

Aliskiren, ALTITUDE, and the implications for ATMOSPHERE

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Blockade of the renin–angiotensin system (RAS) is a core therapeutic strategy in systolic heart failure.¹ The value of angiotensin-converting enzyme (ACE) inhibitors was proven in two pivotal trials conducted > 20 years ago. More recently, angiotensin receptor blockers (ARBs) have also been shown to be beneficial in systolic heart failure both as an alternative to and when added to an ACE inhibitor. Separately, mineralocorticoid receptor antagonists (MRAs) reduce mortality and morbidity when added to an ACE inhibitor or ARB (MRAs are not considered further here). The latest approach to RAS blockade to be tested in clinical practice is renin inhibition. Currently the efficacy and safety of the renin inhibitor aliskiren is being tested in two clinical trials in heart failure, the Aliskiren Trial of Minimizing OutcomeS for Patients with HEart failure (ATMOSPHERE) and the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT), described previously in this journal.^{2,3} However, on 20 December 2011, treatment in another study, the Aliskiren Trial In Type 2 Diabetes Using Cardio-Renal Disease Endpoints (ALTITUDE), was stopped on the recommendation of its Data Monitoring Committee (DMC).^{2,3} ALTITUDE was comparing placebo or aliskiren 300 mg once daily, added to background ACE inhibitor or ARB therapy in patients with diabetes and either (i) increased urinary albumin excretion or (ii) both a reduced estimated glomerular filtration rate (eGFR 30–60 mL/min/1.73 m²) and established cardiovascular disease. The primary outcome in ALTITUDE is a composite of cardiovascular death, resuscitated sudden death, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure, end-stage renal disease, renal death, or doubling of baseline serum creatinine concentration, sustained for at least a month. As a result of the DMC recommendation, ALTITUDE is currently being closed out in an orderly fashion. 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 (which are unsurprising) as well as an excess of strokes. In the publically released information, the number of patients experiencing a non-fatal stroke in the placebo group was 85 (2.0%) and 112 (2.6%) in the aliskiren group (nominal, unadjusted, *P*-value 0.04).⁶ Although this unexpected finding has provoked concern and discussion, the reported numbers do not represent the final number of events in ALTITUDE (at the time of the DMC's recommendation it was estimated that approximately a third of events remained to be collected and adjudicated). Consequently, while the apparent imbalance in strokes may persist or increase, it may also attenuate. Furthermore, given all prior data relating use of antihypertensive therapy to a reduced incidence of stroke in patients with diabetes, it is also possible that the imbalance in strokes represents a chance finding.^{7–9}

In response to these findings it has been recommended that dual aliskiren and ACE inhibitor/ARB therapy not be used in patients with both hypertension (the current indication for aliskiren) and diabetes or moderate to severe renal dysfunction (eGFR <60 mL/min/1.73 m²).¹⁰ This recommendation has led to questions about the use of dual aliskiren therapy in patients with diabetes in the ongoing ATMOSPHERE trial (and, to a lesser extent, also the ASTRONAUT trial which has almost finished recruitment and will complete follow-up this year). In ATMOSPHERE, patients with systolic heart failure and an elevated B-type natriuretic peptide (BNP) or N-terminal pro BNP (NT-proBNP) concentration are randomized in equal proportions to receive either enalapril 10 mg twice daily, aliskiren 300 mg once daily, or the combination of both drugs.³ ATMOSPHERE is an event-driven trial with a primary composite outcome of cardiovascular death or heart failure

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hospitalization. We believe that the preliminary results of ALTITUDE should not lead to any alteration in the conduct of ATMOSPHERE. The reasons for taking this view are discussed in detail below.

Different patient populations

The patients in ALTITUDE are quite different from those in ATMOSPHERE. Virtually all patients in ALTITUDE had treated hypertension and the median systolic blood pressure (SBP) was 135 (Q1 126, Q3 150) mmHg. In ATMOSPHERE, 59% of patients recruited to date have a history of hypertension and the median SBP at baseline is 120 (Q1 110, Q3 135) mmHg. Whereas all patients in ALTITUDE had diabetes, only 29% of the ~ 5500 patients already randomized in ATMOSPHERE have this co-morbidity (and only one-third of these are receiving dual aliskiren and enalapril therapy). Patients with an eGFR < 35 mL/min/1.73 m² cannot be randomized in ATMOSPHERE. A much smaller proportion of patients in ATMOSPHERE have a moderately (<60 mL/min/1.73 m²; currently 27%) or substantially (<45 mL/min/1.73 m²; currently 7%) reduced eGFR, compared with ALTITUDE (68% and 33%, respectively). More importantly, only 11% of patients in ALTITUDE had heart failure at baseline and, of those with a measurement of left ventricular ejection fraction (EF, *n* = 258), only 62 patients had an EF ≤ 35%.

Different study design: the importance of the active run-in periods

Recognizing that patients with heart failure may suffer hypotension, renal dysfunction, and hyperkalaemia with dual RAS blockade, ATMOSPHERE was designed with enalapril, followed by enalapril plus aliskiren 'open-label' active run-in periods. Patients experiencing clinically important changes in blood pressure, creatinine/eGFR, and potassium at the end of each of these periods were unable to progress to the next treatment period/randomization (Table 1).³ It is expected that this design should protect against some of the adverse effects seen in ALTITUDE which did not have this design feature.

Prior experience with dual renin–angiotensin system blockade in heart failure

As mentioned above, dual RAS blockade with agents other than aliskiren has been shown to be of benefit in two separate trials. Importantly, this benefit appears unique to heart failure, possibly because this syndrome is characterized by intense RAS activation. Similar benefit is not seen after myocardial infarction or in patients with chronic arterial disease. Moreover, the benefit of dual ACE inhibitor and ARB therapy in heart failure was apparent in patients who had and did not have diabetes, without any evidence of heterogeneity of treatment effect in relation to this co-morbidity (CHARM-Added, unpublished; and Val-HeFT¹¹). In addition, dual ACE inhibitor plus ARB treatment was similarly beneficial in patients with, and in those without, renal dysfunction (eGFR < 60 mL/min/1.73m²) in Val-HeFT.¹²

Prior experience with aliskiren in heart failure

Before embarking on ATMOSPHERE, the safety of adding aliskiren to an ACE inhibitor or ARB was tested in a pilot trial, ALOFT, in patients with a history of hypertension and heart failure.^{13–15} Over 3 months, the addition of aliskiren 150 mg daily was not associated with a clinically important excess of elevations in potassium or creatinine, including in patients with diabetes. 'Efficacy' was assessed by measurement of reduction in BNP which was similarly reduced with aliskiren vs. placebo in patients with and without diabetes.¹⁶

Type of clinical events in ATMOSPHERE compared with ALTITUDE

The pattern of clinical events in patients with chronic systolic heart failure is quite different from that of the type of patients enrolled in ALTITUDE. In heart failure, cardiovascular death and heart failure hospitalization are much more common than stroke (or myocardial infarction) and, consequently, ATMOSPHERE is testing the

Table 1 Safety monitoring criteria that need to be met at screening (before open-label active run-in) and randomization (after open-label active run-in)

Parameter	Screening visit (V1)	Randomization visit (V4)
Hyperkalaemia	K ⁺ <5.0 mmol/L	K ⁺ <5.2 mmol/L
Renal dysfunction	eGFR ≥40 mL/min/1.73 m ²	eGFR ≥35 mL/min/1.73 m ² No decrease of eGFR of >25% from visit 1
BP	No symptomatic hypotension SBP ≥95 mmHg	No symptomatic hypotension SBP ≥90 mmHg
AEs	No AEs that preclude continuation according to the investigator judgement	No AEs that preclude continuation according to the investigator judgement

From Krum et al.³

AE, adverse event; BP, blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

effect of aliskiren on a different burden of disease (hence the different primary and secondary endpoints in ALTITUDE and ATMOSPHERE).^{17,18}

Ensuring patient safety: the role of the Data Monitoring Committee

Lastly and most importantly, the safety of patients in ATMOSPHERE is ensured by the group of independent physicians (and a statistician) on the DMC whose primary role is to protect the safety of patients enrolled in this trial.³ The DMC members are the only individuals during the course of the trial aware of treatment allocation, and these members have vast experience in conducting and monitoring trials in heart failure, especially trials with RAS blockers. The DMC have been informed of the results of ALTITUDE and have reviewed the findings of ATMOSPHERE in the light of this new information. Their recommendation is that ATMOSPHERE should continue as planned (DMC communication to ATMOSPHERE co-chairs 20 December 2011).

Based on the above considerations, the authors (who are the academic members of the Executive Committee of the trial) strongly believe that the ATMOSPHERE study should continue unchanged (including continued recruitment of patients with any of a history of hypertension, diabetes, or reduced renal function) with whatever scrutiny is deemed appropriate by the DMC. We believe that this situation is analogous to a previous example of a safety concern raised about a treatment in one condition but the same treatment continuing to be tested in a trial in heart failure.^{19–21} Of course, all patients are being informed of the results of ALTITUDE and will only continue in ATMOSPHERE if they are willing to sign an updated consent form.

Conflict of interest: All authors are members of the Executive Committee for the ATMOSPHERE trial and they or their institutions have received payment from Novartis for this role. J.J.V.M. is also a member of the Executive Committee of the ALTITUDE trial.

References

- McMurray JJ. CONSENSUS to EMPHASIS: the overwhelming evidence which makes blockade of the renin-angiotensin-aldosterone system the cornerstone of therapy for systolic heart failure. *Eur J Heart Fail* 2011;**13**: 929–936.
- Gheorghiadu M, Albaghdadi M, Zannad F, Fonarow GC, Böhm M, Gimpelewicz C, Botha J, Moores S, Lewis EF, Rattunde H, Maggioni A; ASTRONAUT investigators and study coordinators. Rationale and design of the multicentre, randomized, double-blind, placebo-controlled Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT). *Eur J Heart Fail* 2011;**13**:100–106.
- Krum H, Massie B, Abraham WT, Dickstein K, Kober L, McMurray JJ, Desai A, Gimpelewicz C, Kandra A, Reimund B, Rattunde H, Armbrecht J; ATMOSPHERE Investigators. Direct renin inhibition in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale and design of the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE) study. *Eur J Heart Fail* 2011;**13**: 107–114.
- Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, Ghadanfar M, Weissbach N, Xiang Z, Armbrecht J, Pfeffer MA. Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design. *Nephrol Dial Transplant* 2009;**24**:1663–1671.
- Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, Persson F, Nicolaidis M, Richards A, Xiang Z, Armbrecht J, Pfeffer MA. Baseline characteristics in the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE). *J Renin Angiotensin Aldosterone Syst* 2012;in press.
- Novartis.com. http://www.pharma.us.novartis.com/assets/pdf/TKT-1118923%20Dear_HCP_Letter_email_with%20Tek-Val%20PIs_vf.pdf
- Redon J, Mancia G, Sleight P, Schumacher H, Gao P, Pogue J, Fagard R, Verdecchia P, Weber M, Böhm M, Williams B, Yusuf K, Teo K, Yusuf S; ONTARGET Investigators. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). *J Am Coll Cardiol* 2012;**59**:74–83.
- ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;**362**:1575–1585.
- Reboldi G, Gentile G, Angeli F, Ambrosio G, Mancia G, Verdecchia P. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. *J Hypertens* 2011;**29**:1253–1269.
- European Medicines Agency http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500122919.pdf
- Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–1675.
- Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation* 2009;**120**:1577–1584.
- McMurray JJ, Pitt B, Latini R, Maggioni AP, Solomon SD, Keefe DL, Ford J, Verma A, Lewsey J; Aliskiren Observation of Heart Failure Treatment (ALOFT) Investigators. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail* 2008;**1**:17–24.
- Sidik NP, Solomon SD, Latini R, Maggioni AP, Wright M, Gimpelewicz CR, Pitt B, McMurray JJ. Effect of aliskiren in patients with heart failure according to background dose of ACE inhibitor: a retrospective analysis of the Aliskiren Observation of Heart Failure Treatment (ALOFT) trial. *Cardiovasc Drugs Ther* 2011;**25**: 315–321.
- Pitt B, Latini R, Maggioni AP, Solomon SD, Smith BA, Wright M, Prescott MF, McMurray JJ. Neurohumoral effects of aliskiren in patients with symptomatic heart failure receiving a mineralocorticoid receptor antagonist: the Aliskiren Observation of Heart Failure Treatment study. *Eur J Heart Fail* 2011;**13**:755–764.
- Maggioni AP, Latini R, McMurray JJ, Solomon S, Chung JO, Prescott MF, Keefe DL, Pitt B; on behalf of the ALOFT Investigators. Efficacy and tolerability of aliskiren added to optimized medical therapy in diabetic patients with heart failure. *Eur Heart J* 2008;**29**(suppl 1):255–503.
- McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;**362**:767–771.
- Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–776.
- Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJ, Parfrey P, Parving HH, Remuzzi G, Singh AK, Solomon SD, Toto R; TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;**361**:2019–2032.
- van Veldhuisen DJ, McMurray JJ; RED-HF Executive Committee. Are erythropoietin stimulating proteins safe and efficacious in heart failure? Why we need an adequately powered randomised outcome trial. *Eur J Heart Fail* 2007;**9**:110–112.
- McMurray JJ, Anand IS, Diaz R, Maggioni AP, O'Connor C, Pfeffer MA, Polu KR, Solomon SD, Sun Y, Swedberg K, Tendera M, van Veldhuisen DJ, Wasserman SM, Young JB; RED-HF Committees and Investigators. Design of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF): a Phase III, anaemia correction, morbidity-mortality trial. *Eur J Heart Fail* 2009;**11**: 795–801.