Columbia University College of Physicians and Surgeons
1000 10th Avenue
Suite 3B-30
New York, New York 10019
E-mail: messerli.f@gmail.com

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From the †Division of Cardiology, St. Luke's–Roosevelt Hospital, Columbia University College of Physicians and Surgeons, New York, New York; ‡New York University School of Medicine, New York, New York; and the §International Centre for Circulatory Health, Imperial College London, United Kingdom.

Please note: Dr. Bangalore is a member of the advisory boards of Abbott, Daiichi Sankyo, and Boehringer Ingelheim. Dr. Sever is a consultant for Pfizer. Dr. Messerli has served as an ad hoc consultant/speaker for Novartis, Daiichi Sankyo, Pfizer, Takeda, Abbott, PharmApprove, Gilead, Medtronic, Servier, Ipca Laboratories, and Bayer. Dr. Makani has reported that he has no relationships relevant to the contents of this paper to disclose.

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