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Effect of single and dual renin-angiotensin blockade on stroke in patients with and without diabetes in VALIANT

Azmil H Abdul-Rahim[1], Kieran F Docherty[2], Hicham Skali[3], Lars Køber[4], Kenneth Dickstein[5], Aldo P Maggioni[6], Viacheslav Mareev[7], Faiez Zannad[8], Eric J Velazquez[9], Robert M Califf[9,10], Marc A Pfeffer[3], Scott D Solomon[3], Kennedy R Lees[1] and John JV McMurray[1]

Abstract

Introduction: Concern has been raised about a possible increase in risk of stroke in patients with diabetes treated with the combination of the renin-inhibitor aliskiren and an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. We compared the rate of stroke in patients with and without diabetes treated with single or dual renin-angiotensin system blockade after acute myocardial infarction.

Patients and methods: We performed a post hoc analysis of the Valsartan in Acute Myocardial Infarction trial in which 14,703 patients with heart failure, left ventricular systolic dysfunction or both, were randomised to captopril (C), valsartan (V) or both (C + V) after 0.5–10 days after acute myocardial infarction and followed for a median of 2.1 years. We used Cox proportional-hazard regression to estimate the hazard ratios [HR (95% CI)] of stroke in each treatment group.

Results: Among patients *with* diabetes, 60/1303 (4.6%) receiving captopril, 60/1337 (4.5%) valsartan and 41/1340 (3.1%) valsartan plus captopril suffered a stroke: V + C versus V or C HR 0.68 (0.47–0.96), $p = 0.03$. The corresponding numbers in patients *without* diabetes were 106/3606 (2.9%), 97/3572 (2.7%) and 99/3545 (2.8%): V + C versus V or C HR 0.99 (0.78–1.26), p = 0.92 (interaction $p = 0.08$).

Conclusion: The risk of stroke after myocardial infarction in patients with diabetes was lower in patients treated with both an angiotensin converting enzyme inhibitor and angiotensin receptor blocker than in patients receiving either monotherapy.

Keywords
Renin-angiotensin system, stroke, diabetes

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Introduction

Concern has been raised that dual blockade of the renin-angiotensin system (RAS) may increase the risk of stroke in patients with diabetes mellitus.[1–5] This concern arose as a result of the early termination of the aliskiren trial in type 2 diabetes using cardio-renal endpoints (ALTITUDE) on the recommendation of the data monitoring committee (DMC).[2–5] ALTITUDE compared placebo and 300 mg once daily of the direct renin-inhibitor aliskiren, added to background angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy in 8606 patients with diabetes and either (1) increased urinary albumin

[1]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[2]Department of Cardiology, Western Infirmary, Glasgow, Scotland, UK
[3]Brigham & Women's Hospital, Boston, MA, USA
[4]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark
[5]Stavanger University Hospital, Stavanger, Bergen, Norway
[6]ANMCO Research Center, Florence, Italy
[7]University Clinic M.V.Lomonosov Moscow State University, Moscow, Russia
[8]Clinical Investigation Center 1493, INSERM, Nancy, France
[9]Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, NC, USA
[10]Duke Translational Medicine Institute, Durham, NC, USA

Corresponding author:
John JV McMurray, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK.
Email: john.mcmurray@glasgow.ac.uk

excretion or (2) both a reduced estimated glomerular filtration rate (eGFR, 30–60 ml/min/1.73 m^2) and established cardiovascular disease.[5,6] The basis of the DMC recommendation was futility (i.e. no prospect of demonstrating the treatment benefit anticipated in the protocol), as well as safety concerns. These concerns included renal dysfunction, hyperkalaemia and hypotension, as well as an excess of strokes. At that time, the number of patients experiencing a non-fatal stroke was 112 (2.6%) in the aliskiren group and 85 (2.0%) in the placebo group (nominal, unadjusted, $p = 0.04$), but by study completion these numbers were 147 (3.4%) and 122 (2.8%), respectively; HR 1.22 (0.96–1.55), $p = 0.11$.[1–3,5,6] Although follow-up of ALTITUDE was not complete and only about two-thirds of the final number of endpoints had been collected at the time premature trial closure was recommended, the European Medicines Agency (EMA) and the US Food and Drugs Administration both recommended that the combination of aliskiren with an ACE inhibitor or ARB not be used in patients with type 2 diabetes; the EMA also recommended avoidance of combination therapy in patients with moderate or severe kidney impairment.[2,3] Concerns raised included the possibility that dual RAS blockade might have increased the risk of stroke by excessively lowering blood pressure and/or that patients with *both* diabetes and renal dysfunction (as enrolled in the ALTITUDE trial) might be particularly susceptible to harm from dual RAS blockade.

To further explore the effect of dual RAS blockade on the risk of stroke in patients with diabetes, we have undertaken a post hoc analysis of the Valsartan in Acute Myocardial Infarction trial (VALIANT) in which 14,703 patients with left ventricular systolic dysfunction, heart failure or both after acute myocardial infarction (MI) were randomised equally to valsartan, captopril or the combination of valsartan and captopril.[7,8] In addition to investigating the effect of dual RAS blockade on risk of stroke according to diabetes status, we also examined potential interactions between diabetes status, renal function and change in systolic blood pressure and risk of stroke.

Methods

Trial design

The design and baseline characteristics of VALIANT are described in more detail elsewhere.[7,8] In summary, eligible patients were enrolled between 12 h and 10 days after acute MI, complicated by either clinical or radiological signs of heart failure, evidence of left ventricular systolic dysfunction or both. Patients were excluded if there was evidence of hypotension or shock, renal impairment, ongoing clinical instability (such as angina or arrhythmia). Patients with an intolerance or contraindication to ACE inhibitor were also excluded from the trial. Eligible patients were then randomised equally, to receive captopril (up to 50 mg thrice daily), valsartan (up to 160 mg twice daily) or the combination of these two drugs (up to captopril 50 mg thrice daily and valsartan 80 mg twice daily) and followed-up for a median of 24.7 months. For the purposes of this analysis, we split the study patients into those with diabetes (i.e. history of diabetes or newly diagnosed with diabetes prior to the trial randomisation) and those without. In the original study, VALIANT, diabetes status was based on history of diabetes ('Yes/No' checkbox under medical history in the study case form) following the qualifying MI, or newly developed diabetes from the time of MI to randomisation, as reported by the investigators. We do not have access to the specific diagnostic criteria for diabetes.

Trial end-points

The primary end-point of VALIANT was all-cause mortality. Secondary end-points included cardiovascular mortality and a number of composites of cardiovascular mortality and non-fatal cardiovascular events including MI, hospitalisation for heart failure, stroke and resuscitation after cardiac arrest. All events were centrally adjudicated by an independent endpoint committee.

Stroke

In VALIANT, stroke was defined as a focal neurologic deficit lasting more than 24 h or resulting in death that was presumed to be related to stroke.[7] The definition of stroke used was consistent with the definition in similar trials at that time. While the definition may not be identical to that used in contemporary stroke trials, it was applied consistently by experienced adjudicators blind to treatment allocation and thus gave an unbiased estimate of treatment effect. Our analysis includes first fatal or non-fatal stroke.

Statistical analysis

Descriptive statistics were used to describe and compare patients with investigator-reported history of diabetes prior to their MI and those without, using means (standard deviation [SD]) or medians (interquartile range [IQR]) for continuous variables and count (percentage) for categorical variables. We calculated the hazard ratio (HR) and corresponding 95% confidence intervals (95% CI) using Cox proportional-hazards regression to compare: (i) combination therapy versus captopril (ii) combination therapy versus valsartan (iii) combination therapy versus

captopril or valsartan, according to patients' diabetes status. Adjustment was made based on variables previously shown to be independent predictors of stroke in the VALIANT population (i.e. diastolic blood pressure, history of stroke or transient ischaemic attack, atrial fibrillation, black race, age, percutaneous revascularisation for MI, history of angina, anterior MI, statin use at randomisation).[8]

We examined the effect of RAS blockade (i.e. within each patient subgroup) on systolic blood pressure, eGFR and reported adverse events. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula (unit: ml/min/1.73 m^2).[9]

All analyses were undertaken using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA). All authors have read and agreed to the manuscript as written.

Results

Of the 14,703 patients randomised, 3400 had a history of recognised diabetes prior to their MI and 580 patients had diabetes diagnosed during their index admission prior to enrollment in VALIANT.[7]

Baseline characteristics of patients with and without diabetes

The baseline characteristics of patients with and without diabetes are shown in Table 1. Patients *with* diabetes were more often female, slightly older and more frequently had a history of coronary, peripheral or cerebrovascular disease. Their systolic blood pressure was slightly higher than patients without diabetes. Patients *with* diabetes were less likely to be treated with a beta-blocker but more likely to receive a calcium channel blocker and statin. Almost half of patients with diabetes were treated with insulin at the time of randomisation.

Incidence of stroke

The number of patients who experienced a stroke is shown in Table 2. The risk of stroke was higher in patients *with* diabetes than in those without (HR 1.32, 95% CI 1.07–1.61). Among the 3980 patients *with* diabetes, 161 (4.0%) experienced a stroke, whereas in the 10,703 patients *without* diabetes, 302 (2.8%) experienced this outcome.

Among patients *with* diabetes, the number of patients who had a stroke was similar in those assigned to captopril (n = 60, 4.6%) and valsartan (n = 60, 4.5%); however, fewer patients had a stroke in the group receiving both captopril and valsartan (n = 41, 3.1%). The stroke rates for patients *with* diabetes treated with captopril, valsartan or both were 2.63, 2.51, and 1.73, per 100 patient years, respectively. The risk of stroke was significantly lower in patients receiving dual RAS blockade than in those receiving monotherapy; captopril plus valsartan versus either monotherapy alone, unadjusted HR (95%CI), 0.68 (0.47–0.96), $p = 0.03$ (Table 2).

In contrast, among patients *without* diabetes, the number of strokes was similar in each treatment group: captopril, n = 106 (2.9%); valsartan, n = 97 (2.7%); and combination of both, n = 99 (2.8%). The stroke rates for patients *without* diabetes treated with captopril, valsartan or both were 1.52, 1.41, and 1.45, per 100 patient years, respectively. The risk of stroke was similar in patients receiving dual RAS blockade and in those receiving monotherapy; captopril plus valsartan versus either monotherapy alone, unadjusted HR 0.99 (0.78–1.26), $p = 0.92$ (Table 2). The p value for interaction between diabetes status and the effect of dual RAS blockade (vs. single RAS blockade) on the risk of stroke was 0.08. These findings remained essentially the same after adjustment for other variables previously shown to predict the occurrence of stroke in patients in VALIANT.[8]

Effect of treatment on systolic blood pressure

Systolic blood pressure rose over time after acute myocardial infarction (AMI). Among patients *with* diabetes, the mean (SD) change in systolic blood pressure from baseline to one year was +3.8 (20.4) mmHg in the captopril group, +4.2 (22.1) mmHg in the valsartan group and +2.4 (22.0) mmHg in the captopril plus valsartan group ($p = 0.15$ between group difference). The respective changes among patients *without* diabetes were +4.9 (20.1) mmHg, +4.4 (20.8) mmHg and +2.6 (20.2) mmHg ($p = <0.001$ between group difference). There was no interaction between presence of diabetes and effect of therapy on systolic blood pressure at one year (p for interaction = 0.67).

Interaction with eGFR

The unadjusted HR for stroke with combination therapy (captopril plus valsartan) versus monotherapy (either captopril or valsartan) was HR 0.91 (0.69–1.19) in patients with an eGFR ≥60 and HR 0.83 (0.62–1.12) in those with an eGFR <60 (p for interaction = 0.68).

Among patients *with* diabetes, and an eGFR ≥60, the unadjusted HR for stroke with combination therapy versus either monotherapy alone was 0.65 (0.40–1.06) and 0.71 (0.42–1.18) in those with an eGFR <60 (p for interaction = 0.81). Among patients *without* diabetes and an eGFR ≥60, the unadjusted HR for combination therapy versus either monotherapy alone was 1.07 (0.77–1.48) and 0.90 (0.63–1.29) in those with an eGFR <60 (p for interaction = 0.49).

Table 1. Clinical characteristics at randomisation.

Characteristic	History of or newly diagnosed diabetes (n = 3980)	No diabetes (n = 10,723)	*p*
Age, years	66.1 ± 10.7	64.4 ± 12.2	<0.001
Female sex	1563 (39.3)	3007 (28.0)	<0.001
Body-mass index, kg/m^2	29.3 ± 5.8	27.4 ± 5.0	<0.001
Current smoker	768 (19.3)	3807 (35.5)	<0.001
Hypertension	2707 (68.0)	5393 (50.3)	<0.001
Peripheral arterial disease	556 (14.0)	681 (6.4)	<0.001
Angina pectoris	1734 (43.6)	4107 (38.7)	<0.001
Prior myocardial infarction	1309 (32.9)	2797 (26.1)	<0.001
Prior heart failure	820 (20.6)	1354 (12.6)	<0.001
Prior stroke	335 (8.4)	560 (5.3)	<0.001
Prior PCI	379 (9.5)	688 (6.4)	<0.001
Prior CABG	410 (10.3)	616 (5.7)	<0.001
Atrial fibrillation[a]	1514 (14.3)	643 (16.2)	0.004
History of atrial fibrillation[b]	668 (6.3)	292 (7.3)	0.024
Evidence of atrial fibrillation on ECG[c]	1271 (12.0)	543 (13.6)	0.007
Heart rate, beats per minute	78 ± 13	75 ± 13	<0.001
Systolic BP, mmHg	125 ± 18	122 ± 17	<0.001
Diastolic BP, mmHg	72 ± 12	75 ± 11	0.680
Killip class >1 (%)	3024 (76.0)	7512 (70.1)	<0.001
Non-Q-wave MI (%)	1412 (37.8)	3046 (29.8)	<0.001
Creatinine Kinase, ×ULN	7.9 ± 8.9	10.8 ± 26.6	<0.001
Ejection fraction, %[d]	35 ± 10	35 ± 10	0.034
Creatinine level, mg/dL	1.1 ± 0.3	1.1 ± 0.3	<0.001
eGFR (MDRD)	67 ± 22	71 ± 21	<0.001
eGFR ≤60	1589 (40.4)	3273 (30.9)	<0.001
Median time to randomisation, days	5 ± 3	5 ± 3	<0.001
Medications at randomisation			
Aspirin	3582 (90.0)	9836 (91.7)	<0.001
β-blocker	2617 (65.8)	7733 (72.1)	<0.001
Calcium-channel blocker	463 (11.6)	798 (7.4)	<0.001
Statin	1454 (36.5)	3560 (33.2)	<0.001
Insulin	1872 (47.0)	0 (0)	<0.001
Oral hypoglycemic agent	1721 (43.2)	0 (0)	<0.001

PCI: percutaneous coronary intervention; BP: blood pressure; MI: myocardial infarction; ULN: upper limit normal; eGFR: estimated glomerular filtration rate; CABG: coronary artery bypass grafting; MDRD: modification of diet in renal disease.
Note: Categorical variables are expressed as number (percentage). Continuous variables are presented as mean ± standard deviation, unless otherwise stated.
[a]Atrial fibrillation prior to randomisation (history of atrial fibrillation or evidence of atrial fibrillation on ECG between index-MI and randomisation).
[b]History of atrial fibrillation before index-MI.
[c]Evidence of atrial fibrillation on ECG recorded between the index-MI and randomisation.
[d]Measured in 77% of patients.

Table 2. Risk of stroke in patients with and without diabetes mellitus, according to treatment assignment.

	Number of patients with stroke/number of patients n treatment group			Hazard ratio (95% CI)			*p* for interaction
	Captopril[a]	Valsartan[a]	Combined Treatment[b]	Combined Treatment[b] vs. Captopril[a]	Combined Treatment[b] vs. Valsartan[a]	Combined Treatment[b] vs. (Captopril or Valsartan)[a]	0.08
No diabetes	106/3606 (2.9%)	97/3572 (2.7%)	99/3545 (2.8%)	0.95 (0.72–1.26) *[0.85 (0.64–1.12)]*	1.03 (0.78–1.35) *[1.10 (0.83–1.47)]*	0.99 (0.78–1.26) *[1.02 (0.80–1.31)]*	
Diabetes	60/1303 (4.6%)	60/1337 (4.5%)	41/1340 (3.1%)	0.66 (0.45–0.98) *[0.71 (0.47–1.07)]*	0.69 (0.46–1.02) *[0.66 (0.43–0.99)]*	0.68 (0.47–0.96) *[0.68 (0.47–0.98)]*	

Note: The *p* value shows the interaction between diabetes status and the effect of dual RAS blockade (vs. single RAS blockade) on the risk of stroke.
Values in italics indicate HR adjusted for diastolic blood pressure, history of stroke or transient ischaemic attack, atrial fibrillation, black race, age, percutaneous revascularisation for myocardial infarction, history of angina, anterior myocardial infarction, statin use at randomisation.
[a]Monotherapy only.
[b]Combined treatment indicates dual RAS blockade with captopril and valsartan.

Adverse events

Overall, adverse events were more common in patients with or without diabetes mellitus receiving dual RAS blockade, compared with patients assigned to monotherapy. Hypotension, in particular, was more common with dual therapy in both patients with and without diabetes. Renal dysfunction was slightly more frequent in patients without diabetes assigned to dual RAS blockade therapy, compared with either monotherapy. However, in patients with diabetes, this adverse effect was most common in those taking valsartan alone. Hyperkalaemia was most frequent in patients with or without diabetes who were taking valsartan monotherapy. (Table 3)

Discussion

In this analysis of VALIANT, we found no evidence that dual RAS blockade (with and ACE inhibitor and ARB) increased the risk of stroke in patients with diabetes. Indeed, there was a strong trend to a lower incidence of stroke in diabetic patients treated with both captopril and valsartan, compared with each monotherapy (and a significantly lower incidence when compared with either monotherapy).

Our analysis was provoked by the regulatory reaction to the early termination of ALTITUDE and the reported increase in risk of stroke in the high-risk patients with diabetes in that trial treated with aliskiren in addition to an ACE inhibitor or ARB. Although the unexpected finding led to much concern and discussion, the excess of stoke at the time of early termination had diminished by the time the final results of ALTITUDE were available (at the time of the DMC's recommendation it was estimated that just over a quarter of events remained to be collected and adjudicated). Consequently, the concerns of the regulatory authorities related to an apparent imbalance in stroke that did not persist (or at least diminished). Furthermore, given all prior data relating use of antihypertensive therapy, including ACE inhibitors and ARBs, to a reduced incidence of stroke in patients with diabetes, it was likely that the imbalance in stroke represented a chance finding.[10–12] We believe that our findings support this possibility, although both the combination of RAS blockers used and the patients studied differed between VALIANT and ALTITUDE, i.e. an ARB plus ACE inhibitor as opposed to a direct renin-inhibitor and ACE inhibitor/ARB. The findings of the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) are also relevant. In ASTRONAUT, patients with heart failure were randomised to the addition of placebo (n = 807) or aliskiren 300 mg daily (n = 808) to standard therapy, including an ACE inhibitor or ARB. The number of patients with a first fatal or non-fatal stroke was 18 (2.2%) in the aliskiren group and 27 (3.3%) in the placebo group, hazard ratio 0.63 (0.34–1.14), p = 0.13.[13] Although

Table 3. Adverse events leading to a reduction in dose of study drug.

	No diabetes				Diabetes			
Cause	Captopril[a] (n = 3582), %	Valsartan[a] (n = 3557), %	Combined treatment[b] (n = 3527), %	*p*	Captopril[a] (n = 1115), %	Valsartan[a] (n = 1127), %	Combined treatment[b] (n = 1141), %	*p*
Hypotension	12.7	16.2	18.8	<0.001	9.8	12.2	16.5	<0.001
Renal dysfunction	2.5	4.0	4.1	<0.001	4.5	7.4	6.5	0.009
Cough	5.2	1.6	4.6	<0.001	4.5	2.1	4.7	<0.001
Hyperkalaemia	0.8	1.1	1.0	0.387	1.2	1.9	1.6	0.405
Skin Rash	1.5	0.6	1.2	<0.001	0.6	0.9	0.7	0.698
Angioedema	0.4	0.3	0.4	0.396	0.5	0.2	0.5	0.380
Taste disturbances	0.7	0.3	0.9	<0.001	0.4	0.3	0.4	0.924
Any of above adverse events	22.3	22.7	29.0	<0.001	20.5	23.0	28.6	<0.001
Any adverse event	28.6	28.7	34.5	<0.001	27.9	31.3	35.4	<0.001
Any reason	43.1	42.3	47.7	<0.001	42.7	45.2	49.4	0.002

Note: The *p* values describe the difference between treatment groups.
[a]Monotherapy.
[b]Combined treatment indicates dual RAS blockade with captopril and valsartan.

a follow-up report suggested a possible excess of cardiovascular events with aliskiren in patients with diabetes, that report did not itemise stroke.[14]

Furthermore, it is not immediately obvious why a direct renin-inhibitor should have a fundamentally different effect on the risk of stroke than an ACE inhibitor or ARB. RAS blockers are believed to reduce stroke primarily by lowering blood pressure.[11] ACE inhibitors and ARBs, although pharmacologically distinct, reduce blood pressure to a similar degree and have similar clinical effects, including reduction in stroke.[11] As in VALIANT, blood pressure in ALTITUDE increased during follow-up, but the overall increase was smaller with aliskiren than with placebo (between-group differences, 1.3 mm Hg systolic and 0.6 mm Hg diastolic). This is slightly less than the difference in blood pressure between patients assigned to captopril plus valsartan, compared with captopril alone in VALIANT.

While there were many similarities between the subgroup of patients with diabetes in VALIANT[15,16] and those in ALTITUDE, the proportion of patients with diabetes in VALIANT previously reported to have an eGFR <60 (40%) was smaller than in ALTITUDE (68%).[15] However, in VALIANT, the effect of dual RAS blockade (compared with either monotherapy) was qualitatively similar in diabetic patients with and without a reduced eGFR. Baseline systolic blood pressure in ALTITUDE (135 mmHg) was considerably higher than that in VALIANT (126 mmHg in patients with diabetes).[6] However, again, it is difficult to see how this difference could lead to an increased risk of stroke with dual RAS blockade and patients in VALIANT with a history of hypertension or a persistently elevated systolic blood pressure had an elevated risk of stroke.[17]

The effects of dual RAS blockade with an ACE inhibitor and ARB on stroke were examined in another similarly designed trial, the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET). In that trial, in patients with chronic stable arterial disease (or diabetes and end-organ damage), stroke occurred in 4.7% of patients treated with ramipril, 4.3% of those assigned to telmisartan and 4.4% of patients receiving both drugs.[18] Post hoc analysis of the same trial involving high-risk diabetic patients suggests that there was no difference in the stroke rates between dual RAS blockade and RAS blockade monotherapy, despite greater reduction in blood pressure with combination therapy.[19] Our finding supports this, although we found that there was a strong trend to a lower incidence of stroke in patients with diabetes, who were treated with dual RAS blockade than with monotherapy.

The other completed studies comparing dual RAS blockade with an ACE inhibitor and ARB to ACE inhibitor monotherapy are uninformative. All but one of these were trials in heart failure, where the proportion of patients with diabetes was relatively low and the absolute numbers of stroke, overall, were small.[20,21] The exception was the Veterans Affairs Nephropathy in Diabetes trial (VA NEPHRON-D) in patients with type 2 diabetes, an estimated GFR of 30–90 ml/min/1.73 m^2 and a high urinary albumin to creatinine ratio. All patients received losartan 100 mg daily and were randomised to receive placebo or lisinopril 10–40 mg daily in addition. This trial, like ALTITUDE, was stopped early, in this case owing to safety concerns. There were 18 strokes in each treatment group.[22]

Our report has a number of limitations, some of which have been mentioned already. Our analysis was

retrospective and the combination of drugs used was different than in ALTITUDE. In addition, classification of stroke subtype was not carried out in VALIANT. When VALIANT was conducted, neuroimaging was not standard in patients with suspected stroke in many, if not most countries, involved. Our analysis does, however, have the strength of including over 460 patients with an independently adjudicated incident stroke, including 161 among patients with diabetes.

In summary, while dual RAS blockade caused more hypotension and renal dysfunction in patients with diabetes in VALIANT, we found no evidence that the combination of an ACE inhibitor and ARB increased the risk of stroke in these patients and, if anything, evidence to the contrary.

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Contributorship

JJV McMurray coordinated the study. JJV McMurray and SD Solomon supervised the data access. K Docherty, H Skali and AH Abdul-Rahim, performed the statistical analysis. K Docherty, JJV McMurray and AH Abdul-Rahim, drafted the initial manuscript. All authors have read and commented on the drafts with regards to the intellectual contents, interpretation of the data and editing of the manuscript. All authors have seen and approved the final version. H Skali, SD Solomon and JJV McMurray have direct access to the original data and attest to the accuracy and completeness of this report.

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