metabolic stress, and increased excretion. In such patients, single agent supplementation might be ineffective or exacerbate deficiencies elsewhere with no overall change in status. Furthermore, the potential benefits of micronutrient supplementation in CHF given high re-admissions rates, poor overall quality of life, and persistent symptoms are significant.

On the basis of our recent data, the prevalence of micronutrient deficiency including copper in patients with CHF and the effects of supplementation deserve further research.

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

The cornerstone of each therapy’s recommendation should be the impact on survival. In the August 2004 issue of the European Heart Journal, expert consensus opinion on beta-blockers stated that during the acute phase of myocardial infarction, oral beta-blockers are indicated in all patients without contraindications (Class I, level of evidence A). The consensus group opinion was supported by the data from the pre-reperfusion ISIS-1 and MAMI trials and post-reperfusion TIMI-II trial which compared two time protocols of metoprolol administration and, therefore, was not controlled with a non-beta-blocker or another beta-blocker. It is understandable that the results from pre-reperfusion studies cannot be simply incorporated into a modern concept of AMI treatment.

Retrospective analysis from PCI studies (PAMI-2, Stent PAMI, Air PAMI, PAMI noSOS, and CADILLAC) was used to support the premise of mortality reduction with pre-PCI intravenous and post-PCI peroral use of beta-blockers.2,5,6 However, none of these studies were designed to randomly assess the effects of beta-blockers on mortality.

Oral beta-blockers are further recommended for long-term use and for survival improvement in all patients who recover from AMI and do not present contraindications (Class I, level of evidence A); this recommendation is based on the data from a meta-analysis of 31 randomized trials, Hjalmarson’s trial, Cooperative Cardiovascular Project, BHAT and Norwegian trial.7,8 However, all these trials are from the pre-reperfusion era or use registry as a database. None of these trials included random assessment of beta-blockers in the post-reperfusion modern algorithm, including PCI, fibrinolysis, ACE-inhibitors, aspirin, and statines. Furthermore, the document states that the benefit of beta-blockers in low-risk patients is questionable.

CAPRICORN, the only randomized post-reperfusion trial in AMI patients with ventricular dysfunction, showed all-cause mortality reduction with carvedilol when compared with placebo.9 However, CAPRICORN did not reach the pre-specified higher level of statistical significance for the original primary endpoint of all-cause mortality (the primary endpoint was changed for co-primary during the study). Therefore, the statistical power of CAPRICORN is only borderline in favour of mortality reduction with carvedilol in high-risk AMI patients (P = 0.031).

Intravenous beta-blocker administration for primary prevention of sudden death was marked as a Class I, level of evidence B. The document admitted that post hoc analysis of GUSTO-1 trial does not support intravenous use of beta-blockers in the reperfusion era.10 In TIMI-IIIb trial, early intravenous metoprolol administration had no advantage over the peroral treatment.4

Evidence for the use of beta-blockers in the early stage of AMI thus results from studies in the pre-reperfusion era, registries, meta-analyses, and post hoc analysis, not designed for beta-blockers’ random assessment in regard to mortality reduction after AMI.

In the absence of powerful statistical evidence for mortality reduction in the reperfusion time, we believe the impact of beta-blockers on survival after AMI has not been proved sufficiently. For a better evaluation of the role of beta-blockers in patients with AMI, randomized large trials assessing the impact on survival are obviously missing.

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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.1

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.2 A large number of other trials, meta-analysis, and careful analysis form large registries supported the earlier results2 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 benefit from other therapies, including the use of antplatelet 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—the 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, but 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 Clopigroil 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,4 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


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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