had similar myocardial infarction rates, but cardiovascular mortality was significantly greater with losartan when compared with captopril (RRR 1.17, 95% CI 1.01–1.34, \( P = 0.032 \)). In Volpe’s meta-analysis, the myocardial infarction data for VALIANT-favoured valsartan, but the number of patients with myocardial infarction is in fact greater with valsartan than captopril as reported by McMurray et al.10 (587 vs. 559, respectively). CHARM Added was appropriately excluded from the meta-analyses as background therapy included ACE-inhibitors but VALIANT should also have been excluded, as 39% of patients received ACE-inhibitor prior to randomization.3

It cannot be emphasized enough, that an apparent lack of difference between ACE-inhibitors and ARB in these meta-analyses does not meet the “burden of proof” that a difference does not exist. Even with out large trial data comparing ACE-inhibitors and ARB directly, the evidence from individual trials of ACE-inhibitors and ARB suggest that ACE-inhibitors have a unique vascular protective effect on blood pressure lowering,4 whereas the meta-analyses suggest ARB are at best, vascular neutral.5–8 The results from the two recent large meta-regression analyses that included over 310,000 patients are consistent with these conclusions.2,3

The distinct difference between ACE-inhibitors and ARB on coronary artery events may reflect their unique mechanisms of action. Despite both modulating the renin–angiotensin system, ACE-inhibitors decrease angiotensin II levels, whereas ARB block the AT1 receptor, which in turn inhibits a negative feedback loop resulting in angio-
tensin II levels that increase three to five-fold over baseline. ARB result in unopposed stimulation of both AT2 which shares many of the deleterious effects of AT1, as well as AT4, which promotes the release of prothrombotic PAI-1. ACE-inhibitors upregulate bradykinin levels which enhances vascular protection via endothelial function, ischaemic preconditioning, and fibrinolysis.11

‘Is the jury out’ or ‘Is the jury in?’ is simply a metaphor, which recognizes that ‘while knowledge will continue to evolve, therapeutic choices must be made today.’ ACE-inhibitors should be considered as first-line therapy in preference to ARB for the high-risk patient.

References

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Letters to the Editor

Three-year duration of benefit from abciximab in patient receiving stents for acute myocardial infarction in the randomized double-blind ADMIRAL study

We would like to raise the following issues in response to the article reporting results of the ADMIRAL study by Montalescot et al.1

Although the initial ADMIRAL trial2 demonstrated superiority of combined glycoprotein IIb/IIIa receptor inhibitor and coronary stenting therapy, the outcomes of the 3-year follow-up data are subject to limitations. First, the effect of confounders such as status of coronary risk factors, life style modifications and treatment compliance in both study groups on outcomes at 3 years of unblinded follow-up is unclear.

Secondly, ascertainment of outcomes is subject to recall bias when self-reported data from a patient questionnaire is utilized for surveying endpoints.3 If recall bias exists, this can lead to misclassification of outcomes that may invalidate study findings.

Further, the results of primary and secondary endpoints were either marginal or not statistically significant at an alpha level of 0.05 with wide confidence intervals that include the null hypothesis. Therefore, caution needs to be exercised when concluding that the ‘treatment elicits favourable clinical outcomes through the third year’, given the marginal differences between treatment groups, especially when the role of bias and confound-

Blinded, controlled long-term randomized interventional studies are further needed to clarify the interesting observations raised by this informative study.

References

Three-year duration of benefit from abciximab in patient receiving stents for acute myocardial infarction in the randomized double-blind ADMIRAL study: reply

We have read carefully Dr Kanna’s comments trying to perform a critical appraisal of our manuscript, but it appears that most of these critics are inaccurate. Potential confounders such as coronary risk factors are important to consider, but by definition randomization is used to balance the different groups and the ADMIRAL study was randomized and the two study groups were well balanced for all baseline characteristics. Treatment compliance, another concern in Dr Kanna’s letter, is unlikely to be an issue because abciximab is administered intravenously for 12 h during and immediately after PCI and of course there was no further study drug administration during the 3-year follow-up of the ADMIRAL study. Blinded evaluation is another criterion of quality for studies and an issue in the letter; however, this critic does not apply to our study; of all randomized studies testing abciximab in primary stenting of STEMI, ADMIRAL remains, so far, the only double blind study. Moreover, the 3-year follow-up was performed blindly as indicated in Methods.

The following concern in the letter is about the validity of self-reporting data in patient questionnaires but as we indicated this was not the only mode of data collection, and physicians were surveyed, medical records consulted and for hard endpoints, especially mortality which was the main objective, self-reporting is clearly not an issue.

Finally, the author does not concur with the conclusions of a favourable effect of abciximab in primary stenting of STEMI. However, ADMIRAL is a positive study for its primary hypothesis showing the superiority of the study drug over placebo to reduce death, re-infarction, and urgent revascularization at 30 days, confirmed also at 6 months. Because we believe that it is important to provide information on the long-term, a three-year follow-up was conducted to determine whether the benefit observed initially was preserved; we acknowledged that the study was not powered to detect a difference in hard clinical endpoints at 3 years. However, the expression of the results with Kaplan-Meier curves demonstrated the preservation of the initial absolute benefit, with two parallel curves for death or MI, over 3 years.

Our data along with other studies confirm the benefit of GPIIbIIIa inhibition with abciximab in primary PCI. Meta-analyses have also shown a significant impact on mortality and a greater benefit when the drug is administered early. All guidelines recommend its use in primary PCI.

References


