

Outcomes among those who are ineligible for thrombolysis is worse than for those who are eligible and receive thrombolytic agents (2,3). Thus, one would expect a mixed group of thrombolysis eligible and ineligible patients to be older, more likely to be male and to have a higher degree of comorbidity than a group of only thrombolysis eligible patients. To conclude that there was true selection bias in the recruitment of study participants, one needs to compare the characteristics of participants with those who were nonparticipants but met study criteria for randomization. Because Jha et al. do not have access to data that would allow this comparison, they cannot show true selection bias. Additionally, observational studies, such as this one, which attempt to show outcome differences, must adjust for case mix of the different patient groups. The authors duly note that outcome in acute myocardial infarction is highly dependent on a number of physiologic variables, such as admission heart rate, blood pressure and Killip class. None of these data were available for nonparticipants. In the absence of these data, it is difficult to determine whether outcome differences occurred due to differences in treatment received or because of differences in unmeasured baseline characteristics.

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### References

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2. Muller DWM, Topol EJ. Selection of patients with acute myocardial infarction for thrombolytic therapy. *Ann Intern Med* 1990;113:949-60.
3. Cragg DR, Friedman HZ, Bonema JD, et al. Outcome of patients with acute myocardial infarction who are ineligible for thrombolytic therapy. *Ann Intern Med* 1991;115:173-7.

### Reply

In part, Sada simply echoes a caveat that we presented along with our findings, namely, that better characterization of patients would be important to explain observed outcome differences (1). We also agree that examination of eligibility for thrombolysis in all participants would be the most rigorous way to pin down selection bias. That is where the agreement ends.

Sada would have us believe that thrombolysis eligibility alone accounts for the observed differences between trial participants and nonparticipants. Ironically, one of the references (2) he cites to support his argument was actually a meticulous dissection of the extent of underutilization of thrombolysis, wherein the authors championed the importance of treating elderly patients and those presenting 6 to 12 h from symptom onset. The second study cited by Sada was by Cragg et al. (3). It examined patients presenting to one center between

1986 and 1988, stated that only 16% of the patients were treated with thrombolytics and cited a whole series of now-obsolete criteria as reasons for deeming patients ineligible for treatment. Among those criteria were age >76 years, presentation >4 h from symptom onset, any previous coronary artery bypass surgery, angioplasty in the preceding 2 weeks and left bundle branch block. We are puzzled as to why Sada cited this study; but having cited it, he might at least have got the authors' message right. Cragg et al. (3) directly challenged the age limits on enrollment in thrombolysis trials as likely to cost many lives and also wrote: "Apart from the significant age difference, why protocol-treated patients had such low-risk characteristics was unclear; the inclusion and exclusion criteria did not specifically preclude enrollment for patients with many of these high-risk characteristics."

The evidence for underuse of thrombolytic therapy among elderly patients continues to roll in. The most recent study (4) in 11 European countries showed that up to 55% of patients with acute myocardial infarction were eligible for thrombolysis. However, compared with those >65 years old, the odds ratios for use of thrombolysis among eligible patients by age bracket were as follows: 65 to 74 years, 0.55 (95% confidence interval [CI] 0.34 to 0.89); 75 to 84 years, 0.24 (95% CI 0.14 to 0.40); and >85 years, 0.04 (95% CI 0.02 to 0.10).

As our article suggested (4), it seems plausible that arbitrary enrollment restrictions in early trials shaped the early perceptions of eligibility for thrombolysis, and these biases have continued to influence patient selection in both newer trials and ordinary practice. The causes, effects and epiphenomena are hard to tease apart; and more studies are needed. However, what matters now is optimizing the use of thrombolysis around the world and ensuring that any new therapies for acute myocardial infarction are tested in a proper spectrum of low and high risk patients of all ages.

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4. European Secondary Prevention Study Group. Translation of clinical trials into practice: a European population-based study of the use of thrombolysis for acute myocardial infarction. *Lancet* 1996;347:1203-7.