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. 1 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 paper1 (Table 5) was not mentioned in the abstract or tried to be explained in the discussion. In fact, at least 10% for the lower doses and up to 20% of patients treated with the highest dose of AZD6140 experienced dyspnoea. The association between treatment with anti thrombotic agents and dyspnoea is not new. Few anecdotal observations suggested that aspirin,2 hirudin,3 or eptifibatide4 might cause dyspnoea, although such side effects are extremely rare. It seems that the immune conflict between the hostile platelet receptors subjected to the reversible blockade by the antiplatelet agent(s) may lead to the mild episodes of thrombotic thrombocytopenic purpura and consequent fluid retention contributing to dyspnoea. Being the first ever oral cyclopentyltriazolo pyrimidine to be tested in the clinical trials as an antiplatelet agent, and especially because of its reversible nature, AZD6140 may appear to be safe for the intact platelets in the pre-clinical studies, but hurt already activated platelets during the unbinding from the cell surface in patients with vascular disease, as was previously documented for the oral platelet glycoprotein IIb/IIIa inhibitors.5 Lack of dyspnoea episodes after clopidogrel or prasugrel, which are irreversible P2Y12 receptor inhibitors also indirectly supports this hypothesis. Additional pulmonary function tests, immunological and platelet receptor studies are needed to determine the cause of dyspnoea after AZD6140 and to figure out how such serious adverse reaction can be prevented or at least minimized. Last but not least is the fact that clopidogrel replaced ticlopidine based not on the superior efficacy, or more potent platelet inhibition, but because of the better safety profile.

In conclusion, although the initial clinical results with AZD6140 are promising, the unusually high incidence of dyspnoea is not an artefact. Such serious adverse reaction requires straightforward acknowledgement, much better understanding, and possible prevention plan, especially in the chronic long-term setting.

References


Viktor L. Serebruany
Johns Hopkins University
Towson
MD 21204
USA
E-mail address: heartdrug@aol.com

doi:10.1093/eurheartj/ehi888

Online publish-ahead-of-print 12 May 2006

Dyspnoea after AZD6140: safety first?: reply

I would like to thank Dr Serebruany for his interest in our manuscript. In his letter, he expressed concern about the adverse event of dyspnoea reported in the Phase 2a study of the reversible, oral P2Y12 antagonist, AZD6140. Results describes the 23 patients with reported dyspnoea, none of which was considered serious and only one patient dis continued therapy due to this adverse event. Most of these events did not trigger further diagnostic evaluations and were not thought by the investigators to be related to heart failure or bronchospasm. Further investigation of AZD6140 has occurred in DISPERSE2, a Phase 2b study with longer exposure in 990 patients with non-ST elevation ACS.2 This second study confirms that dyspnoea occurs more frequently with AZD6140 than with clopidogrel. The clinical impact again appeared low with few cases in either group being considered serious or leading to discontinuation of therapy. The incidence of new cases reduced after 30 days.

Dr Serebruany also speculates on potential mechanisms for the dyspnoea. Dyspnoea is a non-specific symptom that has been occasionally reported both with aspirin and clopidogrel,3 but except for ASA-induced asthma, and is probably not causally related to these agents. The examples given for hirudin and eptifibatide similarly are more likely related to the underlying condition than to the antithrombotic per se. No thrombocytopenia has been observed with any of the AZD6140 cases of dyspnoea in studies to date, so there is no evidence to support thrombotic thrombocytopenic purpura as a mechanism. Furthermore, there is no reason to believe that reversible blockade of 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 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 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.

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
Quinton TM, Muragappan S, Kim S, Jin J, 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,
until 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.1 to a meta-analysis,2 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,3 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.1 The ‘personal war’ of Strauss et al., indeed, began in 2004 with a surprising
narrative editorial,4 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 disappoint-
ment 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 criti-
cisms on the new arguments of the ‘prosecution’.

First, Strauss et al. refer as the ‘most robust data 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.5
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 com-
parison, 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.6 As shown
in the BPLTTC analysis,7 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 pro-
tective than ARBs in terms of MI in hyperten-
sion, and not in post-MI or in patients with
heart or renal failure.8,9 Finally, the
BPLTTC analysis is limited to studies in
hypertensives, and it is confounding for
the reader to conclude that ONTARGET/TRANS-
CEND 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 cor-

nary circulation. To support this view, they keep quoting the only available refer-
ence that could support their hypothesis (the same article used 2 years ago).8
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.9,10

It is recognized that ARBs may reduce stroke, development of heart failure, and prevent the progression of diabetic nephrop-
athy and new onset of diabetes.11 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 com-
parison of classes, and so on), the ‘unex-
plained’ risk of MI could be well justified by
the play of chance. Therefore, the ‘jury’ should stay away from a ‘verdict’

References
1. Husted S, Emanuelsson H, Hepotinstall S, Sandset PM, Wikens N, Peters G. Pharmacodynamics, pharmacokinetics, and
safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with athero-
sclerosis: a double-blind comparison to clopi-
dogrel with aspirin. Eur Heart J. Published online ahead of print February 2006.
of AZD6140, the first oral reversible ADP receptor antagonist, compared with clopidogrel
http://aha.scientificposters.com/
postersearch.cfm.
4. 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 Roxifiban Oral Compound Kinetics Evaluation

Steen Husted
Department of Cardiology
Aarhus Sygehus
Tage Hansens Gade 2
Aarhus C 8000
Denmark
Tel: +45 89 497613
Fax: +45 89 497619
E-mail address: steen.husted@as.aaa.dk
doi:10.1093/eurheartj/eh892
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