Do We Need a Randomized Trial (TRIANA) on Reperfusion in Patients Aged Over 75 Years?

To the Editor:

The interesting editorial dealing with reperfusion strategies in older patients with acute myocardial infarction (AMI)[1] poses several questions. I should like to hear the opinion of those responsible for the design of the TRIANA trial. As the authors of the editorial point out, only one small randomized trial compares intravenous thrombolysis (IVT) with primary angioplasty (PA) in patients aged over 75 years, the results of which were in favor of the latter treatment. However, multiple clinical trials and registries are available in which subgroup analyses of those ≥75 years of age show that PA is superior to IVT, since it improves survival and reduces the risk of stroke.[2] With this information, together with that from studies undertaken in the general population, which demonstrate the superiority of PA,[3] do we really need confirmation in patients ≥75 years of age? The lack of randomized trials in persons ≥75 years of age is not sufficient reason. The requirement for a study is due to the existence of data that suggest the possibility of a different result, in so far as the general population is concerned, in the subgroup of older patients. Do these data exist? Yes, but against the use of IVT. No specific clinical trials exist on the efficacy of IVT in the elderly, but the meta-analysis of the large studies[4] showed a significant 16% reduction in mortality. However, the data from the registries provide discordant results, unlike the uniformity between the trials and registries for PA.[2] Moreover, it is clear that with IVT the risk of intracranial hemorrhage (ICH) is greater in those >75 years of age,[5] and that this risk is less with PA. In the TRIANA registry,[6] the incidence of stroke with IVT was 5.5%, most (4.1%) due to ICH, a figure that is probably not acceptable. The latest American guidelines[5] recommend not giving IVT if the risk of ICH is ≥4%. On the other hand, in the TRIANA 1 registry, the success rate of the PA procedure was similar in persons both older and younger than 75 years of age.[7] PA opens the occluded vessel in a very high percentage of patients, with a minimal risk of ICH. Moreover, all the reperfusion strategies have shown their greater benefit in absolute terms in the populations at greater risk, such as the elderly. And PA is no exception.[8] The Achilles heel of PA is its availability and its performance without delay by an experienced team. Is it logical to carry out a randomized trial in hospitals that have had active PA programs for several years, and that clearly comply with the recommendations regarding the volume of patients? We believe not and, at the very least, many doubts exist concerning its convenience, even with ethical problems in extensive AMI with a delay >3 hours. More justification could be given to a study of IVT as compared with conservative management in centers that lack the possibility of performing PA, which are in fact the majority.

Finally, two basic considerations on the design of the TRIANA trial. In order to avoid important bias in the inclusion of the patients, a registry should exist of all AMI admitted to participating centers, and in which the reason for excluding any patients should also be recorded. Furthermore, the estimated relative risk reduction of 40% for an α error of .05 and a power of 80% facilitates a small sample size, but it loses its ability to show important clinical benefits. The meta-analysis of the studies with IVT[4] showed a reduction in risk of 16% and a number of patients needed to treat (NNT) to avoid one death of 30. In a trial such as the TRIANA, if we estimate a mortality for IVT of 25%, a relative risk reduction of 16% would require a NNT of 25, with 40 deaths avoided for every 1000 patients treated (IVT in the general population with AMI treated within the first six hours avoids 30 deaths). This finding would have great clinical relevance, but in order to be able to demonstrate this, the inclusion of 1800 patients would be required in each of the groups. The fact that the TRIANA trial failed to show statistically significant differences does not exclude the presence of clinically important differences (without the power to demonstrate a NNT>10).

The results have recently been reported of the SENIOR PAMI (Grines C. [personal communication] TCT 2005) which compared PA with IVT in patients ≥70 years of age, and which has highlighted several problems. The study was interrupted after five years and included 483 of the 530 patients expected, with a lower frequency of complications than expected in the IVT group (inclusion bias?). The number of patients was calculated to demonstrate an absolute difference in the primary endpoint (death or incapacitating stroke at 30 days) of 10%! No significant differences were found in the main endpoint (11.3% vs 13%). However, the secondary endpoint (death, incapacitating stroke or reinfarction at 30 days) was favorable to PA (11.6% vs 18%; *P*=.05). The lack of statistical power to demonstrate a clinically important benefit could suggest that PA is similar to IVT in the older patient, though detailed examination of the reported data shows the benefit of PA in these patients, which is in concordance with currently available knowledge.

In summary, it is not at all clear that the TRIANA trial is necessary and its design may be inadequate to demonstrate which reperfusion treatment is more appropriate in the older patient.

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Reply

To the Editor:

We thank Dr. Berjón for his comments about the convenience of carrying out a clinical trial to determine the best reperfusion treatment in the elderly, and which he considers unnecessary and inappropriate. This consideration is based mainly on the meta-analyses which sustain that primary angioplasty (PA) is superior to fibrinolysis for the management of acute myocardial infarction (AMI). The author comments that the need for a study is due to the existence of data that suggest the possibility of a different result in older patients as compared with the general population, since the success of PA is independent of age. However, the fact is that, although the angiographic success is high for all ages, the resolution rates of the ST segment and myocardial perfusion after PA fall progressively with age and they are associated with a proportional increase in mortality.[1] Furthermore, although some studies indicate that the benefit of PA as compared with fibrinolysis is greater in older patients, other studies are contradictory.[2] Strangely, he fails to mention that most of the clinical trials comparing PA with fibrinolysis excluded patients who were older than 75 years of age or included just very small proportions of these patients, and that several observational studies suggest that the benefit of PA over fibrinolysis is not as clear in real life as in the clinical trials.[3] He states that, according to the meta-analysis of the Fibrinolytic Therapy Trialists, fibrinolysis significantly reduces mortality in 16% of patients aged over 75 years. However, a later study, based on patients aged over 75 years with the current selection criteria, i.e., ST segment elevation or left bundle branch block with admission within the first 12 hours, revealed an absolute reduction in death of 3.4% (from 29.4% to 26%; relative risk reduction [RRR], 15%; *P*=.03), which represents 34 lives saved for every 1000 patients older than 75 years of age treated.[4] Dr. Berjón criticizes the undertaking of a clinical trial that compares PA with fibrinolysis in the elderly, when the overall benefit shown by PA as compared with fibrinolysis in the whole population is lower than that shown by fibrinolysis in this same age group. It therefore remains to be determined whether selection of an older population for this new study is justified. To this extent, it is noteworthy that the lead author of the meta-analysis that Dr. Berjón uses as an argument to defend that PA is superior to fibrinolysis in the subgroups at greatest risk, including the elderly,[5] is not so convinced as he is of this statement. In fact, it was she who promoted the first large clinical trial to compare PA and fibrinolysis in older patients (SENIOR PAMI). Unlike the predictions of Dr. Berjón, this study was unable to demonstrate that PA is superior to fibrinolysis in patients aged over 70 years with AMI of less than 12 hours evolution. Thus, the incidence of the primary endpoint (death or incapacitating stroke at 30 days) was 11.3% with PA and 13% with fibrinolysis (*P*=.57). This difference was greater in the patients aged from 70 to 80 years (7.7% vs 12%; *P*=.18), but in the patients aged over 80 years, those at highest risk, no clear benefit of PA over fibrinolysis could be demonstrated (C. Grines, personal communication, TCT, Washington, October 2005).

Dr. Berjón argues that fibrinolysis presents a risk of stroke (5.5% in TRIANA 2),[6] but he nevertheless fails to mention the much more favorable results of the latest clinical trials on fibrinolysis (e.g., 0.8% with tenecteplasa in combination with unfractionated heparin in ASSENT-3 PLUS).[7] On the other hand, when he questions whether the clinical trial should be carried out in centers that have PA, he fails to consider the important information that the TRIANA Registry collected in those Spanish centers with PA: 42% of the patients aged 75 years or over, with AMI and ST segment elevation, did not receive any reperfusion treatment and that, among those who did receive this treatment, the most used was fibrinolysis. Only 1 in every 5 patients received treatment with PA.[6] Thus, even although the information showed that PA is superior to fibrinolysis in older patients, this indication has not been incorporated into daily clinical practice in Spain, which strengthens interest in this study.

We agree with the technical considerations concerning the design of a relatively small clinical trial to compare fibrinolysis with PA in older patients, but we disagree that its inability to provide a definitive response to the question reduces the usefulness of the study. Studies that do not by themselves provide a definitive response are very necessary, in order to obtain the results of the meta-analysis upon which Dr. Berjón bases his opinion. Our posture is modest. We recognize that a not very large clinical trial may not provide a definitive response to the question considered, but we believe that it will be of use, in conjunction with other

studies, to help take clinical decisions in such a complex and controversial subject as is reperfusion in the older patient with AMI.

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