Letter to the Editor

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No evidence for a reduction of myocardial infarctions by acarbose

With great interest we read the article of Hanefeld et al., in which a meta-analysis of seven randomised controlled trials was presented. This meta-analysis compared acarbose with placebo in patients with type 2 diabetes with respect to the incidence of cardiovascular events. The conclusion that acarbose can prevent myocardial infarctions surprised us because, currently finishing a Cochrane systematic review on the topic, we found only scarce outcomes regarding diabetes-related morbidity so far. Moreover, we were very disappointed that the design and conduct of this study was not critically discussed at all, even more so because they suggest major flaws that seriously undermine the conclusions.

The criteria for the selection of these seven long-term randomised controlled trials are not clear. Studies that are included in meta-analyses should be the result of an extensive and systematic search strategy. Failing to do so could result in selection bias, affecting the outcome significantly, usually in the direction of the desired outcome. Also, the results from the largest included study were never published as a journal article and thus not subject to the peer-review process, and two studies were not published at all. The inclusion of unpublished studies is a virtue, but the reasons why a study has not been published should be made clear because this might reflect methodological flaws or conflicting interests.

Heterogeneity should not be investigated solely by statistical methods, but firstly with a visual inspection of the main study characteristics of each trial. In this meta-analysis clinical heterogeneity is obvious. For example, different kinds of co-interventions were used. We also have concerns about the way the main outcome data were collected and handled. The authors use the so-called safety data from the original studies, an idea that is creative in a fashion. However, safety-data were not collected following the rigorous methods as required in controlled trials.

Possible other causes for a reduction of myocardial infarctions should be investigated carefully. First, it should be made clear which study contributes most to the results. This might lead to possible other factors related to study design that also might explain the results. Secondly, special attention should be paid to the possible contribution in each study of additional medication and lifestyle factors. And thirdly, the data should be analysed accounting for the intervention that was actually received. Since the authors used data from the safety group, an unknown number of patients did not actually use acarbose. Usually, dropouts receive some other form of anti-diabetic treatment and thus it cannot be excluded that the measured effect on cardiovascular events is merely the result of anti-diabetic treatment in general, rather than the effect of acarbose.

Finally, we wonder if the outcome ‘any cardiovascular event’ would still be significant if myocardial infarctions were excluded. If so, the conclusion that acarbose has shown preventive effects on ‘any cardiovascular event’ is not logical.

In summary, this meta-analysis is subject to publication bias, heterogeneity, detection bias and confounding factors. The conclusion that there is evidence for a reduction of myocardial infarctions by acarbose is not justified.

References

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Meta-analysis of long-term studies to assess the effect of acarbose on cardiovascular risk reduction — scientifically credible: Reply

The authors criticised our meta-analysis of seven long-term studies to assess the effect of acarbose on cardiovascular risk reduction. Two different approaches are generally accepted as standard procedures for meta-analyses. These are systematic literature reviews or meta-analyses of all randomised controlled trials. Our meta-analysis is based on the latter approach. As clearly stated in our article, data from all randomised, double-blind, placebo-controlled clinical trials with a minimum treatment duration of 52 weeks were included. The source was the Bayer Acarbose clinical database. As a consequence, publication and selection bias (regarded as substantial risks in the situation of systematic literature review) can be excluded.

Whilst it is true that two studies included in the analyses were not formally published and therefore not subject to peer review, both studies were part of the New Drug Application for acarbose. Although we highly respect the quality and rigour of the science journal peer review procedure, we doubt that the drug approval process is any less strict. The study by Bachmann et al., has in the meanwhile recently been published.

We agree with Dr. van de Laar et al., that heterogeneity should not be investigated by statistical testing alone. We consider only heterogeneity in the treatment effect to be problematic for statistical analysis (in accordance with CPMP). Some deviations concerning other characteristics could be seen as an advantage for increasing its generalisation and external validity. This said, co-intervention was balanced between acarbose and placebo because of the randomisation. It should be mentioned that it is important to formal statistical testing, graphical and descriptive methods were also employed to confirm homogeneity of treatment effect.

The use of individual patient data has the advantage of enabling a common outcome variable to be defined across studies. Therefore it seems straightforward to use safety data to define an outcome based on cardiovascular events. Indeed, we are surprised to note the concerns of Dr. van de Laar et al., regarding the safety data collection procedure. As a matter of fact, in clinical trials
performed according to Good Clinical Practice the occurrence of adverse events is monitored carefully and recorded in detail during the trial.

We would like to point out that in the Cox Proportional Hazards model, patients contribute only for the time that they are observed under treatment and only to the corresponding treatment group. Moreover, not only the actual number of events under treatment and placebo contribute to the analysis, but also the event-free times in both groups.

Finally, the ‘any cardiovascular event’ outcome is indeed still significant, even after exclusion of myocardial infarction-from the cardiovascular events (HR = 0.69, 95% CI: 0.50–0.95).

In summary, our meta-analysis was conducted based on scientifically sound and credible principles. Thus the data published in the European Heart Journal suggest that acarbose, in addition to its effect on glycemic control, could have a beneficial effect on cardiovascular complications in patients with established type 2 diabetes. These results are in line with the beneficial effect of acarbose on cardiovascular events, as found in the STOP-NIDDM trial.

References


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Elevation of CK-MB following percutaneous coronary intervention

We read with great interest the meta-analysis by Roe and colleagues on the prognostic significance of creatinine kinase MB isoenzyme (CK-MB) elevations following percutaneous coronary interventions (PCI) in patients with acute coronary syndromes. We do concur with the conclusions of this study regarding the prognostic significance of even minor degrees of iatrogenic necrosis. However, this observation is not relevant only to this particular clinical setting. Although not referenced by Roe et al., we have previously shown that any increase in CK-MB following PCI, in general, is associated with a statistically and clinically significant increase in the subsequent risk of death, regardless of the presence of an acute coronary syndrome. Our meta-analysis included seven studies with CK-MB measurements and survival outcomes on 23,230 subjects who underwent PCI (mean follow-up, 6–34 months per study). By random effects, 19% of the subjects had 1–5-fold CK-MB elevations, while only 6% had >5-fold elevations. The mortality relative risk increased 1.5-fold with 1–3-fold CK-MB elevations, 1.8-fold with 3–5-fold elevations and 3.1-fold with over 5-fold CK-MB elevations. Thus, approximately 1 in 5 subjects undergoing PCI will have an even larger increase. Any CK-MB increase is associated with a potential increase in the subsequent risk of death during follow-up. One to 3-fold CK-MB elevations increase the risk of death by approximately 50%. In a step-wise fashion the risk is increased by 80% with 3–5-fold CK-MB elevations and is tripled with over 5-fold CK-MB elevations. This is of clinical importance, since post-PCI the CK-MB isoenzyme increases of up to five times the upper limit of normal have typically not been found to be statistically significant predictors of survival and their clinical meaning has been questioned. Nevertheless, the majority of post-PCI CK-MB elevations are in this range, with the majority in the range of 1 to three times the upper limit of normal.

Therefore, there is now evidence that risk stratification should include routine surveillance of cardiac enzyme levels post-procedure. This should be undertaken not only in ACS patients as suggested by Roe et al., but also in any patient subjected to PCI.

References


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