
Assessing the effect of ACE inhibitors on exercise tolerance: a question of study design: Reply

Dear Prof. Van de Werf

Williams et al. raise interesting questions on our study design.1

In general, in a parallel group study with a significant difference in survival – all other comparisons must be interpreted with caution, partly because the original balanced groups may be distorted and partly because patients completing and providing data may be selected, but the result is still relevant from a clinical perspective. It is indeed true that exercise capacity was identical in patients who survived and completed the study. Therefore, in clinical practice, we cannot expect to obtain improved exercise capacity in the average patient receiving an ACE inhibitor.

Williams et al. imply that a crossover study would have been preferable. In such a study design patients who die only complete part of the study and the comparison is made only on patients who survive, but this change in design removes only some of the bias of a parallel group study. The baseline characteristic balance is strictly maintained with patients being their own control, but the bias introduced by selected patients surviving is important in this type of study design. The crossover study with only selected patients completing the study is difficult to extrapolate to clinical practice. A crossover study introduces further hazards of carryover and time-dependent effects. Therefore, it is fair to say that there is no ideal way of studying exercise tolerance and other non-fatal phenomena whenever the intervention has a substantial effect on survival.

Finally, we have to correct a misunderstanding of the numbers of dropouts. As it is shown in Table 2 and Fig. 1, out of 254 patients who participated in the first exercise test, 196 patients ended 1-year follow-up. Thus, only 58 (23%) patients were withdrawn or died – a difference that was not statistically significant in a comparison of the two treatment arms.

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References
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The angiotensin enzyme inhibitor trandolapril has neutral effect on exercise tolerance or functional class in patients with myocardial infarction and reduced ventricular systolic function.


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Do statins really interfere with clopidogrel-induced platelet function?: Reply

To the Editor

Dr. Shechter correctly notes that there exist three different techniques to measure ex vivo the effects of clopidogrel on
platelet activity, with the flow cytometry is probably the most sensitive method. Using aggregometry, Lau et al.\textsuperscript{1} observed a strong and dose-dependent interference between atorvastatin and the inhibitory effect of clopidogrel on platelet function. We measured instead platelet activation by flow cytometry,\textsuperscript{2} and observed only a marginal interference, predominantly in the loading phase, and to an even lesser extent in the maintenance phase after clopidogrel application. A recent study used 600 mg clopidogrel for loading, and did not observe a significant interference between various statins and clopidogrel on ADP-induced platelet aggregation.\textsuperscript{3}

All studies used ex vivo platelet function tests and measured only indirectly the drug–drug interaction between lipophilic statins and conversion of the prodrug clopidogrel into an active metabolite. Certainly, this potential interference between statins and clopidogrel cannot directly be translated into clinical outcome. A retrospective analysis of clinical studies (MITRAplus registry,\textsuperscript{4} CREDO-study\textsuperscript{5}) revealed no significant influence of different statins on the clinical outcome in clopidogrel treated patients. Thus, we agree to the suggestion of Dr. Shechter that large, well-designed and prospective trials may be helpful to further resolve this potential dilemma.

Perhaps more important as the potential interference between statins and clopidogrel may be the observation that a certain percentage of patients apparently does not respond at all to clopidogrel treatment.\textsuperscript{2,6} Others noted a pronounced variability in the effectiveness of clopidogrel.\textsuperscript{7} Prospective studies will also be helpful to further characterize these patients, and to re-define antithrombotic therapy for this subgroup.

Given the marginal interference in our study and the high variability, there is no need to discontinue the statin use during the clopidogrel treatment or to prefer hydrophylic statins in patients with clopidogrel comedication.

References


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