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 Thus, only 58 (23%) patients were withdrawn or died—a difference that was not statistically significant in a comparison of the two treatment arms.

Diane Barker
Lip-Bun Tan
Unit of Molecular Cardiology
University of Leeds, UK


References
1. Abdulla J, Burchardt H, Abdilstream SZ et al. The angiotensin enzyme inhibitor trandolapril has neutral effect on exercise tolerance or functional class in patients with myocardial infarction and reduced ventricular systolic function.
2. Blocking only one pathway does not necessarily predict stent restenosis (and/or in-stent thrombosis) and/or a worse clinical outcome. The medical community urgently needs a large, well-designed prospective trial, using the three tests—all together—as surrogate endpoint for platelet function in order to conclude this dilemma and better guide our daily practice. Until then, physicians are urged to continue implement the guidelines and prescribe statins to CAD patients with or without clopidogrel coadministration.

Jawdat Abdulla
Department of cardiology
Gentofte University hospital
Copenhagen, Denmark

Lars Køber
Christian Torp-Pedersen

Do statins really interfere with clopidogrel-induced platelet function?

To the Editor

Following Lau et al.1 publication last year, suggesting that lipophilic statins may inhibit clopidogrel-induced platelet function, the medical community is torn apart between implementing the guidelines and prescribing statins to patients with coronary artery disease (CAD) undergoing percutaneous coronary interventions to further reducing mortality and morbidity and the possibility of harm, although not yet proven, by increasing platelet activity when statins are coadministered with clopidogrel.

Neubauer et al.2 recently contributed this uncertainty and dilemma. In a well-designed study they demonstrated that lipophilic statins (atorvastatin and simvastatin) reduced significantly the inhibitory effects of clopidogrel, especially during the loading phase, measured by flow-cytometry P-selectin (CD62P) activity.

Platelet activity is measured by the combination of the following three tests: (a) platelet aggregation by ADP or collagen-induced whole blood (or platelet-rich plasma) platelet aggregometry; (b) platelet adhesion by ex vivo perfusion (Badimon) chamber; and (c) platelet activation by flow-cytometry measurement of the surface membrane expression of CD62P (P-selectin, GM140) in the whole blood.4-6 All three tests together are needed to test platelet function.

Lau and Neubauer based their conclusions on one test only out of the above three tests: Lau et al. studied only the in vitro anti-aggregation effect of clopidogrel in patients after stent deployment1 and Neubauer et al. only the flow-cytometry P-selectin (CD62P) activity.2 Blocking only one pathway does not necessarily predict stent restenosis (and/or in-stent thrombosis) and/or a worse clinical outcome.7 The medical community urgently needs a large, well-designed prospective trial, using the three tests—all together—as surrogate endpoint for platelet function in order to conclude this dilemma and better guide our daily practice. Until then, physicians are urged to continue implement the guidelines and prescribe statins to CAD patients with or without clopidogrel coadministration.

M. Shechter
Sheba Medical Center
Heart Institute, Tel Aviv University
Tel Hashomer 52621, Israel
Tel.: +972-3-5302645
Fax: +972-3-6780581
E-mail address: shechter@netvision.net.il


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