Editorial

Angiotensin Receptor Blockers for Heart Disease: Are They the Same?

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Cardiovascular diseases (CVD) are the leading cause of death in many developed and developing countries, such as China, The modifiable risk factors for CVD are well recognized and appear to be applicable to different ethnic groups world-wide[1] and include hypertension, diabetes mellitus and hypercholesterolaemia. The occurrence of each of these risk factors contributes about 2-4 times to the risk of myocardial infarction and when they occur in combination the risk increases geometrically. Apart from anti-platelet and lipid lowering therapy, are there specific medical agents that can ameliorate the risk of CVD?

The renin-angiotension system (RAS) is a ubiquitous hormonal system present in the circulation and specific tissues such as the heart, kidneys, blood vessels and the brain,[2] and has been implicated as a pathogenic mediator of CVD. Blockade of the RAS using angiotension converting enzyme inhibitors (ACEI) has been shown to be effective for blood pressure control, heart failure prevention and treatment, stroke reduction and renal preservation (especially in the presence of diabetes mellitus). These seem to be class effects rather than agent-specific. Of particular interest is the ability of ACEI to prevent CVD deaths, myocardial infarction or stroke as observed in the use of ramipril in the Heart Outcome Prevention Evaluation (HOPE) trial,[3] in patients with established coronary artery disease, peripheral or cerebrovascular disease or diabetes with end-organ damage. This beneficial impact was subsequently confirmed in other placebo controlled randomised studies using perindopril and enalapril.

These observations are thought to be independent of blood pressure lowering effect by the ACEI. As such, ACEI should be considered along with antiplatelet and lipid lowering therapy for preventing adverse CVD outcomes.

However, the use of ACEIs has its own set of complications. They include hypotension, renal dysfunction and especially unproductive cough. In one study[4] in heart failure patients, about 20%, could not tolerate the ACEI.

On the contrary, type I angiotensin receptor blockers (ARB) act down-stream to ACEIs. Thus, unlike the latter, ARBs do not interfere with the action of alternative vasoactive compounds (such as bradykinin) and other mediators. So might they be able to offer similar benefits but be better tolerated? Furthermore, will there be added benefit in combining ACEI and ARB?

In patients with symptomatic systolic dysfunction, two ARBs have been shown to be effective. Valsartan has been compared with captopril in patients with recent myocardial infarction,[5] in which the former at 160 mg/day was similar to captopril for CVD outcomes. However, the combination of captopril and 80 mg valsartan increased the liability to hypotension without benefit for primary endpoints. However, the use of

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valsartan in patients with symptomatic heart failure with a background of ACEI reduced hospitalization in heart failure patients.[6] Similarly in patients with symptomatic heart failure with a recent history of hospitalization, candesartan at a target dose of 32 mg reduced death and hospitalization in those intolerant of ACEIs,[7] and further benefits may ensue if given in combination with low doses of ACEI.[8] The use of this possibly beneficial combination, is nevertheless associated with more hypotension, and increases creatinine and potassium levels. The use of other ARBs has either not been studied or found not to be effective in heart failure patients. About 30% of those hospitalized with heart failure have normal or mildly depressed ejection fractions (≥40%), and several randomised studies have been carried out in this patient population. Candesartan has been shown to be marginally effective in reducing hospitalization and death compared to placebo (p=0.051), particularly the former.[9] On the other hand, the recently reported i-PRESERVE study using irbesartan 300 mg daily[8] in the elderly with class II or higher grades of heart failure with normal ejection fraction did not yield improved CVD outcomes. Reasons for such differences may be related to the dose of irbesartan used, the high concomitant use of ACEIs (>1/3), and non-adherence to ARB therapy. In this regards, an earlier published study[10] of a collaborative effort from the two Hong Kong universities also reported absence of benefit of ramipril or irbesartan in this patient group.

Preventing CVD outcomes has been tested using telmisartan (80 mg) versus ramipril (10 mg) using a protocol similar to the HOPE study. In the ON TARGET study,[11] telmisartan was shown to be non-inferior to ramipril in reducing untoward CVD outcomes, but had a lower incidence of cough (1.1 vs 4.2%, p<0.001) and angio-oedema (0.1 vs 0.3%, p<0.001). However, the combination of telmisartan and ramipril increased the liability to hypotension, syncope and worryingly renal dysfunction that may require dialysis. Thus such a combination should not be used in this population. Similarly, in patients with ACEI intolerance, whilst telmisartan confers reduction of CVD complication in this patient population, combining ACEI and ARB have been reported to increase the liability to hypotension, renal dysfunction and medication withdrawal in heart failure patients.[12]

Conclusion

How are we going to synthesize these sets of conflicting data? While blood pressure lowering effects of ARBs appear class specific, the same cannot be said for the treatment of heart failure and prevention of CVD outcomes in high risk patients. Based on randomised trials, valsartan and candesartan have been shown to be effective for symptomatic heart failure, and they constitute effective alternatives for those who are ACEI intolerant. Candesartan may confer marginal benefits in terms of hospitalization when added to ACEIs. However, the use of ACEI and ARB together should be balanced against the higher risk of adverse effects, especially worsening renal function. Amongst all ARBs, only candesartan has been shown to be effective for patients with heart failure in patients with relatively preserved left ventricular function. For preventing adverse CVD outcomes, ACEIs constitute the preferred treatment, but telmisartan used alone is a useful alternative for patients in whom ACEI intolerance is a potential or established concern.

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