Patients with acute coronary syndromes and elevated levels of natriuretic peptides: the results of the AVANT GARDE-TIMI 43 Trial

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Received 21 January 2010; revised 29 April 2010; accepted 11 May 2010; online publish-ahead-of-print 17 June 2010

Aims
Elevated natriuretic peptides (NPs) are associated with an increased cardiovascular risk following acute coronary syndromes (ACSs). However, the therapeutic implications are still undefined. We hypothesized that early inhibition of renin–angiotensin–aldosterone system (RAAS) in patients with preserved left ventricular function but elevated NPs but following ACS would reduce haemodynamic stress as reflected by a greater reduction NP compared with placebo.

Methods and results
AVANT GARDE-TIMI 43 trial, a multinational, double-blind trial, randomized 1101 patients stabilized after ACS without clinical evidence of heart failure or left ventricular function ≤ 40% but with an increased level of NP 3–10 days after admission to aliskiren, valsartan, their combination, and placebo. The primary endpoint was the change in NT-proBNP from baseline to Week 8. NT-proBNP declined significantly in each treatment arm, including placebo, by Week 8, though there were no differences in the reduction between treatment strategies (42% in placebo, 44% in aliskiren, 39% in valsartan, and 36% in combination arm). Although several subgroups had higher baseline levels of NP and greater reductions over the study period, there were no differences among treatment groups in any subgroup. There were no differences in clinical outcomes but there were more adverse events, including serious events and adverse events leading to early study drug discontinuation, in patients treated with active therapy.

Conclusion
In this study of a high-risk population with elevated levels of NPs but relatively preserved systolic function and no evidence of heart failure following ACS, there was no evidence for a benefit of early initiation of inhibition of RAAS with valsartan, aliskiren, or their combination compared with placebo with respect to a reduction in NP over 8 weeks of therapy. Moreover, adverse events were reported more frequently in patients assigned to active therapy.

Keywords
Natriuretic peptides • Acute coronary syndrome • Renin–angiotensin–aldosterone system

Introduction
Despite continued improvements in medical and revascularization strategies, a significant proportion of patients hospitalized with acute coronary syndromes (ACSs) eventually succumb from cardiovascular complications, most frequently heart failure. Identifying high-risk patients early in their clinical course is a central goal of the evaluation of patients with ACS. Circulating natriuretic peptides (NPs) are released from ventricular myocardium in response to increased wall stress and when elevated in patients with ACS.
are associated with a three- to five-fold higher risk of death or heart failure compared with patients with low concentrations.\(^2\) The therapeutic implications of an elevated concentration of NPs in patients with ACS are still undefined, as no study has yet demonstrated that a specific therapy will reduce concentrations of NPs in patients stabilized after ACS or has conclusively been shown to reduce the risk associated with increased levels in this population.

The renin–angiotensin–aldosterone system (RAAS) is a key hormonal axis modulating cardiac function, vascular haemodynamics, and renal function. The RAAS can be blocked at multiple levels by angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, aldosterone receptor inhibitors, and now by direct renin inhibitors. Aliskiren, the first clinically available direct renin inhibitor, has been shown to be both an effective antihypertensive agent\(^6\)\(^\text{-}\)\(^7\) and a potent inhibitor of the RAAS.\(^8\) In this proof-of-concept study, we tested the hypothesis that in patients with relatively preserved left ventricular function but elevated levels of NPs following ACS, early proximal inhibition of the RAAS with aliskiren, distal inhibition with valsartan, or the combination will reduce haemodynamic stress as reflected by a greater reduction in levels of NPs compared with placebo after 8 weeks of treatment.

**Methods**

**Study population**

The Aliskiren and Valsartan to Reduce NT-proB-type natriuretic peptide (BNP) via Renin-Angiotensin-Aldosterone-System Blockade (AVANT GARDE)-TIMI 43 Trial was a randomized, double-blind, placebo-controlled trial that randomized 1101 patients determined to be at high clinical risk on the basis of an elevated concentration of a NP 3–10 days after an ACS event. A total of 144 sites in 12 countries enrolled patients between April 2007 and March 2009 (Figure 1). The protocol was approved by all applicable national and local ethical review boards.

Eligible patients were 18 years or older, hospitalized for ischaemic chest discomfort at rest lasting at least 10 min and consistent with cardiac ischaemia with a final diagnosis of an ACS, including unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), or ST segment elevation MI (STEMI). In addition, to be eligible, a patient must have had an elevated concentrations of NP (NT-proBNP level >400 pg/mL or BNP level >80 pg/mL) within 3–10 days after admission. All patients must have been clinically stable without any of the following spontaneous events for 24 h prior to randomization: recurrent ischaemia at rest, symptomatic hypotension or systolic blood pressure (BP) <90 mmHg, acute mechanical complications of MI, and significant arrhythmias including new onset atrial fibrillation. A cut-point of 80 pg/mL for BNP was chosen for BNP based on our previous work\(^2\)\(^\text{-}\)\(^4\)\(^,\)\(^9\) and clinical guidelines.\(^10\) For NT-proBNP, 400 pg/mL was chosen to approximate a BNP of 80 pg/mL.

Exclusion criteria included: clinically overt heart failure defined as the presence of rales greater than one-third of both lung fields, chest radiography with pulmonary venous congestion, or the presence of a third heart sound; known evidence of left ventricular ejection fraction ≤40% at any time before randomization; CABG within 3 months or PCI within 24 h before randomization; chronic ACE-I or ARB therapy that could not be discontinued; estimated creatinine clearance <45 mL/min (MDRD calculation); or a serum potassium ≥5.2 mEq/L.

**Endpoints**

The primary efficacy endpoint was the relative change in NT-proBNP between baseline and the end of study. Secondary efficacy endpoints included the change in BNP and plasma renin activity between baseline and the end of study, a clinical composite endpoint of cardiovascular death, myocardial infarction, and hospitalization for heart failure, and a combined biochemical–clinical endpoint of cardiovascular death, myocardial infarction, hospitalization for congestive heart failure, or NT-proBNP level >200 pg/mL at Week 8. Clinical endpoints were adjudicated by members of an independent clinical events committee that was unaware of treatment assignment.

Blood samples were collected in EDTA-anticoagulated and serum separator plastic tubes and then centrifuged and stored frozen in aliquots at −20 to −80°C at the enrolling site until shipped to the TIMI Biomarker Core Laboratory, Boston, MA, USA where they were maintained at −80°C. Serum NT-proBNP concentrations were determined using a sandwich immunoassay (Elecys 2010, Roche Diagnostics GmbH). The analytic range of NT-proBNP assay extends from 50 to 20 000 pg/mL. The total coefficient of variation was 2.9% at a level of 49 pg/mL and 0.75% at a level of 19882 pg/mL. BNP was measured in plasma samples using the ADVIA Centaur (Siemens Medical Solutions, Malvern, PA, USA)\(^11\) at the first thaw. The analytic range of the BNP assay extends from 5 to 5000 pg/mL. The total coefficient of variation was 9.0% at a level of 5 pg/mL. Plasma renin activity (radioimmunoassay of generated Ang I, DiaSorin, Saluggia, Italy) were measured from plasma samples analysed at the first thaw. The total coefficient of variation was 20.3% at the lower level of quantification (0.2 ng/mL) and 8.1% at the highest level (20 ng/mL).

**Statistical consideration**

**Efficacy analysis**

The co-primary objectives of this study were to determine whether: (i) aliskiren reduces the levels of NT-proBNP from baseline to Week 8 when compared with placebo, (ii) valsartan reduces the levels of NT-proBNP from baseline to Week 8 when compared with placebo,
Figure 1 Patient flow diagram.
(iii) the combination of aliskiren and valsartan reduces the levels of NT-proBNP from baseline to Week 8 when compared with each individual monotherapy and as well as to placebo. A closed test procedure was applied to control the trial-wise error rate at level $\alpha = 0.05$.

The primary endpoint was the relative reduction to baseline in NT-proBNP, expressed as a ratio of Week 8 divided by baseline levels. The log ratio in NT-proBNP (Week 8 over baseline) was analysed using an analysis of covariance model (ANCOVA) with treatment, region, gender, index diagnosis, renal function (eGFR at baseline $\leq 60$, $>60$ mL/min/1.73 m$^2$), beta-blocker use, prior angiotensin converting enzyme inhibitor/angiotensin-receptor blocker use, and diabetes as factors, and log baseline NP levels as a covariate. The treatment difference between the least square means for all three hypotheses and two-sided 95% confidence interval of the back transformed ratio are presented.

Of the 1101 randomized patients, 9 patients were inadvertently randomized instead of being screen-failures and did not receive study drug. These patients were identified before database lock and were excluded from all subsequent efficacy and safety analyses, therefore a total of 1092 patients were included in the final analysis. The primary efficacy analysis (the change in NT-proBNP from baseline to end of study) could not be assessed in patients without a baseline NT-proBNP or in patients with only a baseline sample (13 patients in placebo, 33 in aliskiren, 22 in valsartan, and 22 in valsartan/aliskiren). They were, however, included in all analyses of clinical events. The safety population included all subjects who received at least one dose of study drug ($n = 1089$). For patients who discontinued prior to Week 8, the last post-baseline NT-proBNP measurement collected was used for the analysis (last observation carried forward). BNP, Plasma renin activity (PRA), and BP results were evaluated using the same analysis plan. Unless otherwise noted, biomarker data are presented as geometric means and BP as least square means.

Clinical cardiovascular events were compared using a logistic-regression model that includes index diagnosis, prior angiotensin converting enzyme inhibitors/angiotensin-receptor blocker use, and treatment group as variables. Baseline characteristics, concomitant medication use, and safety outcomes were compared using chi-squared test for categorical variables and a t-test for continuous variables.

**Study organization**

The AVANT GARDE-TIMI 43 trial was a collaboration between the TIMI Study Group, Novartis, and the Steering Committee (Supplementary material online, Appendix). Novartis was responsible for data management. All primary analyses in this manuscript were confirmed by the TIMI Study Group using an independent copy of the complete database. The academic authors wrote all drafts of the manuscript and vouch for the veracity and completeness of content. The database was locked on 17 June 2009. The trial was registered in a public database (ClinicalTrials.gov Identifier: NCT00409578).

**Results**

**Baseline characteristics**

Baseline demographic and clinical characteristics are presented in Table 1. The mean age was 63 years with almost 20% of patient at least 75 years old. Women accounted for 31.6% of the study population. The index diagnosis was STEMI in 58.5% of patients, NSTEMI in 28.2%, and unstable angina in 12.9%. Most patients presenting with STEMI received immediate reperfusion (80.3%) and overall almost two-thirds of patients underwent PCI (64.6%) during the index hospitalization. The mean left ventricular ejection fraction [assessed in 931 patients (85.1%)] was 52.8%. Most patients were moderate to high risk according to their clinical risk score (Table 1). Over 50% of patients received RAAS inhibitors before randomization. There were no clinically important differences between treatment groups in terms of their concomitant medications during hospitalization or after randomization (Table 2).

**Plasma renin activity (PRA)**

Among patients assigned to placebo, PRA decreased by 58% by Week 4 and 51% at Week 8. Plasma renin activity decreased by 89% at Week 4 and 88% at end of study in patients assigned to aliskiren, increased by 17% at Week 4 and 15% at end of study in patients assigned to valsartan, and increased by 18% at 4 weeks and then decreased by 72% among patients assigned to the combination therapy which began with 4 weeks of valsartan monotherapy followed by the addition of aliskiren. All changes were significantly different compared with placebo (Figure 2).

**Blood pressure**

The mean seated BP at randomization was 127/76 mmHg. Blood pressure increased in all treatment groups with a greater increase in patients assigned to placebo (7.7 mmHg systolic) compared with patients assigned to aliskiren (3.7 mmHg, $P = 0.0037$), valsartan (4.2 mmHg, $P = 0.013$), and valsartan/aliskiren (2.8 mmHg, $P = 0.0003$). (Figure 3) There were no significant differences in the change of systolic BP measurements between active treatments. A similar pattern was present for diastolic BP measurements (Figure 3).

**NT-proB-type natriuretic peptide**

The level of NT-proBNP at randomization was 896 pg/mL (95% CI 847–947). Levels of NT-proBNP decreased during the study in all treatment groups ($P < 0.001$ for each group) (Figure 4, top). NT-proBNP fell by 42% in patients assigned to placebo (Figure 3, top). There were similar declines in patients assigned to aliskiren (44%), valsartan (39%), or valsartan/aliskiren (36%). There was also no difference when comparing all treatment groups vs. placebo ($P = 0.54$).

The fall in levels of NT-proBNP occurred primarily between Week 4 and the end of study (Week 8). Between randomization and Week 4, levels of NT-proBNP fell by 14% in patients assigned to placebo, 24% in patient assigned to aliskiren, 17% in patients assigned to valsartan, and 24% in patients assigned to the combination therapy but were on valsartan alone during the first 4 weeks ($P = $NS for the comparison of each active therapy vs. placebo and $P = 0.080$ comparing the pooled active treatment groups to placebo).

There were also no differences in the numbers of patients who achieved a pre-defined level of NT-proBNP <200 pg/mL by 4 weeks after randomization (6.5% in placebo, 7.8% in aliskiren, 5.7% in valsartan, or 9.5% in valsartan/aliskiren) or at Week 8 (14.2% in placebo, 16.5% in aliskiren, 14.9% in valsartan, or 14.5% in valsartan/aliskiren).
B-type natriuretic peptide

The level of BNP at randomization was 130 pg/mL (95% CI 121–138). Levels of BNP fell in a similar pattern as NT-proBNP in terms of timing and treatment assignment (Figure 4, bottom).

Subgroup analysis

The baseline levels of NT-proBNP and the change during study in patients assigned to placebo and patients assigned to one of the active treatment groups are presented in Figure 5. Baseline levels of NT-proBNP were higher in certain subgroups such as patients ≥75 years old, females, patients with diabetes, hypertension, low GFR, and an ejection fraction <45%. However, there was no difference in any specific subgroup in terms of the decline in NT-proBNP in patients assigned to active therapy vs. placebo.

Clinical events

The incidence of the composite clinical endpoint—CV death, myocardial infarction, or hospitalization for HF—was low without significant differences between treatment groups (Table 3). There was also no difference in the incidence of the primary composite clinical when comparing all three active treatment groups combined with placebo (OR 1.57, 95% CI 0.72–3.41, P = 0.26). There was also no significant difference between treatment groups in terms of the combined clinical–biochemical endpoint (composite clinical endpoint or
Table 2  Medical therapy before and after randomization

<table>
<thead>
<tr>
<th>Medical therapy during index hospitalization</th>
<th>Placebo, n = 280</th>
<th>Aliskiren, n = 271</th>
<th>Valsartan, n = 269</th>
<th>Valsartan/aliskiren, n = 281</th>
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<tbody>
<tr>
<td>Aspirin (%)</td>
<td>265 (94.6)</td>
<td>246 (90.8)</td>
<td>259 (96.3)</td>
<td>260 (92.5)</td>
</tr>
<tr>
<td>Theinopyridine (%)</td>
<td>246 (87.9)</td>
<td>216 (79.7)</td>
<td>226 (84.0)</td>
<td>235 (83.6)</td>
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<tr>
<td>Beta-blocker (%)</td>
<td>257 (91.8)</td>
<td>245 (90.4)</td>
<td>250 (92.9)</td>
<td>251 (89.3)</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor (%)</td>
<td>152 (54.3)</td>
<td>161 (59.4)</td>
<td>157 (58.4)</td>
<td>164 (58.4)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker (%)</td>
<td>28 (10.0)</td>
<td>26 (9.6)</td>
<td>15 (5.6)</td>
<td>18 (6.4)</td>
</tr>
<tr>
<td>Aldosterone antagonist (%)</td>
<td>15 (5.4)</td>
<td>10 (3.7)</td>
<td>10 (3.7)</td>
<td>16 (5.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical therapy after randomization</th>
<th>Placebo, n = 280</th>
<th>Aliskiren, n = 271</th>
<th>Valsartan, n = 269</th>
<th>Valsartan/aliskiren, n = 281</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (%)</td>
<td>256 (92.1)</td>
<td>241 (91.3)</td>
<td>250 (93.3)</td>
<td>255 (91.4)</td>
</tr>
<tr>
<td>Theinopyridine (%)</td>
<td>236 (84.9)</td>
<td>209 (79.2)*</td>
<td>225 (84.0)</td>
<td>229 (82.1)</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>249 (89.6)</td>
<td>238 (90.2)</td>
<td>250 (93.3)</td>
<td>251 (90.0)</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor (%)</td>
<td>44 (15.9)</td>
<td>48 (18.2)</td>
<td>37 (13.8)</td>
<td>41 (14.7)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker (%)</td>
<td>9 (3.4)</td>
<td>12 (4.6)</td>
<td>6 (2.3)</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Aldosterone antagonist (%)</td>
<td>9 (3.2)</td>
<td>4 (1.5)</td>
<td>5 (1.9)</td>
<td>8 (2.9)</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>53 (19.1)</td>
<td>43 (16.3)</td>
<td>46 (17.2)</td>
<td>51 (18.3)</td>
</tr>
<tr>
<td>Calcium antagonists (%)</td>
<td>82 (29.5)</td>
<td>70 (26.5)</td>
<td>61 (22.8)</td>
<td>76 (27.2)</td>
</tr>
<tr>
<td>Other antihypertensive agents (%)</td>
<td>15 (5.4)</td>
<td>30 (11.4)*</td>
<td>16 (6.0)</td>
<td>23 (8.2)</td>
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<td>Statins (%)</td>
<td>255 (91.7)</td>
<td>235 (89.0)</td>
<td>242 (90.3)</td>
<td>257 (92.1)</td>
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</tbody>
</table>

*Indicates P < 0.05 compared with placebo using chi-squared test.

NT-proBNP >200 pg/mL (Table 3). Patients who experienced CV death, MI, or hospitalization for HF had higher baseline levels of NT-proBNP compared with those who did not experience an endpoint (2019 vs. 1366 pg/mL, P = 0.026).

Safety

In all three active treatment arms compared with placebo, there were more reported serious adverse events overall (9.4% in placebo vs. 14.4% in all active therapy combined, P = 0.03) and serious adverse events leading to study drug discontinuation (2.5% in placebo vs. 4.1% in all active therapy combined, P = 0.22). The two most common adverse events leading to study drug discontinuation were hyperkalaemia (five cases in placebo, five in aliskiren, three in valsartan, and five in valsartan/aliskiren) and hypotension (one case in placebo, three in aliskiren, three in valsartan, and four in aliskiren and placebo). Orthostatic hypotension occurred more frequently in patients assigned to active treatment (Table 4). Mortality was infrequent and similar between all treatment groups (four in placebo, four in aliskiren, five in valsartan, and four in valsartan/aliskiren). There were small differences in the change in eGFR between treatment groups during the study (mean change: +3 mL/min/1.73 m² in placebo; 0 mL/min/1.73 m² in aliskiren; 0 mL/min/1.73 m² in valsartan; and −2 mL/min/1.73 m² in valsartan/aliskiren). However, increases in serum creatinine to greater than 2.0 mg/dL (>176.8 µmol/L) or potassium greater than 5.5 or 6.0 mEq/L were infrequent and without treatment differences. There were no reported cases of angioedema.

Discussion

In this randomized, placebo-controlled trial of 1101 patients without evidence of heart failure or left ventricular ejection fraction ≤40%, but with elevated levels of NPs following ACS, inhibition of RAAS with the direct renin inhibitor aliskiren, the angiotensin receptor blocker valsartan, either alone or in combination, did not result in any significant change compared with placebo in the level of NPs. There was a substantial decline ranging between 36 and 44% in the levels of NPs among all patients, including patients treated with placebo. However, any treatment effect on a change in NPs was minimal compared with the overall decline observed during the 8-week study treatment.

There are several formal alternatives to be considered regarding the lack of an observed treatment effect on the primary endpoint and may be related to the study population, the study medications, or to the use of NPs as a surrogate endpoint in this population.

AVANT GARDE-TIMI 43 was designed to enrol moderate to high-risk patients based principally on elevated levels of NPs. Given that over one-half of the patients had a high TIMI Risk Score for UA/NSTEMI (7) or STEMI (≥3), this strategy appears to have identified patients who, based on contemporary risk-stratification algorithms, would be considered to be at increased risk following ACS. In fact, the aggregate event rate of cardiovascular death, myocardial infarction, or heart failure was higher than in the PROVE IT-TIMI 22 Trial, which had similar inclusion criteria with the exception of the NP criteria (4.1 vs. 2.8% at 60 days). Even at the end of study, over half of all study patients still had a BNP >80 pg/mL (Table 4), which based on other studies, would indicate that they would be at significantly increased risk of subsequent death or heart failure. Thus the patients enrolled in AVANT GARDE-TIMI 43 because of their elevated level of NP were at high clinical risk.
The effect of early initiation of inhibitors of the RAAS in this population of patients without overt left ventricular dysfunction or heart failure following ACS is relatively unstudied. The predominance of data regarding the benefit of early initiation of RAAS is from patients following myocardial infarction with evidence of depressed left ventricular function (ejection fraction <40%) and/or clinical heart failure. In older studies that included an unselected MI population in whom there was less aggressive revascularization and medical therapy, most patients had STEMI and the greatest clinical benefit was seen in patients with anterior STEMI, prior MI, or a depressed left ventricular function. Furthermore, in over 8600 patients in the Gruppo Italiano per lo Studio della Sopravivenza Nell’infarto Miocardico (GISSI)-3 trial echocardiography substudy, for example, the improvement in ventricular dimensions among patients assigned lisinopril was only evident in patients with evidence of greater left ventricular dysfunction. Thus, despite recommendation to begin RAAS inhibition in general following ACS, there is little information regarding the benefit of early RAAS inhibition in patients without evidence of heart failure or systolic dysfunction, though these constitute the majority of patients admitted with ACS. The lack of change in NPs with RAAS inhibition compared with placebo in AVANT GARDE-TIMI 43 revealed no clear clinical benefit of early inhibition of RAAS with respect to a change in NP over 8 weeks of therapy. This is consistent with recent placebo controlled trials of RAAS inhibition in stable CAD that did not demonstrate a clinical benefit in the presence of improved medical therapy and risk factor modification. Compared with older studies of unselected MI patients, the great majority of patients in the AVANT GARDE-TIMI 43 trial underwent catheterization and
revascularization with a high utilization of anti-platelet agents, beta-blockers, and statins. Moreover, BP, even in patients assigned to placebo, was well controlled.

Treatment with aliskiren and valsartan resulted in the expected suppression and increase, respectively, of plasma renin activity and a slightly lower BP compared with placebo. These physiologic effects, however, did not manifest in a significant reduction in NPs compared with placebo. This is in contrast to a study in patients with heart failure where aliskiren, when compared with placebo, did not result in significant BP difference but significant reduced NP.27 In patients following ACS, levels of NP may be influenced by other acute dynamic factors such as ischaemia, inflammation, and necrosis, which obscure the impact of BP alone on NP.

Improvements in remodelling following infarction, the mechanism by which early inhibition of RAAS is proposed to reduce heart failure and death after large infarcts, may not be as substantial in patients who have preserved ventricular function, high rates of revascularization, and well-treated BP as seen in AVANT GARDE-TIMI 43.

Another potential explanation for the lack of observed treatment effect could be related to characteristics of primary outcome measurement. Natriuretic peptides typically rise immediately following ACS and then fall in the subsequent days and weeks. Patients with persistently elevated NPs appear to be at greatest risk.9 By waiting until at least 72 h after admission to assess NPs, our goal was to capture patients in whom the initial increase in NPs due to transient ischaemia would have already declined. However, the natural decline in NPs was more protracted than expected, with significant decline in NPs between 4 and 8 weeks after the index event, even among patients assigned to placebo. Any treatment effect would therefore be difficult to discern within the significant natural decline of NPs following ACS. In addition, the relatively short duration of therapy may have been insufficient to allow for any potential long-term beneficial effects of inhibition of RAAS such as reduction in ventricular hypertrophy or improvements in vascular function, which could have led to reductions in NP after longer treatment exposure.

Both the NT-proBNP and BNP assays utilized in this trial are well-validated, approved diagnostic assays used in many other clinical studies. Samples were collected, stored, and analysed with processes designed to minimize any potential degradation or contamination. Despite a marked association between levels of NPs and outcomes on a population basis, there is substantial variability between patients with similar clinical characteristics. As seen in AVANT GARDE-TIMI 43, there was a wide distribution in the concentrations of NPs, even among a well-defined population. In our proof-of concept trial, we attempted to minimize extraneous influences by minimizing other concomitant medications and examining intra-patient-changes in NPs using an analysis that controlled for many factors that could also affect levels of NPs.

**Figure 3** Blood pressure by visit and treatment group.
Figure 4 NT-proB-type natriuretic peptide (top) and B-type natriuretic peptide (bottom) by visit and treatment group. Individual time points represent values taken at those visits. The Week 8/LOCF values are from Week 8 or the last value obtained in the study carried forward and are the basis for the primary analysis. LOCF, last observation carried forward. P-values from analysis of covariance model (ANCOVA) with treatment, region, gender, index diagnosis, renal function (eGFR level at baseline ≤ 60 and > 60 mL/min/1.73 m²), beta-blocker use, prior angiotensin converting enzyme inhibitor/angiotensin-receptor blocker use and diabetes as factors, and log baseline NP levels as a covariate.
Baseline levels and change in NT-proB-type natriuretic peptide according to treatment in various sub-groups. The decline of NT-proB-type natriuretic peptide was not significantly different between subgroups (for example, male vs. female). Nor was there no evidence of an interaction between the different sub-groups, the decline in NT-proB-type natriuretic peptide, and study treatment.

Figure 5 Baseline levels and change in NT-proB-type natriuretic peptide according to treatment in various sub-groups. The decline of NT-proB-type natriuretic peptide was not significantly different between subgroups (for example, male vs. female). Nor was there no evidence of an interaction between the different sub-groups, the decline in NT-proB-type natriuretic peptide, and study treatment.
Results of the AVANT GARDE-TIMI 43 Trial

2003

Clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 278), n (%)</th>
<th>Aliskiren (n = 268), n (%)</th>
<th>P-value vs. placebo</th>
<th>Valsartan (n = 268), n (%)</th>
<th>P-value vs. placebo</th>
<th>Valsartan/Aliskiren (n = 278), n (%)</th>
<th>P-value vs. placebo</th>
<th>All active therapy (n = 814), n (%)</th>
<th>P-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, myocardial infarction, or heart failure</td>
<td>8 (2.9)</td>
<td>13 (4.8)</td>
<td>0.23</td>
<td>13 (4.8)</td>
<td>0.23</td>
<td>11 (4.3)</td>
<td>0.48</td>
<td>37 (4.5%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2 (0.7)</td>
<td>4 (1.5)</td>
<td>0.39</td>
<td>4 (1.5)</td>
<td>0.39</td>
<td>4 (0.7)</td>
<td>0.41</td>
<td>12 (1.5%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (1.1)</td>
<td>7 (2.6)</td>
<td>0.18</td>
<td>5 (1.9)</td>
<td>0.44</td>
<td>7 (2.5)</td>
<td>0.20</td>
<td>19 (2.3%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Heart failure (hospitalization for)</td>
<td>3 (1.1)</td>
<td>2 (0.7)</td>
<td>0.68</td>
<td>5 (1.9)</td>
<td>0.44</td>
<td>3 (1.1)</td>
<td>1.00</td>
<td>10 (1.2%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Cardiovascular death, myocardial infarction, heart failure, or NT-proBNP &gt;200 pg/mL</td>
<td>221 (79.5)</td>
<td>197 (73.5)</td>
<td>0.10</td>
<td>207 (77.2)</td>
<td>0.52</td>
<td>209 (75.2)</td>
<td>0.22</td>
<td>613 (75.3%)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Table 3  Clinical outcomes

Table 4  Serious adverse events, adverse events, and laboratory abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Placebo, n = 278</th>
<th>Aliskiren, n = 264</th>
<th>P-value vs. placebo</th>
<th>Valsartan, n = 268</th>
<th>P-value vs. placebo</th>
<th>Valsartan/Aliskiren, n = 279</th>
<th>P-value vs. placebo</th>
<th>All active therapy, n = 814</th>
<th>P-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality (%)</td>
<td>2 (0.7)</td>
<td>4 (1.5)</td>
<td>0.37</td>
<td>5 (1.9)</td>
<td>0.23</td>
<td>5 (1.4)</td>
<td>0.41</td>
<td>13 (1.6%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Any serious adverse event (%)</td>
<td>26 (9.4)</td>
<td>39 (14.8)</td>
<td>0.052</td>
<td>33 (12.3)</td>
<td>0.27</td>
<td>46 (16.5)</td>
<td>0.012</td>
<td>118 (14.4%)</td>
<td>0.03</td>
</tr>
<tr>
<td>AE leading to discontinuation (%)</td>
<td>28 (10.1)</td>
<td>41 (15.5)</td>
<td>0.057</td>
<td>29 (10.8)</td>
<td>0.78</td>
<td>33 (11.8)</td>
<td>0.50</td>
<td>103 (12.5)</td>
<td>0.27</td>
</tr>
<tr>
<td>SAE discontinuations (%)</td>
<td>7 (2.5)</td>
<td>12 (4.5)</td>
<td>0.20</td>
<td>11 (4.1)</td>
<td>0.30</td>
<td>11 (3.9)</td>
<td>0.34</td>
<td>34 (4.1%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Orthostatic hypotension* (%)</td>
<td>26(9.5)</td>
<td>34 (12.9)</td>
<td>0.19</td>
<td>31 (11.6)</td>
<td>0.40</td>
<td>35 (12.7)</td>
<td>0.23</td>
<td>100 (12.2%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Creatinine &gt;176.8 μmol/L (&gt;2.0 mg/dL)</td>
<td>2 (0.7)</td>
<td>6 (2.4)</td>
<td>0.07</td>
<td>3 (1.1)</td>
<td>0.62</td>
<td>3 (1.1)</td>
<td>0.66</td>
<td>12 (1.5%)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Potassium

<table>
<thead>
<tr>
<th></th>
<th>Placebo, n = 278</th>
<th>Aliskiren, n = 264</th>
<th>P-value vs. placebo</th>
<th>Valsartan, n = 268</th>
<th>P-value vs. placebo</th>
<th>Valsartan/Aliskiren, n = 279</th>
<th>P-value vs. placebo</th>
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<th>P-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.5 mmol/L (&lt;3.5 mEq/L)</td>
<td>17 (6.4)</td>
<td>2 (0.8)</td>
<td>0.001</td>
<td>8 (3.1)</td>
<td>0.08</td>
<td>3 (1.1)</td>
<td>0.001</td>
<td>13 (1.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;5.5 mmol/L (&gt;5.5 mEq/L)</td>
<td>12 (4.5)</td>
<td>13 (5.1)</td>
<td>0.74</td>
<td>8 (3.1)</td>
<td>0.41</td>
<td>12 (4.5)</td>
<td>0.99</td>
<td>33 (4.0%)</td>
<td>0.83</td>
</tr>
<tr>
<td>&gt;6.0 mmol/L (&gt;6.0 mEq/L)</td>
<td>4 (1.5)</td>
<td>10 (3.9)</td>
<td>0.085</td>
<td>4 (1.5)</td>
<td>0.96</td>
<td>0</td>
<td>0.044</td>
<td>14 (1.7%)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*Orthostatic hypotension was assessed by the investigator if they determined any of the following after 3 min of changing from a seated to standing position: (i) a reduction in systolic blood pressure ≥ 20 mmHg, (ii) a reduction in diastolic blood pressure ≥ 10 mmHg, (iii) an increase in the heart rate by 20 b.p.m., or (iv) lightheadedness or dizziness.

Safety

This is the first clinical trial to evaluate aliskiren, either alone, or in combination with another inhibitor of RAAS in patients with ACS. Adverse events, including serious events and those that led to study drug discontinuation, occurred more frequently in patients assigned to active treatment groups compared with placebo. Overall mortality was low and without any differences between treatment arms. There were fewer cases of hypokalaemia in patients treated with active therapy compared with placebo and no increase in the risk of hyperkalaemia, even with combination therapy. The effect on eGFR was physiologically expected and consistent with other studies of RAAS inhibition where a decrease in glomerular filtration pressure was observed. 28–30

Clinical implications

Any tool for risk stratification is of greatest clinical utility when it not only improves risk stratification, but also influences treatment decisions that improve long-term outcomes. The establishment of evidence-based links to specific treatment based on elevated levels of novel biomarkers has, however, remained elusive. As highlighted in recent clinical guidelines, NPs are well established as independent markers of future cardiovascular events, however there is a compelling need to identify therapies that modify the high risk associated with increased levels of NPs. 1,10 Based on the results of the AVANT GARDE-TIMI 43 study, a strategy of targeting patients with preserved ventricular function but elevated NPs for early inhibition of RAAS following ACS did not result in greater haemodynamic benefit as assessed by a change NP.

Supplementary material

Supplementary material is available at European Heart Journal online.
Conflict of interest: B.M.S. reports research support from CV Therapeutics, Novartis, AstraZeneca, Daiichi-Sankyo, Bristol Meyer-Squibb, and Roche Diagnostics, honoraria for educational presentations from CV Therapeutics, Novartis, Merck, Schering-Plough, sanofi-aventis, Lilly, Daiichi-Sankyo, and has served as a consultant for AstraZeneca, Novartis, and Cogetus and received an unrestricted research grant from the Michael Lerner Foundation. D.M.M. has received honoraria for educational presentations from CV Therapeutics and Eli Lilly. Lilly has served as a consultant for Beckman-Coulter, Critical Diagnostics, Genentech, Ikaria, Menarini, OrthoClinical Diagnostics, Roche Diagnostics, Sanofi Aventis, Schering Plough, and Siemens, and was compensated as a member of a Clinical Events Committee for a clinical trial by AstraZeneca. J.L.-S. has received research grants from Novartis. K.S. reports having research support and honoraria from AstraZeneca, Novartis, Otsuka, Servier. V.L. and M.M. are employees of Novartis. C.P.C. reports research funding from Accutemcs, AstraZeneca, Bristol-Myers Squibb/Sanofi Partnership, Glaxo Smith Kline, Intekrin Therapeutics, Merck, Merck/Schering-Plough Partnership, Novartis, and Takeda and acted as a Clinical Advisor and having equity in AutoMedics Medical Systems. E.B. has received honoraria from Bristol Myers Squibb, Merck, and Pfizer and has served as a consultant to Bristol-Myers Squibb, and Pfizer. Others report no conflicts.

Funding
AVANT GARDE-TIMI 43 was supported by Novartis. Reagents for NT-proBNP were provided via an unrestricted grant from Roche Diagnostics.

References

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