In-hospital clinical outcome in elderly patients with acute myocardial infarction treated with primary angioplasty

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Key words:
Aging; Angioplasty, primary; Myocardial infarction.

Background. **The aim of the present study was to assess the early clinical outcome following primary coronary angioplasty in elderly patients (aged ≥ 75 years) compared to younger patients (< 75 years).**

Methods. **The study population included 655 consecutive patients (mean age 61.5 ± 12.4 years) with acute ST-elevation myocardial infarction (MI) who underwent primary percutaneous coronary intervention (PCI) within 12 hours of symptom onset. Elderly patients accounted for 14.5% (96 of 655) of all patients. Primary PCI was performed using a balloon and/or coronary stent as well as glycoprotein IIb/IIIa inhibitors. The primary endpoint was the in-hospital incidence of major adverse cardiac events (including death, stroke, reinfarction, target vessel revascularization and new onset of heart failure).**

Results. **Elderly patients were more frequently female (48 vs 20%, p < 0.001) and had more comorbid disease (prior stroke 7.2 vs 2.5%, p < 0.05) and more extensive cardiovascular disease (previous acute MI 13.5 vs 5.5%, p < 0.05; multivessel disease 71.8 vs 44.6%, p < 0.0005) and a significantly lower ejection fraction (48 vs 50%, p < 0.05). Despite a similar rate of TIMI 0-1 flow at presentation (69 vs 74%, p = NS), a similar use of stents (84 vs 86%, p = 0.3) and of glycoprotein IIb/IIIa inhibitor infusion (19.8 vs 22.1%, p = 0.3) and a comparable angiographic residual stenosis (21 vs 19%, p = NS), the final rate of TIMI 3 flow was significantly lower in the elderly population (77.8 vs 91.4%, p < 0.001). Although the in-hospital ischemic event rates for all ages were not significantly different, the in-hospital mortality was higher in the elderly as compared with younger patients (9.3 vs 3.2%, p < 0.0001), even when the patients with cardiogenic shock at the time of admission were excluded (4.4 vs 0.9%, p < 0.0001). Furthermore, more patients aged ≥ 75 had in-hospital heart failure (5.2 vs 1.8%, p < 0.05). In the whole population, multivariate analysis identified baseline Killip class III-IV as the only independent predictor of events. In elderly patients, multivariate analysis identified baseline Killip class III-IV and the time from the onset of chest pain to PCI as independent predictors of events.**

Conclusions. **Our data suggest that in elderly patients with acute ST-elevation MI primary PCI yields positive results: successful reperfusion can be achieved in a high proportion of elderly patients and the mortality rates are lower than those reported in non-PCI registries. A high Killip class and late reperfusion therapy predict an unfavorable outcome in elderly patients treated with primary PCI.**

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Background

Advanced age is associated with an increased mortality in acute myocardial infarction (MI)[1]. The mechanism by which increasing age contributes so dramatically to mortality is unknown.

This has been reported with both thrombolytic therapy[2-7] and primary percutaneous coronary intervention (PCI)[8-11]. In addition, to avoid the increased bleeding risk and intracranial hemorrhage, many early trials excluded patients aged > 75 years[12-18].

Although primary PCI may offer an attractive alternative for these high-risk patients, only few and conflicting data exist regarding the effect of advanced age on the success rate, complications and clinical outcome of primary PCI[19-22].

In this study we addressed the question whether primary PCI is beneficial in elderly patients: to this end we analyzed a large series of consecutive patients with acute ST-elevation MI comparing the effects of this procedure in patients aged ≥ 75 years with those aged < 75 years.

Methods

Patient population. All consecutive patients with acute ST-elevation MI who un-

derwent primary PCI within 12 hours of symptom onset between January 2000 and March 2002 were included in this analysis. All patients met the following criteria: 1) symptoms of myocardial ischemia lasting > 20 min, 2) persistent ST-elevation ≥ 1 mV in ≥ 2 limb leads or ≥ 2 mV in ≥ 2 contiguous precordial leads on a 12-lead electrocardiogram, and 3) creatine kinase (CK) elevation > 2 times the normal value with an MB elevation above upper normal limit. All patients gave formal written consent before the procedure.

Direct coronary angioplasty. Emergency coronary angiography and angioplasty were performed by the percutaneous approach (femoral or radial artery). PCI was performed by an experienced interventional cardiologist with the primary goal of restoring flow in the infarct-related artery (IRA) as soon as possible. At the time of admission in the emergency room or coronary care unit, all patients received a single bolus of heparin (5000 IU) and 500 mg of chewable aspirin. During angioplasty heparin was given at such a dose as to achieve an activated clotting time of 300 to 350 s. The angiographic success of PCI was defined as the achievement of a residual stenosis < 30% with TIMI flow grade 2-3. Glycoprotein (GP) IIb/IIIa inhibitors (abciximab or eptifibatide) were administered by operator decision. Coronary stent deployment was decided on the basis of the angiographic result after balloon dilation and on the operator's discretion. In patients with cardiogenic shock, an intra-aortic balloon pump was used.

All patients who received a coronary stent were treated for 1 month with aspirin 100 mg qd plus ticlopidine 250 mg bid. Beta-blockers and angiotensin-converting enzyme inhibitors were routinely administered to all patients if not contraindicated.

Clinical course and follow-up. All patients were screened for electrocardiographic changes; CK and CK-MB titers were assayed every 6 hours during the first day and then every day before discharge, unless clinical events suggested the repetition of the measurements. Platelet count, hemoglobin, hematocrit and white blood cell count were assessed at 6, 12, 18, and 24 hours after the procedure.

Adverse clinical events (including death, reinfarction, target vessel revascularization, stroke and heart failure) were evaluated during the in-hospital follow-up. Reinfarction after 24 hours was diagnosed on the basis of recurrent ischemic symptoms, of a CK-MB re-elevation to above 3 times normal (> 2 times the normal value after day 7) and persistent (> 20 min) ST-elevation not responding to nitroglycerin infusion. Stroke was diagnosed on the basis of an imaging study (computed tomographic scan) and of the consultant neurologist's opinion. Congestive heart failure was diagnosed on the basis of the criteria set by the guidelines of the European Society of Cardiology[23].

Bleeding complications were classified according to the GUSTO III definitions[5]. Severe or life-threatening bleeding was defined by substantial hemodynamic instability requiring treatment; moderate bleeding was defined by the need for transfusion; minor bleeding was defined as bleeding that did not require transfusion or cause hemodynamic instability. The classification of adverse clinical events was defined by a clinical events committee consisting of two expert cardiologists who performed a *post-hoc* review of all data.

Statistical analysis. Categorical data are presented as absolute values and percentages whereas continuous data are summarized as mean value ± SD. Comparison of categorical variables between the two groups of patients was performed using the Fisher's exact test. Comparison of continuous variables was performed using the Student's t-test or Mann-Whitney test, as appropriate. All variables associated with the occurrence of adverse clinical events during the in-hospital follow-up and showing a p value of < 0.1 at univariate analysis were entered in Cox's proportional hazard regression analysis. P values of < 0.05 were considered statistically significant.

Results

Patient characteristics. The baseline clinical characteristics according to age are summarized in table I. A total of 655 patients (497 males, 158 females, mean age 61.5 ± 12.4 years) were included in the study; 96 patients (14.5%) were ≥ 75 years (older) whereas 559 were < 75 years (younger). Elderly patients were more frequently female (48 vs 20%, p < 0.001), with a higher prevalence of prior stroke (7.2 vs 2.5%, p < 0.05) and more advanced cardiovascular disease (previous acute MI 13.5 vs 5.5%, p < 0.05). Furthermore, older patients were less likely to be current smokers (7.2 vs 37.3%, p < 0.001). No significant differences in the time from symptom onset to treatment were found in older vs younger patients (4.7 ± 7.7 vs 3.9 ± 6.5 hours, p = 0.4). At admission, 6 older patients (6.3%) and 30 younger ones (5.3%) (p = 0.4) were in Killip class IV.

Angiographic and procedural characteristics. The patients' angiographic characteristics are summarized in table II. The baseline TIMI 0-1 flow rates of the IRA were similar in the two groups. Just as the IRA, the involvement of the left anterior descending coronary artery was the same. Aged patients had more diseased vessels (two-vessel disease: 71.8 vs 44.6%, p < 0.0005) and a lower left ventricular ejection fraction (47.5 ± 9.1 vs 49.7 ± 8.5%, p < 0.05). Moreover, the procedural success (reopening of the IRA 91.3% in older and 96.8% in younger, p = NS) and the residual stenosis after PCI (21 vs 19%, p = NS) were similar in the two groups, but the rate of the final TIMI 3 flow was sig-

Table I. Baseline characteristics of the patients according to age.

Variable	< 75 years (n=559)	≥ 75 years (n=96)	p
Age (years)	58 ± 10.2	81 ± 4	< 0.0001
Female	112 (20%)	46 (48%)	< 0.001
Current smokers	209 (37.3%)	7 (7.2%)	< 0.001
Hypercholesterolemia	174 (31%)	25 (26%)	0.1
Hypertension	208 (37.2%)	39 (40%)	0.2
Diabetes	63 (11.2%)	16 (16.6%)	0.1
Previous MI	31 (5.5%)	13 (13.5%)	< 0.05
Previous stroke	14 (2.5%)	7 (7.2%)	< 0.05
Killip class I-II	496 (88.7%)	81 (84%)	0.3
Killip class III-IV	63 (11.3%)	15 (16%)	0.3
Symptom onset to PCI (hours)	3.9 ± 6.5	4.7 ± 7.7	0.4
Anterior MI	276 (49.3%)	41 (42.7%)	0.8
Peak CK (U/l)	2161 ± 1932	1589 ± 1332	0.02

CK = creatine kinase; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table II. Angiographic and procedural characteristics according to age.

Variable	< 75 years (n=559)	≥ 75 years (n=96)	p
IRA (LAD)	271 (48.5%)	39 (40%)	0.6
TIMI 0-1 flow pre-PCI	412 (74%)	64 (68.8%)	0.2
TIMI 2 flow final	30 (5.4%)	13 (13.5%)	< 0.005
TIMI 3 flow final	510 (91.4%)	74 (77.8%)	< 0.001
Multivessel disease	250 (44.6%)	69 (71.8%)	< 0.0005
GP IIb/IIIa	123 (22.1%)	19 (19.8%)	0.3
Stenting	486 (86%)	81 (84%)	0.9
LVEF (%)	49.7 ± 8.5	47.5 ± 9.1	< 0.05

GP = glycoprotein; IRA = infarct-related artery; LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction.

nificantly lower in older patients (77.8 vs 91.4%, p < 0.001). The prevalence of stenting in the two groups was also similar (84 vs 86%, p = 0.9). The frequency of administration of GP IIb/IIIa inhibitors was similar in the two groups (22.1% in < 75 years and 19.8% in ≥ 75 years, p = 0.3). An intra-aortic balloon pump was used in 6 patients ≥ 75 years (6.3%) and in 28 of the younger (5%) (p = 0.4).

Clinical outcome. The results of the in-hospital course are reported in table III. The incidence of in-hospital adverse cardiac events was significantly higher in the elderly group than in the younger. Among the single components of an unfavorable outcome, in-hospital death was more frequent in elderly and remained so even after excluding patients in cardiogenic shock on admission (4.4 vs 0.9%, p < 0.0001). The mean value of the peak CK was significantly higher in the younger than in older patients (2161 ± 1932 vs 1589 ± 1332 U/l, p = 0.02). No significant differences in the rate of major bleeding, blood transfusion and reinfarction between the two groups were recorded. An unfavorable trend of a higher incidence of stroke (2.1 vs 0.5%, p = 0.07) and of early heart failure (5.2 vs 1.8%, p < 0.05) was present in older patients. The prevalence of in-hospital target vessel revascularization was the same in the two groups. The overall length of the hospital stay, including the permanence in the intensive coronary care unit, was similar in the two age groups (6.6 ± 2.4 vs 6.3 ± 2.7 days, p = 0.3). In order to identify the variables associated with the occurrence of major adverse cardiac events during the in-hospital follow-up in the whole population an univariate analysis was initially performed showing that Killip class III-IV (p < 0 .001), left ventricular ejection fraction (p < 0.05), age > 75 years and the final TIMI 3 flow (p < 0.01), were the variables associated with major adverse cardiac events.

These variables were subsequently entered in the Cox's proportional hazard regression analysis. Multivariate analysis showed that only Killip class III-IV (p < 0.05) was independently related to major events.

In elderly patients the initially performed univariate analysis showed that Killip class III-IV (p < 0.0001), the time from pain onset to PCI (p < 0.01) and the final

Table III. In-hospital follow-up.

Variable	< 75 years (n=559)	≥ 75 years (n=96)	p
Death	18 (3.2%)	9 (9.3%)	< 0.0001
Re-MI	3 (0.5%)	1 (1.1%)	0.07
Heart failure	10 (1.8%)	5 (5.2%)	< 0.05
Ischemic TVR	19 (3.3%)	1 (1.1%)	< 0.5
Stroke	3 (0.5%)	2 (2.1%)	0.07
All MACE	53 (9.4%)	18 (18.7%)	< 0.05
Major bleeding	11 (1.9%)	2 (2.1%)	0.5
Hospital stay (days)	6.3 ± 2.7	6.6 ± 2.4	0.3

MACE = major adverse cardiac events; MI = myocardial infarction; TVR = target vessel revascularization.

TIMI 3 flow ($p < 0.01$) were the variables associated with major adverse cardiac events during the in-hospital follow-up.

These variables were subsequently entered in the Cox's proportional hazard regression analysis. Multivariate analysis showed that the time from pain onset to PCI ($p = 0.04$) and Killip class III-IV ($p = 0.04$) were independently related to major events.

Discussion

As life expectancy continues to increase, cardiologists will observe an ever increasing number of elderly patients with acute MI. Before the "reperfusion era" in elderly patients with acute MI the mortality rate was 30% at 1 month and > 50% at 1 year[24,25]. Thrombolytic therapy, actually, represents a major advance in the care of patients with acute MI. In a meta-analysis of the nine largest randomized trials[26], this treatment was found to be associated with a reduction in the 35-day mortality in patients < 75 years (treated within 12 hours). Despite the fact that such therapy has been shown to improve survival in patients with acute MI, conflicting data exist about its efficacy and safety in patients > 75 years[27-29]. Several studies[27,28] showed a lower mortality rate even in elderly patients with acute MI treated with thrombolysis. However, a large observational study has recently suggested that thrombolytic therapy might be deleterious in patients > 75 years, especially in women[29]. Furthermore, aged patients with acute MI are usually admitted later (due to the atypical presentation with non-diagnostic electrocardiograms or to the absence of chest pain) than younger ones[30], and this has been considered the main reason of exclusion and/or less use (and less efficacy) of reperfusion treatment in these patients. Finally, elderly patients are at a higher risk of intracranial hemorrhage.

Primary PCI could represent an attractive alternative treatment for these patients. However, data regarding the effect of old age on the success rate, the incidence of complications and on the clinical outcome of this procedure are limited[19-22].

In the GUSTO IIb substudy, the 30-day composite endpoint of mortality and stroke among patients aged 70-79 years and submitted to primary PCI were markedly lower than those of patients treated with tissue plasminogen activator[9].

The aim of the present study was to assess the in-hospital clinical outcome of elderly patients with acute MI and treated with primary PCI. In our study population, as previously reported in the literature[19-22], patients ≥ 75 years represented a high-risk population, with a high percentage of women (about 50%), more severe comorbid conditions and more extensive cardiovascular disease. In addition, the mean time from symptom onset to PCI tended to be longer in elderly patients.

Baseline angiography showed the same incidence of TIMI 0-1 flow in the two groups of patients. However, despite the similar procedural success (same percentage of vessel reopening and of residual stenosis after PCI) and use of GP IIb/IIIa inhibitors, the rate of final TIMI 3 flow in the culprit vessel was significantly lower in the elderly patients. This phenomenon has been previously described by DeGeare et al.[19] in a pooled analysis of 3032 patients with acute MI and treated with primary PCI; they showed a lower final TIMI 3 flow in older patients (85 vs 92% $p < 0.01$). Besides, at multivariate analysis this factor turned out to be one of the strongest predictors of in-hospital mortality.

What explanations have been offered for the lower rate of TIMI 3 flow after PCI in elderly patients? Some hypotheses derived from the literature considered the concurrence of multiple elements: an increased prothrombotic substrate secondary to the higher levels of coagulation factors (such as factors VII, VIII and IX) in the presence of a low-intensity intrinsic fibrinolysis; extensive fragmentation of the thrombus after mechanical reperfusion with peripheral embolization, in addition to the lower adaptability of the cardiac microvasculature with aging (rarefaction of the coronary arterioles) and to the age-associated increase in interstitial fibrosis (a significantly larger connective tissue fraction) contribute to increase the endomyocardial stiffness, hence reducing tissue perfusion[31].

In the present study the in-hospital mortality of elderly patients was lower than that reported in the overall population of randomized thrombolytic trials[2-7], and markedly lower if compared to the results obtained with the best thrombolytic regimen administered to older patients[27-29,32]. Anyway, the in-hospital mortality still remains higher in older, as compared with younger patients even when the patients presenting with cardiogenic shock at admission are excluded.

Similar data have been reported by DeGeare et al.[19] who showed a 5-fold higher mortality in older than in younger patients treated with primary PCI (10.2 vs 1.8%, p = 0.001).

In our study the in-hospital major adverse cardiac event rate was significantly higher in the elderly patients than in the younger ones. In contrast to what reported in a previous report[9], the rates of recurrent ischemia, reinfarction and target vessel revascularization both in hospital and at the long-term follow-up were very low in the present series and were not significantly different between the two groups. Holmes et al.[9] showed, after primary PCI, a 5% incidence of reinfarction at 30 days in patients > 70 years and a 9.1% incidence in octogenarians. This was substantially higher than the 1.1% reinfarction incidence observed in aged patients in our study. The less favorable outcome in the GUSTO IIb substudy might be in part due to the less frequent use of stents (about 5% of the total compared with 85% of our population) and to the routine use of antiplatelet therapy instead of anticoagulation[9]. In accordance with our results, in a cohort of 48 patients > 80 years and treated with primary PCI (> 50% of stenting), Matetzky et al.[21] recently reported an incidence of in-hospital reinfarction of 2.1% and a long-term target vessel revascularization of 4.8%; on the other hand, DeGeare et al.[19] reported a 0.6% incidence of reinfarction and a 5.6% incidence of recurrent angina at 30 days after primary PCI in elderly patients.

Furthermore, in our series, in contrast to what observed for the overall population, for patients > 75 years multivariate analysis identified both the Killip class III-IV and the time from symptom onset to PCI as independent predictors of major adverse events. Therefore, in a high-risk group of patients (old patients), the time to reperfusion probably becomes a major determinant of the short-term prognosis.

The use of GP IIb/IIIa inhibitors was similar (about 20%) in the two age groups with a relatively low incidence of major bleeding complications irrespective of age. Two patients (2.1%) suffered a stroke during hospitalization, one was clinically disabling, with a residual long-term hemiplegia. DeGeare et al.[19] described a stroke rate (or transient ischemic attack) of 2.9% in a cohort of 452 patients ≥ 75 years who underwent primary PCI. The low incidence of significant bleeding and of hemorrhagic stroke strengthened the benefit of an early PCI reperfusion in a high-risk population, when compared with previous studies of thrombolytic therapy[27-30].

Study limitations. These results were achieved in an experienced interventional single center with a planned program of systematic PCI for acute MI patients, and may not be reproducible in all centers. The assessment of the final TIMI flow was done separately by two interventional cardiologists and not by a specific Core-Lab.

In conclusion, the results of the present study support the indication to primary PCI with stenting and the temporary use of GP IIb/IIIa inhibitors as a feasible and safer alternative to thrombolytic therapy in elderly patients with acute MI.

Although successful reperfusion can be achieved in a significant proportion of elderly patients and seems to be associated with a remarkable short-term survival, the mortality rate is still higher in elderly than in younger patients.

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