Diabetes, aliskiren, and heart failure: let’s bring ASTRONAUT down to earth

John G. Cleland1,2*, Andrew L. Clark2, Pierluigi Costanzo2, and Darrel P. Francis1

1 National Heart and Lung Institute, Imperial College London, London, UK; and 2 Hull York Medical School, University of Hull, Kingston-upon-Hull, UK

Online publish-ahead-of-print 2 September 2013

This editorial refers to ‘Effect of aliskiren on post-discharge outcomes among diabetic and non-diabetic patients hospitalized for heart failure: insights from the ASTRONAUT trial’, by A.P. Maggioni et al., on page 3117

ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes) failed to show that aliskiren was superior to placebo in reducing cardiovascular events when prescribed to patients with a reduced left ventricular ejection fraction who had recently recovered from worsening heart failure requiring hospital admission. Clinicians are tempted to look at outcome in patient subgroups because they are required to evaluate the efficacy and safety of an intervention for individual patients and believe that such analyses may help them in their practice. Unfortunately, subgroup analyses are commonly misinterpreted and often misleading.

In ASTRONAUT, interactions between the effects of treatment and patient characteristics were sought in 21 subgroups, including two separate analyses by age. For the primary endpoint, cardiovascular death or re-hospitalization for heart failure at 6 months, no statistically significant subgroup interactions were identified, although a trend \( (P = 0.08) \) was noted for diabetes. The analysis was then repeated for four secondary endpoints; now potentially 105 subgroup analyses. For all-cause mortality, this identified a nominally statistically significant subgroup interaction \( (P < 0.01) \) between treatment assigned and diabetes; patients who did not have diabetes who were assigned to aliskiren appeared to fare better. This led the investigators to speculate that the neutral outcome in ASTRONAUT might be due to a lack of effect, or even harm, amongst patients bearing a diagnosis of diabetes mellitus and that substantial benefit may have accrued in other patients. However, the simplest explanation for most subgroup effects is a chance observation due to multiple testing.

Some corroborative evidence can be found suggesting that aliskiren might be harmful in patients with diabetes. ALTITUDE (Aliskiren Trial In Type 2 Diabetes Using Cardio-Renal Disease Endpoints) investigated the effects of aliskiren in 8561 patients with type 2 diabetes (T2DM) and chronic kidney or cardiovascular disease. The study was stopped prematurely because the risk/benefit ratio was considered unattractive after a median follow-up of almost 3 years. Trends to an excess of cardiovascular deaths (5.8% vs. 5.0%), stroke (3.4% vs. 2.8%), and end-stage renal disease (2.8% vs. 2.6%) were noted in patients assigned to aliskiren. Although the study did not provide conclusive evidence of harm from aliskiren, it provided no evidence of benefit. An excess of hyperkalaemia, hypotension, diarrhoea, and renal impairment was observed in those assigned to aliskiren. As a consequence of the results of ALTITUDE and ASTRONAUT, regulatory authorities required investigational treatment to be withdrawn from patients with diabetes in ATMOSPHERE (Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure), a study of >7000 patients with heart failure and left ventricular systolic dysfunction comparing aliskiren and enalapril alone and in combination. This decision was made against the recommendation of the data monitoring committee that had full access to the data, implying that they had no concerns about the safety of adding aliskiren to enalapril in patients with diabetes.

The possibility of an interaction between the effects of aliskiren and diabetes raises at least three important issues. (i) What was the definition of diabetes? (ii) What was the mechanism of benefit in patients without diabetes? (iii) Why was this benefit lost or reversed in those with diabetes?

As the authors admit, the diagnosis of diabetes was not robust. Indeed, it is not clear that T2DM, as currently defined, should be considered a discrete disease entity. Classical, type 1 diabetes mellitus due to insulin deficiency causes symptoms, morbidity, and death unless treated by insulin. In contrast, patients labelled as having T2DM have high plasma concentrations of insulin due to resistance to its effects and is usually asymptomatic. Although T2DM augurs an increase in long-term cardiovascular risk, there is scant evidence that ‘improving’ glucose control is beneficial, except in extreme cases. The current definition of T2DM is arbitrary, based on laboratory tests. However, there is a continuous spectrum of insulin resistance. It is not a question of whether someone has insulin resistance or not, just a question of how much; patients with heart failure will generally have more. Insulin resistance is strongly related to the health and mass of skeletal muscle. Inactivity, by choice

* Corresponding author: Hull York Medical School, University of Hull, Kingston-upon-Hull HU6 5JQ, UK. Tel: +44 1482 46 1776, Fax: +44 1482 46 1779. Email: j.g.cleland@hull.ac.uk

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

1 doi:10.1093/eurheartj/ehx342

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2013. For permissions please email: journals.permissions@oup.com
or as a consequence of disease, and age impair insulin sensitivity by reducing the metabolic mass of skeletal muscle. From the cardiovascular perspective, in a largely sedentary population, obesity may be a harmless, or possibly protective, by-product of insulin resistance. Presumably carrying extra weight imposes greater stress on skeletal muscle for a given activity. The dogma that obesity is bad is now being sorely tested by the increasing evidence that moderate obesity, especially amongst older people, including those with diabetes, is associated with lower cardiovascular mortality.\textsuperscript{11,12} Low or normal body weight is bad news for those with heart failure.\textsuperscript{13} Obesity may be a stress test of the integrity of the relationship between insulin and glucose. Those with poor glycemic control because they are obese may be at much lower metabolic risk than those who have poor glycemic control despite the absence of obesity-induced stress.

In ASTRONAUT, as might be expected, patients with diabetes were slightly older, more likely to have ischaemic heart disease, had slightly worse renal function, and were more likely to be treated with an angiotensin receptor blocker (ARB) than an angiotensin-converting enzyme (ACE) inhibitor. Patients aged \textgtrless 75 years and those with a glomerular filtration rate of \textasciitilde 60 mL/min/1.73 m\textsuperscript{2} were also less likely to benefit from aliskiren, and diabetes might merely have been acting as a surrogate for one or both of these.

Type 2 diabetes mellitus should be associated with an increased rate of adverse cardiovascular and renal events. In the placebo group of ASTRONAUT, there were fewer deaths in patients with diabetes (16.6\% vs. 19.6\%), an effect that was driven by lower cardiovascular mortality, and only a slightly higher rate of first cardiovascular events over 12 months (42.0\% vs. 38.1\%). At least part of the observed interaction between aliskiren and diabetes appears to have been driven by an unexplained, possibly spurious, low event rate amongst patients with a diagnosis of diabetes assigned to placebo. Such observations in small subsets of patients are common.

How might aliskiren have delivered benefit? Aliskiren suppresses the generation of angiotensin-I\textsubscript{L}, reducing the risk that inhibition of ACE will be overwhelmed by an excess of its substrate and possibly by reducing the generation of angiotensin-II by other pathways. There is a large body of evidence suggesting that several agents that block the renin–angiotensin–aldosterone system (RAAS) improve outcomes.\textsuperscript{14} It is clear that adding mineralocorticoid antagonists (MRAs) or beta-blockers to ACE inhibitors improves long-term survival of patients with chronic heart failure associated with left ventricular systolic dysfunction. The evidence for a benefit of adding ARBs to ACE inhibitors is less robust.\textsuperscript{14} As with ARBs, the effect of aliskiren appeared greater in the small subgroup of patients who were taking neither an ACE inhibitor nor an ARB [hazard ratio 0.75, 95\% confidence interval (CI) 0.44–1.29 for those taking these agents compared with 0.95, 95\% CI 0.78–1.17 for those who were not], although, as for the subgroup interaction for diabetes, this was not significant. The simplest explanation for benefit is that aliskiren is a useful alternative to other means of suppressing RAAS activity. Only \textasciitilde 60\% of patients were treated with an MRA, and patients who had diabetes and were assigned to aliskiren were less likely to receive this treatment. The apparent underutilization of MRAs in this study requires explanation. The study might have been even more neutral had patients been more intensively treated with conventional therapy. Presumably the RAAS exists for a reason. Genetic models suggest that knocking out renin completely is not a good thing.\textsuperscript{15} Renin inhibition may reduce the production of angiotensin 1–7, a molecule that is thought to have cardioprotective and anti-fibrotic effects.\textsuperscript{16} As with most things in life, too much or too little is bad. Achieving the right amount, in the appropriate context, is likely to lead to the best outcome.

No adequate explanation for why a diagnostic label of diabetes should determine the benefits of aliskiren has been identified. Patients with diabetes may have been slightly more likely to develop hyperkalaemia, but the effect does not appear large enough to account for an adverse effect on prognosis. However, serum potassium concentrations fluctuate markedly throughout the day, and single measurements may not represent the true risk of hyperkalaemia. Potassium is a powerful stimulus to aldosterone secretion, and hyperkalaemia may have accounted for less suppression of aldosterone by aliskiren in patients with diabetes who were not taking MRAs. Had appropriate statistical tests been applied it is unlikely that a different effect of aliskiren in patients with and without diabetes on any biomarker other than aldosterone would have been reported.

In summary, aliskiren might be a valuable additional or alternative treatment for heart failure. If it is effective only in some subgroups and the effect is substantial, then this should be welcomed, but it will require careful definition of the relevant subgroups and plausible explanations for why it is selectively effective. The simplest explanation of the results of ALTITUDE and ASTRONAUT is that aliskiren does not improve outcome when added to other agents that block the RAAS. The results of ATMOSPHERE are eagerly awaited despite treatment being curtailed in patients with diabetes. If ATMOSPHERE suggests a similar interaction between aliskiren and diabetes, then further investigation of the mechanisms will be required. This should provoke a review of whether T2DM is a real identifiable disease and, if so, how it should be defined.

**Conflict of interest:** J.C. is an investigator in the ATMOSPHERE trial and has received research funding from Novartis.

**References**


4. Freemantle N. Interpreting the results of secondary end points and subgroup analyses in clinical trials: should we lock the crazy aunt in the attic? BMJ 2001;322:989–991.


