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Is the level of evidence for the use of beta-blockers in acute myocardial infarction satisfactory enough?: reply

Thanks very much for your interest in the European Society of Cardiology consensus document on beta-blockers.  

Norwegian Timolol study, together with other early studies with beta-blockers after an acute myocardial infarction, provided the first convincing evidence that a drug used for cardiac disease could prolong life. A large number of other trials, meta-analysis, and careful analysis form large registries supported the earlier results and the use of beta-blockers soon became standard of care for patients recovering from myocardial infarction. Progress in the understanding of the disease and new studies also demonstrated benefits from other therapies, including the use of antiplatelet agents, ACE-inhibitors, statins, thrombolysis, and percutaneous coronary interventions on top of standard care, which included beta-blockers. With the addition of more and more effective therapies, the question of the relative benefit of earlier background therapies including but not limited to beta-blockers arises. Without direct evidence of an interaction between a new therapy and an established therapy, it is unethical to repeat studies of established therapies—and the recommendations for established therapies must remain. Oral beta-blocker therapy early after myocardial infarction is beyond question and should be maintained long-term. The problem, if any, is the grading of evidence, not the level of recommendation itself.

Immediate intravenous administration of beta-blockers in large groups of patients admitted with myocardial infarction and who are candidates for reperfusion therapy is a different problem. New relevant information has emerged after the publication of the consensus document on beta-blockers. Another important study, the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT/CCS-2) was conducted in China. In this trial, presented at the American College of Cardiology meeting in March 2005, a total of 45 851 patients with suspected acute myocardial infarction (ST change or LBBB) admitted to Chinese hospitals within 24 h of symptom onset were randomly allocated to receive metoprolol (intravenous and then oral during 16 days) or placebo. Mortality was similar in both groups; re-infarction rate was significantly lower in the beta-blocker group, as well as ventricular fibrillation, but beta-blocker administration was associated with a significant increase in risk for cardiogenic shock, particularly in patients in Killip classes II and III at randomization. The results of this trial raise important questions about the selection of patients who obtain benefit from the early intravenous use of beta-blockers. Limited data from the COMMIT trial can be found in the study web page, but the results have not been published yet, which does not allow for a sound discussion and conclusions. Finally, although we do agree that mortality is a very important outcome, it is not the only reason for using therapies, particularly with the progressive decrease in mortality with appropriate management. Other well established targets for treatment include relieve of symptoms, prevention of re-infarction, infarct complications, hospital re-admission, and progression of the disease as well as functional capacity, secondary effects, and cost of treatment. New therapies are admitted as effective without an impact on survival, either because there is no effect on mortality or because it would be extremely difficult, costly, and futile to demonstrate such an effect.

References


4. Clopidogrel & metoprolol in myocardial infarction trial (COMMIT/CCS-2) www.commit-ccs2.org

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Are tirofiban and abciximab identical in efficacy?

We read the paper by Mukherjee et al. on similar efficacy outcomes with tirofiban and
ReoPro with a lot of interest and considerable reservations.

The paper was hand-delivered to me by the representative of one of the drugs in the study with the proud claim that both drugs were equivalent. The authors are to be applauded in conducting a very well-designed trial with 100% follow-up in terms of mortality. The outcome reported was pre-specified, in line with modern concepts of trial execution. The authors also do well to point out a significant limitation of their study in their discussion, i.e. the trial was significantly underpowered to detect a difference in death. However, here is where we feel that the authors fail to emphasize how important this limitation is and how scientifically inconclusive the results of this trial are (as far as the mortality endpoint is concerned).

The hazard ratio (HR) for total mortality in this study is reported as 1.10 for tirofiban vs. abciximab with a 95% confidence interval (CI) of 0.72–1.67. The latter represents the range of HRs within which the ‘true’ HR lies. As clinicians, we decide (albeit somewhat arbitrarily) on how much benefit or harm is clinically meaningful. Thus, one might consider an HR of ≤0.80 as clinically meaningful benefit and an HR of ≥1.10 as clinically relevant harm. One also decides (again somewhat arbitrarily) on a ‘zone of equivalence’ (say, an HR of 0.9–1.05) within which if the trial result and its 95% CI falls, one considers the two therapies as truly equivalent. Then there is the ‘grey zone’ where the results may be statistically significant but the clinical relevance may be marginal. These concepts have been well outlined by Sackett et al.,2 and I am certain that the esteemed authors are extremely well versed in them.

Using these parameters as an example, if we examine the wide 95% CI of the trial result, the ‘true’ HR may actually lie anywhere—in the zone of benefit (HR < 0.80), harm (HR ≥1.10), equivalence (HR 0.9–1.05), or the ‘grey’ zone (HR 0.8–0.9 or 1.05–1.10). Thus, the results of the trial are clearly inconclusive at best. The result would have been conclusive only if the outcome estimate and its 95% CI fell into one zone [something that even the primary outcome of the trial was unable to achieve (HR of 1.26 with 95% CI 1.01–1.57)].

Although the trial was designed to demonstrate non-inferiority of tirofiban as far as the primary outcome was concerned, it was never meant to do the same for the 1-year mortality outcome. The authors should have been more emphatic in their discussion about the fact that the study does not demonstrate equivalence of both drugs. It is likely that, following the publication of this paper, and given the fact that the authors are clearly pioneers and world leaders in the field, a lot of ‘touting’ for or against one or the other drug will take place.

We appreciate the comment of Dr. Jafary and agree that we clearly stated the limitation that the TARGET trial was not powered based on the pre-specified secondary endpoint of 1-year mortality. We stated that the primary limitation of the analysis was the potential lack of power to detect a mortality difference (i.e. a type I error due to the sample size and the low event rate in the study population). We believe that the physician readership of the journal understands this limitation as stated, although some pharmaceutical representatives may not. As the word-count restriction of the journal precluded an in-depth explanation of the confidence intervals around the 1-year mortality hazard ratio, we thank Dr. Jafary for detailing this.

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References

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