Too much is too much: evidence against dual RAAS inhibition in hypertensives with heart failure symptoms

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This editorial refers to ‘Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial’\(^1\), by Y. Sakata et al., on page 915.

The Supplemental Benefit of an Angiotensin Receptor Blocker in Hypertensive Patients with Stable Heart Failure Using Olmesartan (SUPPORT, NCT00417222) trial, a prospective, randomized, open-label blinded endpoint study reported by Sakata et al. in this issue of the journal, demonstrated that additive use of angiotensin receptor blockers (ARBs) did not improve clinical outcomes but worsened renal function in hypertensive patients with symptoms of heart failure (HF) treated with angiotensin-converting enzyme (ACE) inhibitors and beta-blockers.\(^1\) In particular, the triple combination therapy with olmesartan, ACE inhibitors, and beta-blockers was associated with increased incidence of all-cause death and renal dysfunction, whereas the dual combination of olmesartan and ACE inhibitors or beta-blockers was not associated with any increase in primary [composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and worsening chronic HF (CHF) requiring hospitalization] or secondary (the modes of death, hospitalization for cardiovascular reasons, surrogate markers for CHF, and development of cardiovascular disease, atrial fibrillation, diabetes, and renal failure) endpoint. Furthermore, combination of olmesartan and beta-blockers was associated with decreased mortality without development of renal dysfunction.

Neurohormonal dysregulation plays a crucial role in the pathophysiology of HF with reduced ejection fraction (HFrEF). The strategy of inhibiting the renin–angiotensin–aldosterone system (RAAS) has led to remarkable advances in the treatment of CHF patients with or without hypertension.\(^1\) ACE inhibitors have been shown to reduce mortality significantly in all grades of HFrEF (CONSENSUS\(^3\) and SOLVD-Treatment\(^4\)) and left ventricular dysfunction after myocardial infarction (SAVE\(^5\)) by inhibiting conversion of angiotensin I to angiotensin II and multiple beneficial effects at the cellular level on apoptosis, fibrosis, and hypertrophy. Thereby, cardiac remodelling, particularly fibrosis, has been repeatedly shown to attenuate left ventricular remodelling and to improve left ventricular function. Since ARBs do not inhibit bradykinin breakdown and do not cause cough or angioedema, it was anticipated that they would be better tolerated than ACE inhibitors and may extend the theoretical benefit of unopposed angiotensin II receptor agonism. The CHARM-Added trial\(^6\) found that candesartan reduced both HF hospitalization and cardiovascular mortality. However, in the Val-HeFT trial,\(^7\) addition of valsartan did not lower mortality but reduced hospitalization due to CHF. In head-to-head comparisons, ARBs have been shown to be non-inferior (VALIANT\(^8\)), but not superior, to ACE inhibitors (ELITE II\(^9\)).

However, neither ACE nor angiotensin II receptor type 1 (AT1) inhibition alone fully block the RAAS. With the evidence of the above-mentioned trials showing the beneficial effects of ACE inhibitors and ARB and the strong pathophysiological background, studies investigating the effect of a dual RAAS inhibition using combined treatment strategies were pathophysiologically plausible and promising. However, subsequent trials investigating an add-on therapy of an ARB to an ACE inhibitor did not find any benefit in patients with acute myocardial infarction (VALIANT\(^8\)), patients with stable coronary artery disease (ONTARGET\(^10\)), or patients with chronic kidney disease (VA NEPHRON-D\(^11\)). Notably, patients receiving the combination therapy had increased rates of hypotension, renal dysfunction, and hyperkalaemia, and were characterized by a higher rate of permanent discontinuation of trial medications. In the trial published by Sakata et al., the dual combination of olmesartan and ACE inhibitors was not associated with an elevated primary or secondary endpoint.\(^1\) However, olmesartan and ACE inhibitors combined with...
beta-blockers, a class Ia recommended treatment strategy for CHF and used in 91% of CHF patients in the multicentre REFLECT HF registry, was associated with an increased all-cause mortality. Taken together, several studies showed that dual RAAS blockade does not provide an additional clinical benefit compared with standard HF therapy, but even causes harm to the patients.

The pathophysiological concept of a complete RAAS blockade was further challenged by the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE), which compared the combination of an ACE inhibitor or an ARB with the direct renin inhibitor aliskiren with ACE inhibitors/ARB monotherapy. This trial failed to show a benefit on cardiovascular or renal outcomes, and thus was stopped prematurely after the second interim efficacy analysis on the recommendation of its Data Monitoring Committee after it found an increased occurrence of adverse effects and continuation of the study was deemed useless. Furthermore, the double-blind Aliskiren Trial On Acute heart failure oUTcomes (ASTRONAUT) study in which haemodynamically stable hospitalized HF patients with left ventricular ejection fraction of ≤ 40% were randomly assigned to aliskiren or placebo daily, in addition to standard therapy, did not find a reduction in the main outcome measures of cardiovascular death or rehospitalization due to CHF, while the rates of hyperkalaemia, hypotension, and renal impairment/renal failure were higher in the aliskiren group compared with the placebo group at 6 and 12 months.

In response to the negative results, it has been recommended that dual aliskiren and ACE inhibitor/ARB therapy should not be used in patients with both hypertension and diabetes or moderate to severe renal dysfunction. This led to questions about the ongoing Aliskiren Trial of Minimizing Outcomes for Patients with HEmorrhagic failure (ATMOSPHERE), where patients with systolic HF and an elevated brain natriuretic peptide concentration are randomized to either enalapril twice daily, aliskiren once daily, or the combination of both agents. However, the patients in ALTITUDE are quite different from those in ATMOSPHERE. Therefore, the results of ALTITUDE should not lead to any premature appraisal of ATMOSPHERE.

The crucial question is what kind of patients were treated in the SUPPORT trial? Patients had mild symptoms of HF and 93% were in New York Heart Association (NYHA) class II. They had apparent hypertension and potentially non-controlled blood pressure. Therefore, it is open whether mild symptoms of HF are limitations due to blood pressure not being controlled at rest or during exercise. In this situation, the patient population appears to be more close to that in the TRANSCEND trial, which chose the same primary endpoint as SUPPORT and failed to achieve it. Even in high-risk patients of TRANSCEND with non-controlled hypertension, there was only a minor effect with the AT1 antagonist telmisartan even in the absence of an ACE inhibitor, because ACE inhibitor-intolerant patients were studied. If these patients really were in HF, it has to be pointed out that the power of the trial was limited by the lower number of included patients, because only 1147 patients were randomized. In patients with systolic HF, there is an inverse relationship between outcome and blood pressure elevation compared with hypertensives. Therefore, a low number of patients included and low event rates by selecting patients with a good prognosis by high blood pressure limit the power in SUPPORT to show any effects. In patients with moderately reduced activation of the RAAS, such as vascular patients, adverse renal effects had to be expected as shown in ONTARGET on double RAAS blockade. Finally, the ejection fraction in this trial was quite high. So, it appeared to be a mixed population of patients with preserved and impaired ejection fraction. Taking into consideration that AT1 antagonists are ineffective in cases of preserved ejection fraction, this provides an explanation of the failure of the AT1 antagonist olmesartan to provide beneficial effects. Finally, this study was only performed in an Asian and, in particular, Japanese population. Low body weight, although addressed by dosing, might have contributed to increased adverse effects in renal function.

In conclusion, RAAS blockade by ACE inhibition is a main cornerstone in the treatment of HFrEF, with abundant evidence deriving from numerous clinical trials. ARBs clearly represent an excellent treatment alternative in patients which are intolerant to ACE inhibitors. As shown by several clinical trials, a combined RAAS blockade does not provide additional benefit compared with ACE inhibitor/ARB therapy alone but can even cause harm and renal dysfunction. This was again corroborated by the present study, which even showed increased mortality rates in patients receiving dual RAAS blockade combined with beta-blockers.

Conflict of interest: none declared.

References


