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

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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.1,2 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.3–5

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 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 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a consequence of the results of ALTITUDE and ASTRONAUT, regulatory authorities required investigational treatment to be withdrawn from patients with diabetes in ATMOSPHERE (Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure), a study of 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.7,8 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.9 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.10 Insulin resistance is strongly related to the health and mass of skeletal muscle. Inactivity, by choice

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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 glycaemic control because they are obese may be at much lower metabolic risk than those who have poor glycaemic 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 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 antifibrotic 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.

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\textbf{References}


