Relationship Between Delay in Performing Direct Coronary Angioplasty and Early Clinical Outcome in Patients With Acute Myocardial Infarction

To the Editor:

We read with interest the article by Berger et al on the relationship between delay in performing primary coronary angioplasty and 30-day mortality. We have the following concerns about their methodology and conclusions.

1. The use of patients who did not undergo percutaneous transluminal coronary angioplasty (PTCA) as a category of time to reperfusion does not seem appropriate. Patients with no reperfusion have worse outcomes than patients who undergo reperfusion even as late as 12 hours after the event. When patients without PTCA were excluded, the authors still report a significant relationship between time to PTCA and mortality. However, if the reported P value of 0.035 was based on a \( \chi^2 \) test for trend (which was not explained), the test for trend becomes nonsignificant if only one of the deaths in the \( >91 \) minute group had not occurred.

2. TIMI flow after angioplasty is the strongest predictor of mortality after primary angioplasty. Are there any data regarding differences in TIMI flow between categories of time to treatment? This may be important because TIMI-3 flow was achieved in only 73% of patients in the Global Use of Strategies to Open occluded coronary arteries in acute coronary syndromes (GUSTO II-B) trial compared with 91% to 95% in the Primary Angioplasty in Myocardial Infarction (PAMI) trials.2-3

3. It is not clear what physiological meaning the time from randomization to balloon inflation has apart from its impact on the total time from symptom onset to reperfusion. The study found no significant relationship between the time from symptom onset to balloon inflation and 30-day mortality.

The conclusion that time to treatment with primary PTCA is a critical determinant of mortality has not been a consistent finding in other primary angioplasty trials.2-5 The PAMI-2 investigators2 and the stent PAMI investigators3 found no relationship between either time to reperfusion or door to balloon time and 30-day or 6-month mortality. In the Moses Cone Hospital primary angioplasty registry,4 time to reperfusion was important for survival and recovery of left ventricular function only up to 2 hours. After 2 hours, recovery of left ventricular function was modest and survival was relatively independent of time to reperfusion. We think that factors other than myocardial salvage may be responsible for the survival benefit with primary angioplasty after 2 hours and that this is relatively time-independent.

The data from Berger et al should not discourage further investigation into the reasons why the relationship between time to treatment and mortality is different between thrombolytic therapy and primary angioplasty.

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Response

We appreciate Drs Brodie and Kissling’s interest in our article and the opportunity to respond to their questions.

We did use a \( \chi^2 \) test for trends; the association between time to treatment and mortality remained significant even when we excluded patients assigned to angioplasty who did not undergo angioplasty. The 30-day mortality with treatment in 61 to 75 minutes was 1.0%. Mortality was 3.7% with treatment in 61 to 75 minutes, 4.0% with treatment in 76 to 90 minutes, and 6.4% with treatment in \( >91 \) minutes (\( P = 0.035 \)).

Unlike thrombolyis, no relationship existed between time to treatment and TIMI-3 flow with angioplasty. The absence of a time-dependent treatment effect may lessen the slope of the relationship between time to treatment and mortality with angioplasty versus thrombosis, but it does not negate the importance of time to reperfusion with angioplasty. Not all infarctions are completed 2 hours after symptom onset. Often, the infarct artery opens and closes during the early stages of infarction, and collateral blood flow to the infarct artery may be present, delaying myocardial cell death and prolonging the time during which myocardium can still be salvaged well beyond 2 hours.

Regarding the lower TIMI-3 flow rate in the Global Use of Strategies to Open occluded coronary arteries in acute coronary syndromes (GUSTO-IIb) trial, in contrast to prior trials (including the Primary Angioplasty in Myocardial Infarction trial), GUSTO-IIb was designed to reflect worldwide practice. Whether its lower TIMI-3 flow rate also reflects different methodologies in the different angiographic core laboratories remains unknown.

Despite the fact that the preliminary reports Drs Brodie and Kissling cite suggest no relationship between time to treatment and outcome with angioplasty beyond 2 hours, an analysis of 27,080 patients in the National Registry of Myocardial Infarction-2 reveals a linear relationship between time to treatment with angioplasty and survival out to 12 hours, even after adjusting for other risk factors for mortality.1 There have been studies in which unacceptably high mortality rates were seen at hospitals when angioplasty was not performed rapidly; reducing delay reduced mortality.2 We fear that the clear superiority of angioplasty over thrombosis in the randomized trials may lead to the unfortunate application of angioplasty at institutions where it is neither rapidly nor expertly performed; such hospitals may have higher mortality with angioplasty than thrombolysis, a phenomenon that has already been reported.3-5

We also remain puzzled by the lack of a significant relationship between symptom duration until angioplasty and 30-day mortality in our study. This may be explained by “sicker” patients presenting to the hospital more rapidly, introducing confounding bias into analyses of this relationship.

We support Brodie and Kissling’s call for further investigation into these issues.

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