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.

Jesús Berjón Reyero

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REFERENCES

1. Bosch X, Sanchis J. Tratamiento de reperfusión en pacientes de más de 75 años con infarto de miocardio. ¿Necesitamos un estudio controlado y aleatorizado? Rev Esp Cardiol. 2005;58:333-7.
2. Mehta RH, Granger CB, Alexander KP, Bossone E, White HD, Sketch MH Jr. Reperfusion strategies for acute myocardial infarction in the elderly: benefits and risks. J Am Coll Cardiol. 2005;45: 471-8.

3. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003;361:13-20.
4. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1,000 patients. Lancet. 1994;343:311-22.
5. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation. 2004;110:e82-292.
6. Bardají A, Bueno H, Fernández-Ortiz A, Cequier A, Augé JM, Heras M. Tratamiento y evolución a corto plazo de los ancianos con infarto agudo de miocardio ingresados en hospitales con disponibilidad de angioplastia primaria. El Registro TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos) Rev Esp Cardiol. 2005;58:351-8.
7. Cequier A, Bueno H, Augé JM, Bardají A, Fernández-Ortiz A, Heras M. Características y mortalidad del infarto agudo de miocardio tratado con intervencionismo coronario percutáneo primario en España. Resultados del Registro TRIANA 1 (TRatamiento del Infarto Agudo de miocardio eN Ancianos) Rev Esp Cardiol. 2005;58:341-50.
8. Grines C, Patel A, Zijlstra F, Weaver WD, Granger C, Simes RJ; PCAT Collaborators. Primary coronary angioplasty compared with intravenous thrombolytic therapy for acute myocardial infarction: six-month follow up and analysis of individual patient data from randomized trials. Am Heart J. 2003;145:47-57.