Letter by Fresco Regarding Article “Primary Angioplasty Versus Fibrinolysis in Acute Myocardial Infarction: Long-Term Follow-Up in the Danish Acute Myocardial Infarction 2 Trial”

To the Editor:

Nielsen et al. report in *Circulation* the 7.8 years follow-up of the DANAMI-2 trial, showing that the benefit achieved with primary percutaneous coronary intervention (PPCI) over tissue plasminogen activator (tPA) in the acute phase was maintained throughout the follow-up. In addition, and for the first time, in the subgroup of patients admitted to referral hospitals a significant benefit in terms of mortality emerged for PPCI-treated patients. Mortality was 26.7% with PPCI and 33.3% with tPA (a 6.6% absolute difference, odds ratio 0.78, 95%, confidence interval 0.63 to 0.97). On the other side, mortality was insignificantly higher with PPCI in the subgroup of patients admitted in invasive hospitals (a 4% absolute difference, 28.6% PPCI versus 24.6% tPA, odds ratio 1.17, 95%, confidence interval 0.81 to 1.69). According to my calculations, there is a significant interaction between mortality and referral and invasive centers (heterogeneity: $\chi^2 = 3.73, df=1; P = 0.05$).

Interestingly, the absolute mortality difference between tPA and PPCI was 2.8% in favor of PPCI in referral hospital and 2.5% in favor of tPA in invasive centers after 3 years. After 30 days, the absolute difference in mortality was 2.3% in favor of PPCI in referral centers and 0.8% in favor of tPA in invasive hospitals. So both curves are diverging from the very beginning, and are still diverging after 7.8 years.

Reinfarctions were significantly more frequent in tPA-treated patients. In the original publication, the authors pointed out that the decrease in reinfarctions was the main driving force for the positive result of PPCI. Furthermore, mortality in patients who reinfarcted was astonishingly high in the acute phase (24.2%). After 7.8 years, there was an overall 6.8% absolute reduction in reinfarctions with PPCI, and the magnitude of this reduction in reinfarctions was 5.5% in patients admitted in referral hospitals (where mortality was higher with tPA), and 10.3% in patients admitted in invasive centers (where mortality was higher with PPCI). With these premises, it is difficult to understand the true prognostic impact of reinfarctions in DANAMI-2. A recent report coming from almost the same dataset (92% of the DANAMI-2 population) showed that the 3-year mortality rate was around 6% in patients successfully treated with tPA (defined as >70% ST segment resolution after 4 hours). Patients treated with PPCI with complete ST segment resolution had a 3-year mortality rate almost double. Furthermore, there was a significant excess of reinfarctions in patients successfully treated with tPA. These patients had at the same time the lowest mortality AND an excess of reinfarctions. Therefore, one should conclude that, at least in this subset, these reinfarctions had a little, if any, prognostic impact. Counting these reinfarctions as negative events, although technically correct because reinfarctions were a prespecified end point of the study, becomes clinically questionable.

The DANAMI-2 results challenge from the basis our current understanding of the physiopathology of STEMI. PCI outperformed tPA in the subgroup where PCI-related delay was higher (70 minutes), while tPA almost outperformed PPCI in the subgroup where PCI-related delay was shorter (43 minutes). In addition, it is likely that many prognostically irrelevant reinfarctions were counted as endpoints in tPA-treated patients, throwing a shadow on the results of the study. DANAMI-2 study remains a landmark study, but in my opinion, there are some inconsistencies that raise concerns about using the results to determine current strategies for the management of STEMI.

Disclosures

Dr. Fresco received speaking fees from Boehringer Ingelheim, Eli Lilly, The Medicines Company, AstraZeneca, and Servier. Currently Dr. Fresco is National Coordinator for Italy for the STREAM Trial. Neither Dr. Fresco nor his relatives own stocks in pharmaceutical companies.

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References


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