Reperfusion Treatment in an Acute Myocardial Infarction in Patients Older Than 75 Years. Do We Need a Randomized Controlled Trial?

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Fibrinolytic therapy in ST-segment elevation acute myocardial infarction (AMI) constitutes one of the most important advances in cardiology in the last 25 years and has influenced the management and evolution of patients as much as the first coronary care units did. The most important limitations of fibrinolytics are the presence of absolute or relative contraindications to their administration in ≤25% of patients, their limited capacity to restore adequate coronary flow and the risk of inducing cerebral hemorrhage. They are at their most efficient in the first 2 hours' evolution of AMI but lose their efficacy thereafter.[1] Consequently, treatment must be initiated as early as possible and always within 30 minutes of indication.

In contrast, primary percutaneous coronary intervention (PCI) has few contraindications, greater capacity to restore adequate coronary flow and is less time-dependent. The meta-analysis of 23 trials comparing PCI with thrombolysis shows that, if patients in cardiogenic shock are excluded, primary PCI reduces 1-month mortality from 7% to 5% (odds ratio [OR]=0.70; 95% confidence interval [CI], 0.58-0.85) and the combined outcome of mortality, reinfarction or stroke from 14% to 8% (OR=0.53; 95% CI, 0.45-0.63).[2] Consequently, PCI is currently the reperfusion treatment of choice for most patients with AMI.

However, these results pertain to centers with a great deal of experience of PCI and volume of patients has been shown to be inversely proportionate to mortality. So, PCI is only recommended in centers that perform many such interventions per year. Moreover, although the timing of interventions may not be crucial, as it is with thrombolysis, it is still important: it is estimated that mortality increases by 8% for every 30 minutes' delay in intervention following the onset of symptoms. Consequently, PCI cannot be expected to be preferred to thrombolysis in the first 2 hours' evolution, in patients with small infarctions, when anticipated time-to-procedure may be >60 min greater than for thrombolysis (door-to-dilatation time >90 min) or in centers that perform few interventions per year. Clinical practice guideline recommendations clearly specify that PCI is the therapeutic option of choice when it can be performed in <90 min by an experienced team.

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Patients with AMI and >75 years old constitute a growing population (30%-40% of all patients with AMI) with 25% in-hospital mortality and clinical characteristics that differ greatly from those of younger patients. Patients aged >75 years frequently present atypical symptoms or an absence of chest pain, attend hospital later and 70% present non-ST segment elevation infarction. These patients are attended with less urgency, receive less intense treatment and <50% are admitted to a coronary unit. Reperfusion treatment is less successful and restoration of TIMI flow 3 is lower, reperfusion increases myocardial sensitivity to the lesion, contractility recovers more slowly, ejection fraction is lower and left ventricular end-diastolic pressure is greater. These patients present greater comorbidity, a greater frequency of contraindications to thrombolysis, a 2 to 4-fold higher incidence of major bleeding during hospitalization and are implicitly or explicitly excluded from clinical trials[3] casting doubt on any extrapolation of their results to this substantial sector of the population.

The meta-analysis of 9 major randomized trials of thrombolytics[1] described a 10% reduction in mortality

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in these patients, attributed to the lower efficacy of therapy and more adverse effects such as cerebral hemorrhage. Some years ago, Spanish authors questioned the efficacy of thrombolysis in older patients on the basis of data from 2 hospitals; these results were later supported by a 24-hospital register of 733 in-patients.[4] At the same time, the US Medicare registry reported greater mortality among patients aged >75 years and receiving fibrinolytics than among those who were not. Women and patients with AMI of >6 hours' evolution were especially affected.[5] Concern about the poor risk/benefit ratio increased with results of studies that analyzed the efficacy of more specific fibrinolytics or association with direct antithrombins such as hirudin, platelet IIb/IIIa receptor antagonists, high dose sodium heparin, or enoxaparin. In several studies, treatment induced excess mortality due to cerebral hemorrhage in patients aged >75 years.

In 2001, these data moved the Ischemic Heart Disease Working Group of the Spanish Society of Cardiology (SEC) to propose a randomized trial in >75 year-old patients with AMI to compare the efficacy of thrombolysis and PCI. Due to the limited number of patients undergoing PCI at that time, the Ischemic Heart Disease Working Group and the Section of Hemodynamics and Interventional Cardiology jointly decided to first construct a registry of patients in order to determine the viability of the study prior to its being undertaken.

THE TRIANA REGISTRY

The registry was constructed over 3-4 months in 2002 in 25 of the 58 hospitals that perform >25 PCI per year. The TRIANA-1 subgroup included all patients with AMI of whatever age undergoing PCI procedures in the cardiac catheterization laboratory; the TRIANA-2 subgroup included patients aged >75 years with AMI receiving medical treatment undergoing PCI procedures in coronary care units. Centers participated on a voluntary, nonrandomized basis and no quality control was included. Both primary PCI and urgent or facilitated PCI were included but information on the total number of patients with AMI hospitalized in these centers during the inclusion period was not obtained, nor was information on the motive for choosing one or other type of treatment.[6,7] Despite this, the study adds interesting information on the management of these patients.

Results were restricted to the 350 patients of all ages undergoing primary PCI and 90% of procedures were successful. At 1 month, mortality was 11.8% (6.6% after excluding patients in cardiogenic shock). On average, PCI was performed 5.3±4.2 hours following onset of symptoms and a median of 102 min (60-190) after admission,[6] times much above current recommendations. Therefore, nearly two thirds of patients were treated outside the treatment time window currently considered acceptable (<90 min) although this may be an overestimate as 11% of patients included were in cardiogenic shock which in itself can extend time-to-therapy. In contrast, half of the procedures were performed in ideal conditions (in normal working hours). Thus, we assume that the real time frame for action in Spain may be somewhat worse in the few patients attended outside of these hours. One of the groups with most experience of PCI found that both PCI failures and mortality increased 2-fold outside normal working hours.[8] However, results were not homogeneous in the 25 hospitals as the number of procedures per hospital and time-to-therapy varied greatly. Consequently, results cannot be generalized to all hospitals with PCI programs.

Only half the patients aged >75 years received reperfusion treatment and time-to-therapy was excessively long for both fibrinolytics and PCI. As the authors suggest,[7] this is surprising considering that participating hospitals were those with access to more and better resources for treatments of this type. Significantly, the risk profile of patients undergoing PCI was lower than that of those receiving thrombolytics and multivariate logistic regression analysis did not associate reperfusion with survival. Does this confirm that reperfusion treatment is ineffective in patients aged >75 years? Clearly, as we are looking at an observational registry with few patients, we are unable to judge the efficacy of an intervention. Moreover, no adjustment was made for contraindication to thrombolysis, present in 44% of patients undergoing PCI,[6] nor was frequency of contraindication in patients receiving fibrinolytics specified[7]. Patients aged >75 years often present contraindications and these lead to 2- to 3-fold greater mortality.[9,10] Among the 58 patients without contraindications to thrombolysis undergoing PCI, mortality was low (10.2%; 95% CI, 4.5-21.2) as was incidence of death, reinfarction or stroke (12.8%; 95% CI, 5.7-23.3) although the confidence interval was wide. Data available show mortality among the rest of the patients was 4 times greater (41%; 19 of 46).

Results of Reperfusion Treatment in Patients Aged >75 Years

Fibrinolysis

A review of results from several studies confirms that fibrinolysis reduces mortality in patients aged >75 years. The meta-analysis of major studies was based on a population of patients with AMI with or without ST-segment elevation and <24 hours' evolution.[1] When analysis was limited to patients with ST-segment elevation and <12 hours' evolution, the reduction in mortality was not 10% but 16% (from 29.4% to 26%; Figure 1); moreover, absolute benefit was

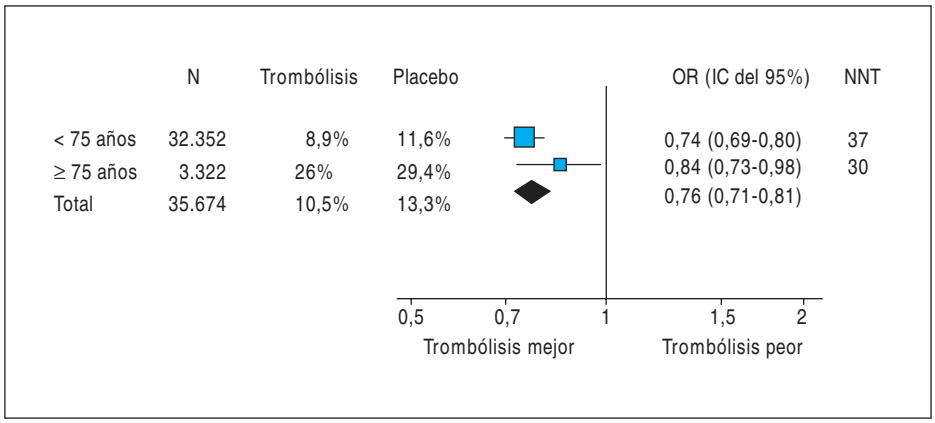

Figure 1. 30-day mortality of patients aged >75 years with acute myocardial infarction and ST-segment elevation of <12 hours' evolution in the meta-analysis of the 9 major trials to compare fibrinolysis with placebos.[1]

greater than in younger patients[11]. The number of lives saved per 1000 patients treated was 34 versus 28 and the number of patients needing to be treated (NNT) to avoid 1 death was 30 and 37, respectively. Most patients included in these studies received streptokinase and many did not receive aspirin or heparin. In the GUSTO-I study of 4625 patients of 75-85 years, administration of t-PA associated with an absolute reduction of 17 deaths or disabling strokes per 1000 patients treated by comparison with streptokinase.

The original Medicare registry analysis[5] only included hospitals without cardiac catheterization laboratories and >25% of patients with contraindications to thrombolysis. Another analysis including all hospitals reported lower 1-year mortality among patients receiving fibrinolytics (OR=0.84; 95% CI, 0.79-0.89).[10] A further registry including 38% of patients with contraindications to thrombolysis found 57% excess mortality among these patients and a reduction in mortality associated with thrombolysis in the rest.[9] The Swedish registry[12] analyzed 6891 patients aged >74 years with a first AMI and reported that administration of a thrombolytic to 57% of the population associated independently with a 13% reduction in risk of mortality or cerebral hemorrhage. The same results were found in the French AMI registry and the American NRMI-2 registry.

It is important to note that in a registry including 2659 patients aged ≥65 years, thrombolysis was associated with reduced mortality in patients aged <80 years and increased mortality in patients aged <80 years[9] whereas GUSTO-1 reported the same findings in patients aged ≥85 years. In the Swedish registry, the benefit of thrombolysis was lower among patients aged ≥85 years (OR=0.94; 95% CI, 0.81-1.09) than in the 80-84 (OR=0.86; 95% CI, 0.75-0.99) and 75-79 year age ranges (OR=0.82; 95% CI, 0.71-0.94).[12]

Time-to-therapy is crucial in these patients and fibrinolytics should probably only be administered within the first 6 hours' evolution. Moreover, the risk of cerebral hemorrhage is high. We should be especially meticulous in administering fibrinolytics to patients without contraindications and use a weight-adjusted dosing regimen. Risk of stroke increases in patients aged >75 years, women, black patients, patients with lower weight (<65 kg in women and <80 kg in men), those with a history of stroke, systolic arterial pressure >160 mm Hg, coagulation abnormalities or excessive anticoagulation (INR>4) and those receiving specific fibrinolytics (streptokinase entails lower risk). The presence of 5 or more risk factors entails a >4% risk of cerebral hemorrhage and determines a poor risk/benefit ratio. The GUSTO-1 study did not use an adjusted dosing regimen for the drug or heparin and reported a mean activated partial thromboplastin time (aPTT) of 103.4 seconds at 12 hours after administering t-PA and that this excess anticoagulation correlated directly with severe bleeding and death. The use of TNK-t-PA appears to have led to lower incidence of cerebral hemorrhage in >75 year old women by comparison with t-PA (1.1% vs 3%).

PCI

Percutaneous coronary interventions are clearly advantageous in older patients with AMI as they can be performed in most cases, achieve >90% success in opening the artery and almost eliminate the risk of cerebral hemorrhage. However, they are less widely available and associated with a greater rate of acute kidney failure and vascular complications. The only randomized trial to compare balloon angioplasty with conservative treatment in 120 >80 year-old patients[13] reported 16.4% and 20.3% 30-day mortality, respectively (Figure 2). The only randomized trial comparing fibrinolysis found PCI reduced mortality from 22% to 6.5% (*P*=.04) and incidence of death, reinfarction or stroke from 29% to 9% (*P*=.01; Figure 2). At 1-year follow-up, mortality was 29% versus 11% (*P*=.03) and incidence of combined events was 44% versus 13% (*P*=.01).[14] Moreover, in subgroup analysis of 11 randomized trials including 805 patients aged >70,[15] inci-

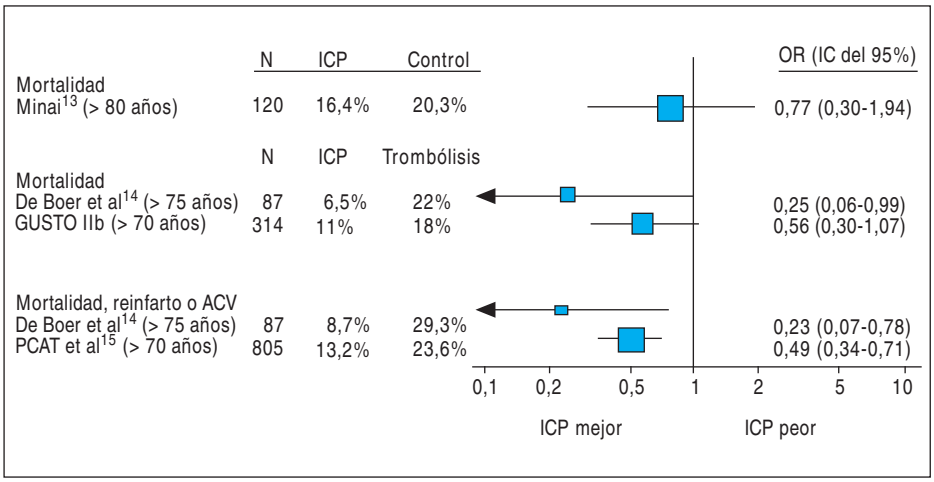

Figure 2. Comparison of results obtained in older patients in trials to compare efficacy of percutaneous coronary intervention (PCI) with conservative treatment (above) or thrombolysis (below). Data from GUSTO IIb and the PCAT meta-analysis refer to analysis of subgroups of patients aged >70 years.

dence of death or AMI decreased from 23.6% to 13.2% (Figure 2). The NNT was 23 in patients aged <60 years, 15 in patients aged 60-70 and 8 in patients aged >70 years. In contrast, PCI only appeared to benefit isolated individuals among patients in cardiogenic shock.

Finally, the German AMI registry analyzed 1630 patients aged ≥75 years and found 24.4% mortality in those receiving fibrinolytics versus 14.4% in those undergoing PCI (OR=0.55; 95% CI, 0.30-0.87; *P*=.02). The Medicare,[10] NRMI-2, and GRACE[16] registries also found a 30%-50% reduction in mortality and combined events.

CONCLUSIONS AND PROSPECTS FOR THE FUTURE

In patients aged >75 years, subgroup analysis of the major randomized trials with thrombolytics and results from wide-ranging registries of clinical practice conclude that fibrinolysis reduces mortality by 16%, with a greater absolute benefit than that found in younger patients. By comparison with fibrinolysis, subgroup analysis of 11 major trials and results from 4 large registries of clinical practice show early PCI performed in centers with a large volume of patients reduces mortality and short- and long-term incidence of death, reinfarction or stroke by 30%-50%.

Despite this, there is no direct, conclusive evidence from a major, statistically sound trial. Soon, the TRIANA study will begin. This open, controlled, randomized, multicenter trial will compare the efficacy and safety of PCI with fibrinolysis using TNK-t-PA in patients aged ≥75 years with AMI of <6 hours' evolution. The study is organized by the SEC Ischemic Heart Disease Working Group and Section of Hemodynamics and Interventionist Cardiology and is part-funded by the SEC and the Instituto de Salud Carlos III. The principal objective of the study is to compare 30-day incidence of all-cause death, reinfarction or disabling stroke. The secondary objectives are individual incidence of each event during the first year, rehospitalization due to cardiac cause, severe bleeding during hospitalization and PCI due to recurrent ischemia in the first 30 days. It is intended to study 564 patients (282 per group) during 3 years based on the results of the TRIANA registries and estimating a 40% relative risk reduction for an α-error of .05 and a β-error of .80.

The study design contemplates all the abovementioned observations and will include only patients without contraindications to thrombolysis attending one of the 26 hospitals with an active PCI program that have agreed to participate, if they present during the first 6 hours' evolution and can undergo PCI in <120 min. Weight-adjusted dosing will be used for TNK-t-PA and enoxaparin (0.75 mg/kg/12 hours without an initial bolus). If abciximab is administered during PCI, the dosage will be lower than normal (60 U/kg).

Interestingly, among its secondary objectives the study includes analysis of special subgroup results for age, gender, overall treatment time, quality of treatment compared with current standards (door-to-needle time <30 min for thrombolysis and door-to-reperfusion <90 min for PCI), and timing (during or outside normal working hours). Of further interest would be information gathered on patients hospitalized but excluded from the study—information that might give rise to another registry (TRIANA-3?).

The trial will supply long-awaited information on treatment of older patients with AMI. However, it will not answer the most difficult question of all: "Should a fibrinolytic be administered if PCI is impossible?" Generally speaking, the answer should be "Yes." However, clinicians must individualize their evaluation of patients to the maximum and estimate the risk/benefit ratio in each case, carefully noting the 5

essential points: clear presence of ST-segment elevation (dubious cases should not receive fibrinolytics); size of infarction (small infarctions should probably not be treated); time of evolution (beyond 6 hours the benefit is small); presence of absolute and relative contraindications; and risk of cerebral hemorrhage. Only after this evaluation should patients indicated receive weight-adjusted dosing of a fibrinolytic drug with heparin, or streptokinase without heparin.

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