Is the jury out?
Class specific differences on coronary outcomes with ACE-inhibitors and ARBs: insight from meta-analysis and The Blood Pressure Lowering Treatment Trialists’ Collaboration

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This editorial refers to 'Do angiotensin II receptor blockers increase the risk of myocardial infarction?'† by P. Verdecchia et al., on page 2381

Over the past year there has been fervent discussion and debate as to whether angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) offer similar coronary vascular protection.1–3 A widely held belief is that ARBs may be used interchangeably with ACE-Is, and that each regimen would offer a similar reduction in coronary vascular outcomes; a notion that argues against the concept of an ACE-I-specific, blood pressure-independent vascular protective effect relative to ARBs. The Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC), recently presented at the European Society of Hypertension (ESH) and provides important insight into this matter.4

The BPLTTC is a prestigious group of clinical trialists’ that is conducting prospectively planned meta-analysis of blood pressure lowering trials.5 At the 15th meeting of the ESH, Dr Turnbull presented the largest and most comprehensive meta-regression analysis of ACE-Is and ARBs.4 In this analysis, the reduction in systolic blood pressure was plotted against the relative risk of the pre-specified end-points of stroke, heart failure, and coronary heart disease. In this study of 21 large-scale randomized trials [16 trials with ACE-Is (AASK, ABCD (H), ABCD (N), ALLHAT, ANBP2, CAPP, DIAB-HYCAR, EUROPA, HOPE, JMIC-B, PART-2, PEACE, PROGRESS, SCAT, STOP-2, UKPDS-HDS) and 5 trials with ARBs (IDNT-placebo and CCB, LIFE, RENAAL, SCOPE, VALUE)], involving 137 356 patients, the BPLTTC concluded that although there were no differences in risk reduction between ACE-Is and ARBs, with respect to the outcomes of stroke and heart failure, a highly statistically significant (P = 0.001) benefit of ACE-I relative to ARBs on myocardial infarction (MI) and cardiovascular death was apparent. To our knowledge, this is the most robust data to support the notion that ACE-Is may offer greater coronary vascular protection compared with ARBs, and that this effect is beyond what could be expected by blood pressure lowering alone. The analysis of the BPLTTC provides clinicians and patients with important information. For patients who are intolerant of an ACE-I, an ARB appears to offer equal risk reduction in terms of stroke and heart failure, recognizing that the effects of an ACE-I on coronary vascular outcomes may exceed that of an ARB. These data add credence to the BPLTTC statement ‘if one regimen proved even slightly better than another, then preferential use of the more effective regimen might prevent tens of thousands of major cardiovascular events every year’.5 It would be appropriate to consider the BPLTTC analysis as an interim verdict of equivalence of the two classes with respect to cerebrovascular outcomes and heart failure, and superiority of ACE-Is for coronary vascular protection with reductions in MI and cardiovascular death.

Much of the discussion about differences between the two classes of renin–angiotensin system inhibitors with respect to coronary outcomes surfaced after a recent editorial,1 which commented that ARBs may not offer similar coronary vascular protection as ACE-Is, and in some isolated trials appeared to be associated with an unexplained increase in MI. The opinions expressed in the editorial with respect to non-equivalence of the two regimens, with respect to CHD, have been systematically evaluated by the BPLTTC, and as discussed earlier, appears to hold true at the present time. Whether ARBs increase MI remains debated.6 Verdecchia et al.6 provide the first meta-analysis suggesting that ARBs, while not associated with an increase in MI, are neutral in terms of coronary vascular protection outcomes.
It is important to emphasize that the methodology employed in this meta-analysis may be challenging to interpret, given the heterogeneity of the trials, especially with respect to mortality. There appeared to be incongruity of the results for the three different subgroups. For example, in the analysis of ACE-I vs. ARB, the authors reported no difference in MI. However, in the subgroup of ARB vs. non-ACE-I therapy (IDNT, LIFE, and VALUE), the ARB group exhibited a preponderance of MI. The assumption that perhaps the non-ACE-I therapy with atenolol or amlodipine, the comparator drugs in these trials, may have reduced MI, compared with the ARB is not supported by the current data. Recently, we have learnt that atenolol in high-risk hypertensive patients does not reduce MI or death, despite effective blood pressure lowering.7 Likewise, dihydropyridine calcium channel blockers compared with placebo in patients with coronary artery disease also appear not to reduce MI or death, despite significant blood pressure lowering, improvement in angina, and reducing the need for both hospitalizations and revascularization.8 In this fashion, the interpretation of the results of the subgroups remains elusive.

It is always challenging to perform a meta-analysis of trials that have different inclusion and exclusion criteria, and have varied background therapies, and the current analysis is no exception. For example, a meta-analysis conducted to evaluate the impact of ARBs on MI, including the CHARM-Added, Val-HEFT, and VALIANT trials, may be criticized by the purest, because 100% of patients in CHARM-Added and 93% in Val-Heft had background therapy with ACE-I. Likewise, in VALIANT, 39% of the patients received non-study ACE-I prior to randomization, which averaged the fifth day post-MI. ACE-I have their greatest mortality reduction in the early post-MI period (7% RRR in 30 days), with 85% of the benefit within the first week.9 Although captopril and valsartan had similar mortality rates at study end, this is in the face of a large number of patients having received early therapy with ACE-I. Therefore, it remains unknown as to whether an ARB driven regimen would offer equal mortality reduction in ACE-I naive patients post-MI. For example, in the OPTIMAAL trial, a study of post-MI heart failure with losartan vs. captopril, no difference in MI rates was observed, although captopril treatment was associated with a significantly greater reduction in cardiovascular death compared with losartan. This sentiment is probably reflected in the recent European Union indications, wherein Valsartan is indicated in the treatment of symptomatic heart failure when an ACE-I cannot be used, or as add-on therapy to ACE-I when beta-blockers cannot be used. This supports the statistical principle that the 'non-inferiority' of valsartan relative to captopril demonstrated in VALIANT does not imply equivalence; rather it simply implies that 'one therapy is not substantially worse than the other'.10

One of the main criticisms of the current meta-analysis, is that the impact of blood pressure changes in the trials is not accounted for, a critical variable as illustrated by the BPLTTC analysis. This is surprising, as the same authors recently published a meta-regression analysis of ACE-I and calcium antagonists in Hypertension,11 where they concluded that a 10 mmHg reduction in systolic blood pressure reduced MI plus cardiovascular death by 15% in high-risk patients and further, that ACE-inhibition offered coronary vascular protection over and above what could be accounted for by blood pressure lowering, very similar to the recent analysis by the BPLTTC. The use of a similar meta-regression in the current article may have allowed a more accurate interpretation of the data with respect to ARBs and MI.

Although we recognize the central importance of blood pressure reduction towards vascular protection, it would be remiss to ignore examples of trials, where blood pressure reduction was not associated with reduction in CHD events. For example, in the CHARM-Alternative trial, candesartan vs. placebo lowered blood pressure 4.4/3.9 mmHg, but had a 36% increase in MI. In CHARM-Preserved, candesartan vs. placebo had no impact on an 11.3% mortality rate, despite lowering blood pressure by 7.3/3 mmHg (170 deaths vs. 170 deaths), while irbesartan vs. placebo in IDNT reduced blood pressure 4/3 mmHg, but had no impact on the 24% cardiovascular event rate. Further insight has been recently published by Strippoli et al.12 in a Cochrane meta-analysis, echoing the proven superiority of ACE-I (vs. ARBs) in reducing death in diabetic nephropathy.

More challenging is defining the impact that a 1.8/1.5 mmHg blood pressure differential in favour of amlodipine over valsartan in VALUE. The authors suggest that this blood pressure differential could account for the 19% preponderance in MI with valsartan. They supported this hypothesis with both a post hoc analysis of serial median matching and a division of the follow-up period into consecutive intervals. This was argued against in a subsequent analysis of VALUE suggesting that for a systolic blood pressure gradient of 2.2 mmHg as seen in VALUE, the predicted odds ratio was 0.98 for MI compared with an observed risk ratio of 1.19 in VALUE (P = 0.03), and stated that ‘with regards to MI, the results of valsartan-based treatment were worse, or conversely, those of amlodipine-based treatment were better, than predicted from the gradient in the achieved systolic blood pressure’.3

A question has been raised as to whether mechanistic differences between ARBs and ACE-I might account for the observed differences in terms of coronary vascular protection.2 Although mechanisms cannot be unequivocally linked to clinical trial data, we take this opportunity to highlight some of these differences, which may have implications for the CHD risk reduction. ARBs selectively block the AT1 receptor, while allowing for unopposed stimulation of the AT2 receptors. The role of the AT2 receptors, although less well defined than the AT1 receptor, have been suggested to counterbalance the deleterious effects of AT1 and produce nitric oxide during chronic stimulation by an ARB.13 However, recent data have accrued to suggest that the physiology of AT2 may be more complex than previously appreciated, and that it may also exhibit deleterious pro-atherogenic and pro-inflammatory effects13 which theoretically may be heightened during chronic AT2 stimulation with an ARB. Less well known is the role that AT4 receptors play in vascular disease. Activation of the AT4 receptor stimulates synthesis of plasminogen activator inhibitor (PAI-I). Although both ACE-I and ARBs may have effects to attenuate PAI-1 levels, in head to head comparisons between ARB and ACE-I for similar blood pressure reduction in insulin resistant hypertensive subjects, ACE-I offered a greater reduction in PAI-1.2 ACE-I are also distinguished from ARBs by their ability to prevent the degradation of bradykinin. Bradykinin not only improves

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endothelial function, but also mediates both the early and late phases of ischaemic pre-conditioning.²

It is apparent that there has been intense discussion with resultant scientific pursuit to evaluate the potential biological differences between ACE-I and ARBs, in respect to coronary vascular outcomes. The BPLTTC have confirmed the superiority of ACE-I over ARB in preventing MI and death.⁴ Furthermore, a meta-regression analysis¹¹ has also confirmed that ACE-I reduce MI and death above that of blood pressure lowering alone in high risk and hypertensive patients. To date, ACE-I should be initiated in all patients with CHD with or without heart failure or left ventricular dysfunction (independent of blood pressure), and in most patients with diabetes, as the drug of choice in the modulation of the renin–angiotensin–aldosterone system. ARBs are a viable alternative for heart failure, hypertension, and diabetes when ACE-I are not tolerated and a consideration for add on to ACE-I for certain patients with heart failure; there is no proof of benefit of ARBs for the large number patients with chronic stable CHD in the absence of heart failure. The meta-analysis by Verdecchia et al.,⁶ despite methodological limitations, suggests that while ARBs do not augment the risk of MI, they are neutral in terms of protecting against coronary vascular events. This appears to be the interim verdict, while the jury awaits the results of further randomized controlled trials, such as ONTARGET/TRANSCEND and population-based cohort trials.

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