Correspondence

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Aspirin Versus Coumadin

A study in Circulation by Meijer et al.1 describes an angiographic study in patients with successful thrombolysis and open infarct-related vessel within 48 hours who underwent repeat coronary angiography at 3 months after having been treated with either 325 mg aspirin or matching placebo or open-label coumadin (INR 2.8-4.0). The authors conclude that when heparin is given in the acute phase of myocardial infarction, this should be followed by aspirin treatment because aspirin reduces recurrent myocardial infarction and the need for revascularization and tends to reduce angiographic reocclusion.

There are several important limitations inconsistent with respect to this conclusion that need to be highlighted. Since a comparison to placebo is outdated, the main comparison of interest is between aspirin and coumadin, which are the two effective strategies for secondary prophylaxis in patients with myocardial infarction. With respect to this comparison, it is important to note that the study was nonrandomized and was stopped prematurely.

Angiographic comparison did not reveal a difference in reocclusion at 3 months; however, there was an insignificant increase in reinfarction, revascularization, and death, which as a combined end point resulted in 93% event-free survival in aspirin group versus 82% in the coumadin arm (P=.03), which is the most important comparison leading to the authors’ conclusion that aspirin is better than coumadin. However, the total number of patients having hard end points (death and reinfarction) contributing to this difference is small (four in the aspirin group and nine in the coumadin group); given the open-label comparison between these two arms, interpretation of softer end points such as revascularization is more difficult. Furthermore, five of the seven reinfarctions in the coumadin group occurred during heparin infusion before coumadin therapy was instituted. This did not occur in patients who ultimately received aspirin while they were receiving IV heparin, suggesting misfortune for those randomized to coumadin arm but not necessarily a difference in treatment effect between coumadin and aspirin. Indeed, if these five reinfarctions are discounted, no significant difference exists in clinical end points between aspirin and coumadin.

In summary, I believe this study shows benefit from the use of aspirin compared with placebo. Unfortunately, this study does not adequately compare the two most frequently used modalities of secondary prophylaxis, aspirin and coumadin, because of open-label design, premature discontinuation of the study, and small number of patients. Given these considerations, the authors’ conclusions should be interpreted with caution.

Anatoly Langer, MD
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Reference

Reply

Dr Langer disputes our conclusion that heparin given in the acute phase of myocardial infarction after successful thrombolysis should be followed by aspirin treatment, because aspirin reduces recurrent myocardial infarction and the need for revascularization and tends to reduce angiographic reocclusion.

Dr Langer states that the study was nonrandomized. However, in the section “Randomization and Statistics,” it is pointed out clearly that the study was randomized, and a detailed description of the randomization procedure is given.

Furthermore, Dr Langer states that five of the seven reinfarctions in the coumadin group occurred during heparin infusion before coumadin therapy was instituted. This is not what the text says. In patients allocated to coumadin treatment, coumadin was started immediately after randomization and heparin infusion was continued until a therapeutic INR (2.8-4.0) was established. Consequently, heparin infusion in the coumadin group lasted longer than in the other two groups. This method of starting oral anticoagulation is in accordance with common clinical practice. Apparently, the potential of this strategy to reduce reinfarction is less successful than the strategy in which heparin treatment is followed by aspirin.

Finally, Dr Langer criticizes our use of a combined end point. However, use of combined end points made up of well chosen separate end points is an accepted way of increasing the statistical power to find differences between treatment strategies in studies of relatively small sample sizes. Nevertheless, we acknowledge that the comparison between aspirin and coumadin was not blinded and consequently is subject to inherent limitations.

We fully agree with Dr Langer that a blinded comparison between aspirin and coumadin studying enough patients to evaluate hard end points would be more than welcome.

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Stability of Plasma Atrial Natriuretic Peptide

As we routinely assay plasma for determination of atrial natriuretic peptide (ANP) levels, we have read with great interest the article by Nelesen et al.1 and a comment written by Flynn et al.2

Indeed, reports concerning storage and stability of ANP are scarce. We have previously published a paper regarding this subject,3 which is also cited by Nelesen et al.1 In our paper, no deterioration of immunoreactive ANP could be detected when plasma was stored for a period up to 6 months at −80°C. For these experiments, we used blood obtained from healthy volunteers containing approximately 30 pg/mL ANP. However, contrary to the statement of Nelesen et al.,1 this value is by no means at the lower (thus, nonsensitive) end of the standard curve. Instead, a value of 30 pg/mL corresponds to 6 pg/tube on our standard curve, which is well into the steep and hence the most precise part of our standard curve.4 Therefore, our results agree with the statements by Flynn et al.2 that ANP immunoreactivity does not deteriorate when plasma is stored at −80°C for a period of up to 6 months.3

To provide a further argument for this statement, we did not observe a significant decrease in ANP immunoreactivity when plasma from one healthy subject (mean value, 23 pg/mL) was divided into several aliquots and assayed several times during a 5-month storage period at −80°C.
Stability of plasma atrial natriuretic peptide.
A C Tan, P W Kloppenburg and T J Benraad

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