Letters to the Editor

doi:10.1093/eurheartj/ehi887

Online publish-ahead-of-print 12 May 2006

Dyspnoea after AZD6140: safety first?

Husted et al. published dose-finding Phase 2 randomized study comparing novel oral reversible platelet P2Y12 antagonist, AZD6140, with conventional clopidogrel on top of low-dose aspirin. The authors should be acknowledged for the thoughtful design, detailed analysis, well-balanced opinions, and perfect timing for such work to appear. Indeed, the era of expanding antiplatelet regimens and indications may require new agents as the substitutes or additions to the available strategies. However, the alarming frequency of dyspnoea reported in the available strategies. However, the agents as the substitutes or additions to regimens and indications may require new. Indeed, the era of expanding antiplatelet dynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J. Published online ahead of print February 2006.

REFERENCES


5. Serebruany VL, Malinin AI, O’Connor CM, Gurbel PA. Effects of roxifiban on platelet aggregation and major receptor expression in patients with coronary artery disease for the thienopyridine active metabolite to the P2Y12 receptor would lead to ‘immune conflict’ as postulated by Dr Serebruany. Covalent binding of the thienopyridine active metabolite to the P2Y12 receptor would probably be more likely to lead to structural changes in the receptor and subsequent immunological response. Neither fluid retention (or other signs of heart failure) nor bronchospasm has been reported as the mechanism for dyspnoea by investigators.

Because AZD6140 is pharmacologically different from the oral platelet glycoprotein IIb/IIIa inhibitors, it would be inappropriate to expect similar harmful effects on platelet function. Increased expression of the platelet activation marker P-selectin seen during GPIIb/IIIa treatment means that platelets still activate and degranulate, whereas P2Y12 antagonists reduce activation as shown by Quinton et al., using cangrelor in vitro and by Storey et al., using blood from cangrelor and clopidogrel treated patients. GPIIb/IIIa antagonists reduce the aggregation of platelets activated by any stimulus, whereas P2Y12 antagonists reduce initial aggregation and subsequent aggregation, which should lead to a more favourable therapeutic effect.

As stated in Discussion of the paper and as suggested by Dr Serbruany, the frequency and aetiology of dyspnoea will be investigated further in future studies. The dyspnoea observations with AZD6140 reported to date have not been clinically limiting and I look forward to further clinical evaluation of this promising antiplatelet agent during which there will be continued diligent monitoring of patient safety.

© The European Society of Cardiology 2006. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org
References


7. Steen Husted
Department of Cardiology
Aarhus Sygehus
Hansens Gade 2
Aarhus C 8000
Denmark
Tel: +45 89 497613
Fax: +45 89 497619
E-mail address: steen.husted@as.aa.dk

doi:10.1093/eurheartj/ehi892

Online publish-ahead-of-print 8 May 2006

Angiotensin II receptor blockers and coronary artery disease: ‘presumed innocents’

A ‘surrealistic’ debate has been progressively mounting on scientific journals on a potentially unfavourable influence of angiotensin II receptor blockers (ARBs) on the development of myocardial infarction (MI). The debate has now evolved in the opening of a ‘trial’ with a virtual jury. However, in any respectable trial, alligations must be proven beyond any reasonable doubt, and the ‘burden of the proof’ is a commitment for the prosecutors. Thus, unitl proofs are convincingly provided to a ‘jury’ (and possibly counterbalanced by the case of the defendant), the accused must be considered ‘presumably innocent’. This does not seem the case in the editorial recently appeared on this Journal, as an opinion-commentary by Strauss et al. to a meta-analysis, which produced evidence of no difference in MI between ARBs and angiotensin- converting enzyme-inhibitors (ACE-Is). Almost at the same time, in an independent meta-analysis, including all available randomized, controlled, international studies with ARBs, no detectable difference on the endpoint MI between ARBs and other active comparators was found; this included ACE-Is, which were tested in a sub-analysis derived from head-to-head studies.

We wish to comment on the positions and interpretations of the editorial by Strauss et al. The ‘personal war’ of Strauss et al., indeed, began in 2004 with a surprising narrative editorial, in which the use of ARBs was related to increased MI. The subtitle of this editorial was simply astonishing ‘These drugs may increase myocardial infarction and patients may need to be told’, and obviously generated disappointment among physicians and, most of all, among patients taking ARBs. Because their article was based, to say the least, on a partial analysis, taking into account only some arbitrarily selected trials, many criticisms were soon raised. Now, before the opinion of ‘popular jury’ is influenced by the ‘interim verdict’ that Strauss et al. anticipate, but mostly while waiting for head-to-head studies that might eventually clarify whether ARBs and ACE-Is have different influence on development of MI, we propose to readers thoughts and critici-sm on the new arguments of the ‘prosecution’.

First, Strauss et al. refer as the ‘most robust data to support’ and ‘the ultimate proof’ of the superiority of ACE-Is vs. ARBs on MI incidence, to a data presentation of the BPLTTC at the recent ESH Meeting. There are major problems in their interpretation: (i) the reference is not due to a written contribution by the BPLTTC Investigators, but rather to the transcription of a medical reporter; (ii) rather than ‘a highly statistically significant benefit of ACE-Is relative to ARBs in MI’, the conference coverage more soberly states that ‘unlike in the case of ACE-Is, there is no BP-independent effect on MI with ARBs’; (iii) as also stated in the conference report, ‘the power of the analysis is limited by the much smaller number of ARBS trials’ (five vs. 21 with ACE-Is). Moreover, the analysis does not consider any head-to-head comparison, thus data are extrapolated by studies where ACE-Is are compared with other treatments, often placebo, not to ARBs; (iv) the greater albeit small reductions in BP achieved with ACE-Is may explain the decrease of MI observed in high-risk patients. In support of this concept is another recent, large meta-analysis, which clearly showed that prevention of coronary artery disease by ACE-Is was unequivocally linked to systolic BP reduction. As shown in the BPLTTC analysis, the benefit provided by ACE-Is on MI could only be shown when ACE-Is were compared with placebo. In addition, the thesis of Strauss et al. does not clarify why ACE-Is should be more protective than ARBs in terms of MI in hypertension, and not in post-MI or in patients with heart or renal failure.

Finally, the BPLTTC analysis is limited to studies in hypertensives, and it is confounding for the reader to conclude that ONTARGET/TRANSCEND study will provide the head-to-head counterproof to this issue, as this is not a hypertension trial.

 Strauss et al. even attempted to explain the differences between ARBs and ACE-Is on coronary events by referring to putative deleterious effects of AT2 receptors on coronary circulation. To support this view, they keep quoting the only available reference that could support their hypothesis (the same article used 2 years ago). Although the pathophysiological role of AT2 receptors is not defined and any speculation on their effect in human coronary disease is under-warranted, more consistent evidence support a favourable role of AT2r in the cardiovascular system.

It is recognized that ARBs may reduce stroke, development of heart failure, and prevent the progression of diabetic nephropathy and new onset of diabetes. Whether the beneficial effects of ARBs is partially independent of BP effects is unclear, and any conclusion is premature, due also to the heterogeneity of the trials examined. However, at this stage, there is no evidence of higher risk of MI in patients receiving ARBs, nor of a superiority of ACE-Is. Given the approach used by Strauss et al. in conceiving and supporting their hypothesis (arbitrary selection of studies not powered for the endpoint, indirect comparison of classes, and so on), the ‘unexplained’ risk of MI could be well justified by the play of chance. Therefore, the ‘jury’ should stay away from a ‘verdict’