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ST Elevation Myocardial Infarction in the elderly

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Abstract

Acute coronary syndromes (ACS) are the leading causes of death in the elderly. The suspicion and diagnosis of ACS in this age group is more difficult, since typical angina is less frequent. The morbidity and mortality is greater in older age patients presenting ACS. Despite the higher prevalence and greater risk, elderly patients are underrepresented in major clinical trials from which evidence based recommendations are formulated. The authors describe, in this article, the challenges in the diagnosis and management of ST elevation myocardial infarction in the elderly, and discuss the available evidence.

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1 Introduction

Acute coronary syndromes (ACS) are the leading causes of death in the elderly, resulting in more than one-third of all deaths in individuals older than 65 years of age. These patients represent the population at highest risk for both morbidity and mortality related to ACS. More than 80% of deaths related to myocardial infarction (MI) also occur in this age group.[1] Despite the higher prevalence and greater risk, elderly patients are under represented in major clinical trials from which evidence based recommendations are formulated. Elderly individuals made up a mere 6.7% of the 719,922 selected individuals in 593 published studies on ACS from 1966 to 2000,[2] thereby making data extrapolation from large trials in this population to the elderly very difficult. Increasing age is indeed one of the foremost risk factors for mortality in MI. In-hospital mortality rises form 2.1% in patients under 55 years to 26.3% in those aged 85 or over.[3] Octogenarians have double the mortality rate at 24 months compared to septuagenarians (33% *vs.* 17%, $P < 0.001$).[4] There are several contributing factors to the poorer prognosis in elderly patients. The major determinants are the higher incidence of co-morbidities, more extensive coronary artery disease, decreased cardiac reserve and an adverse thrombogenic profile.[4,5]

2 The treatment-risk paradox in the elderly

Because elderly patients are those at greatest risk, they have the greatest potential to benefit from more aggressive (invasive) treatment. However, the greatest the risk, the more conservative is the medical approach in clinical practice, especially in the elderly. To a great extent, this is due to the higher risk of complications associated with more invasive procedures, particularly bleeding complications, which drives many practitioners to withhold treatment in these patients. Additionally, several factors contribute to later presentation/ diagnosis of MI in elderly patients, resulting in precious delays, thus, frequently missing the ideal golden window for reperfusion. Consequently, the suspicion and diagnosis of ACS in the elderly is more difficult. Clinical presentation of typical angina is less frequent.[6] Socio-economic factors also contribute to later presentation for medical attention.

3 Diagnosis

According to the National Registry of Myocardial Infarction (NRMI), only 40% of patients older than 85 years expressed chest pain on admission, while other symptoms, such as dyspnea (49%), sweating (26%), nausea and vomiting (24%) and syncope (19%), were common among the elderly.

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Neurological or non-specific manifestations, such as mental confusion or weakness, may also be present.[7,8] Furthermore, obtaining a good medical history can be difficult due to cognitive dysfunction. Anatomical and functional abnormalities, and the presence of co-morbidities common among the elderly, such as osteoarticular pain, hiatal hernia, abdominal pain and neurological symptoms, can mask the usual symptoms and mislead the diagnosis of MI. Electrocardiogram interpretation, key for the diagnosis,[9] can be difficult, because of the presence of pre-existing abnormalities such as left ventricular hypertrophy, previous infarctions, dyskinetic areas and prior bundle branch block. Biomarkers of myocardial necrosis, such as troponins and creatine kinase-MB (CK-MB) should be checked; however therapeutic decisions should not be delayed until the results are available.

Chest radiography can assess the presence of pulmonary congestion and may be useful in the differential diagnosis of aortic dissection. When the diagnosis is certain, its realization should not delay the institution of therapeutic measures.

In cases of diagnostic uncertainty, echocardiography can be useful in assessing possible contractile dysfunctions in ischemic myocardium or in the differential diagnosis of acute aortic dissection.

4 Treatment

Patients with suspected ACS should be referred immediately to the emergency room for cardiac monitoring.

4.1 General measures

Oxygen therapy: Oxygen therapy is recommended in hypoxemic patients (sat O_2 < 92%) with acute myocardial infarction (AMI). Non-invasive ventilation can be used in more severe cases, when pulmonary congestion is present.

Analgesia and sedation: Chest pain and anxiety contribute to increased sympathetic activity, increasing myocardial oxygen consumption and predisposing to the development of ventricular tachyarrhythmias. Morphine sulfate, 2–4 mg intravenously, is recommended. Special care must be taken in cases of hypotension, right ventricular infarction and lowered level of consciousness.

Arterial reperfusion: the main objective in ST Elevation Myocardial Infarction (STEMI) treatment is the rapid, early and sustained complete recanalization of the AMI related artery. Reperfusion can be accomplished with fibrinolytic therapy or percutaneous coronary intervention.

4.2 Fibrinolytic therapy

Fibrinolytic therapy in the elderly is based on subgroup analysis of randomized studies, meta-analysis and registry. Data are particularly scarce in patients aged 80 years and over, in which the higher risk related to infarction is associated with increased risk of bleeding with fibrinolytic therapy.

The meta-analysis of the Fibrinolytic Therapy Trialist (FTT)[10] evaluated 150,000 patients submitted to fibrinolytic therapy compared to placebo. When administered within six hours of symptom onset, fibrinolytic therapy resulted in thirty lives saved per thousand patients treated, and when started between 7–12 hours, twenty lives were saved per thousand patients treated. The absolute benefit in survival for patients over 75 years of age has been questioned for some time. The analysis of this group of patients treated within 24 hours of symptom onset showed little improvement and no statistically significant benefit.[11] An observational study reported deleterious effects on this group of patients.[12] However, analysis from the FTT in 3300 patients over 75 years, with strict eligibility criteria for thrombolysis, showed eighteen lives saved per thousand patients treated in the fibrinolytic group compared to placebo.[13] In another observational study of 6,891 patients of the same age group, 3,897 of whom received fibrinolytic therapy, showed 13% decrease in mortality at one year follow-up compared to placebo.[14] Pooled analysis of GISSI–1 and ISIS–2 in older patients (over age 75) showed significant mortality reduction in patients treated with fibrinolysis.[15]

4.3 Primary Percutaneous Coronary Intervention (PPCI)

PPCI is particularly attractive in the elderly, since it offers both the advantage of strategy with a greater likelihood of successful reperfusion in this very high-risk population, while at the same time avoiding the risks of bleeding associated with fibrinolytic therapy. There is some concern in patients with renal dysfunction, frequent in the older population. The development of acute renal failure after a contrasted procedure is associated with adverse events that may be worsened by co-existing anemia and hemodynamic disturbances, common in the older population presenting with AMI.[16]

The comparison of fibrinolytic therapy with PPCI in a meta-analysis involving 7,739 patients showed lower mortality, non-fatal reinfarction and stroke rates in the PPCI group.[17] However, most patients selected in the studies were young, thus limiting its extrapolation to older individuals. The Primary Angioplasty in Myocardial Infarction (PAMI) study was the first major study to compare the use of fibrinolytic therapy *vs*. PPCI. About 38% of patients were aged ≥ 65 years. Patients undergoing PPCI presented lower rates of combined

mortality and MI (8.6% *vs*. 20.0%, $P = 0.048$).[18] Data from the GUSTO IIb trial showed PPCI was superior to thrombolysis in all age subgroups, with elderly patients deriving the greatest benefit.[19] A small study evaluated 87 patients aged ≥ 75 years comparing PPCI *vs*. streptokinase and revealed a decrease of major adverse cardiovascular events (death, reinfarction and stroke) at 30 days (9% *vs*. 29%, $P = 0.01$) and reduced mortality at 30 days and 12 months of follow-up.[20] The GRACE registry evaluated 2,975 patients undergoing myocardial reperfusion with fibrinolytic therapy or PPCI and showed a decrease in the odds ratio (OR) of death or reinfarction (OR = 0.53) and no differences in stroke and major bleeding.[21] Apparently, PPCI is superior to fibrinolytic therapy in the elderly, reducing recurrent ischemia, reinfarction, stroke and death, but presents five times higher mortality when compared with younger patients undergoing PPCI.[22]

4.4 PPCI versus fibrinolysis in elderly

Evidence from literature indicates more favorable outcomes with PPCI in the elderly,[23] but little information exists about patients over 80 years of age. Adjusting the dose of anti-thrombin therapy may reduce the risk of associated bleeding events in elderly. The decision of reperfusion strategies to be instituted must depend on the availability of resources for reperfusion in each practice.

Overall, PPCI is preferred in patients with higher risk stratification, particularly for those with left ventricular dysfunction and shock. PPCI and fibrinolysis provide similar outcomes when started within the first three hours of pain. PPCI is better after six hours and still can bring some benefit within 12 hours of pain.

PPCI is the reperfusion method of choice and the recommended door-to-balloon time is less than 90 minutes. In patients presenting in the first three hours of symptom onset, a door-to-balloon time minus door-to-needle time of less than 60 minutes is recommended.

Table 1 summarizes the advantages and disadvantages of both methods of reperfusion.

4.5 Antiplatelet therapy

Acetylsalicylic acid (ASA): The efficacy and safety of aspirin in patients with AMI are well established.[24] All patients with suspected ACS should be considered for treatment with aspirin at a dose of 165–325 mg/d, unless there are clear contraindications, such as allergic reaction, severe bleeding or suspected hemorrhagic stroke. In the elderly, a 200 mg loading dose should be administered followed by 100 mg maintenance dose.

Table 1. Advantages and disadvantages of thrombolysis *vs.* PPCI.

	Advantages	Disadvantages
Thrombolysis	-Universal availability -Administration quick and easy -Results similar to primary angioplasty before 3 hours	-Hemorrhagic (stroke, gastrointestinal) risk -Cardiac rupture risk
PPCI	-Results better than thrombolysis (reinfarction, stroke and death)	-Requires experienced, available team -Contrast nephrotoxicity -Complications related to cardiac catheterization

PPCI: Primary percutaneous coronary intervention.

4.6 Adjunctive antiplatelet therapy

4.6.1 Clopidogrel

Two studies evaluated the role of clopidogrel associated with aspirin in the presence of STEMI. The CLARITY-TIMI 28 study randomized 3,491 patients between 18–75 years of age up to 12 hours of pain onset.[25] Patients received aspirin, fibrinolytics and unfractionated heparin when indicated and were randomized to 300 mg clopidogrel loading dose, followed by 75 mg/d or placebo. The use of clopidogrel showed a 36% reduction (21.7% *vs*.15.0%, $P < 0.001$) in the rate of infarct-related artery occlusion on coronary angiography performed within 48 hours after randomization. Cardiovascular mortality, MI and recurrent ischemia requiring urgent revascularization were reduced by 20.0% (14.1% *vs*. 11.6%, $P = 0.03$). There was no difference in the incidence of stroke (0.5% *vs*. 0.7%, $P = 0.38$). The COMMIT study randomized 45,852 patients with suspected MI within 24 hours of symptoms onset, regardless of age, to receive clopidogrel 75 mg, or placebo, without a loading dose.[26] There was a 9% decrease in the MACE rate in the clopidogrel group (3% *vs*. 14%, $P = 0.002$), which corresponds to reduction of 9 ± 3 events per 1,000 patients treated for two weeks. Although a loading dose was not used in this study, the benefit of clopidogrel was evident within 12 hours after starting treatment.

There was no excess bleeding in the clopidogrel group, even in patients older than 70, or those who received fibrinolytic therapy. Evidence of clopidogrel use after STEMI is restricted to 28 days. Its use for a longer period is based upon the extrapolation of demonstrated benefits of this medication in studies of patients with Non-STEMI.[27] Taken together and based on the findings of these two major trials, it is safe to conclude that in elderly patients with STEMI, not treated with PPCI, that clopidogrel should be added to aspirin at a daily dose of 75 mg, without a loading dose, for at least 28 days, regardless of the use of fibrinolytic therapy. The use of a loading dose, such as in the

CLARITY study, may be considered for individuals aged 65 to 75 years, but not above this age, since this study excluded such individuals.

In patients undergoing PPCI, a loading dose of 300 mg or 600 mg is used, followed by 75 mg/d, based on studies of NSTEMI. The CURRENT-OASIS 7 study showed no benefit with the higher dose of clopidogrel in ACS patients.[28]

4.6.2 Prasugel

The TRITON-TIMI 38 trial compared the combination of aspirin and clopidogrel versus aspirin and prasugrel in patients with ACS, with or without ST-segment elevation, undergoing percutaneous therapy.[29] Reduction of the primary endpoint in patients randomized to prasugrel was observed, but with increased rates of major bleeding, especially in patients older than 75 years, with a history of prior stroke or transient ischemic attack, and low body weight. There was no net clinical benefit in the elderly and therefore this drug should usually be avoided in the elderly, or at least, reserved to a truly high-risk subset of patients, such as diabetics or otherwise very high-risk patients. A lower (5 mg) dose of prasugrel for elderly or underweight patients is currently being evaluated in the ongoing TRILOGY study, to establish safety in these populations.[30]

4.6.3 Ticagrelor

Ticagrelor is a new, non-thienopyridine inhibitor of the platelet adenosine diphosphate (ADP) receptor class, recently tested in the PLATO study,[31] which randomized ACS patients to ASA and clopidogrel versus ASA and ticagrelor. A reduction of the primary outcome in the ticagrelor group was observed without increasing the overall rate of major bleeding, and was apparently independent of age.[32] It should be mentioned that 15% (2878) of patients enrolled in PLATO were elderly (≥ 75 years) and although the interaction between treatment effect and age category was non-significant (P = 0.22), patients under 75 years derived a greater benefit from ticagrelor treatment (12-month incidence of the primary endpoint 8.6% with ticagrelor *vs*. 10.4% with clopidogrel, hazard ratio = 0.82, 95%CI: 0.74–0.91), whereas for those ≥ 75 years old the confidence interval crossed the line of unity (17.2% *vs*. 18.3%, hazard ratio = 0.94, 95%CI: 0.78–1.13). Similarly, there was no interaction between bleeding and treatment assignment (P = 1.00). Despite the fact that the beneficial effect of ticagrelor was not associated with an increase in the rate of overall major bleeding, there was an increase in the rate of non-procedure related bleeding. Finally, patients who underwent fibrinolysis were not included in the study.

4.7 Glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors

Studies evaluating the use of isolated GP IIb/IIIa inhibitors in MI without fibrinolysis did not show successful reperfusion.[33] The association of GP IIb/IIIa inhibitors and fibrinolytics showed improvement in angiographic and electrocardiographic parameters without clinical benefit and was associated with an increase in major bleeding when compared to fibrinolytic therapy alone.[34] In the elderly, this association showed an increase in major bleeding when compared to fibrinolytic therapy and unfractionated heparin, suggesting that it should be avoided in the older populations.[35,36] Meta-analysis evaluating 23,166 patients that received the association of abciximab and half dose fibrinolytic, or fibrinolytics and unfractionated heparin, showed no difference in 30 day mortality (5.8% *vs*. 5.8%, P = 0.95) and after 6-12 months (8.6% *vs*. 8.3%, P = 0.41). A lower incidence of reinfarction in the abciximab group (2.3% *vs*. 3.6%, $P < 0.001$) was observed, but was associated with an increase in major bleeding (5.2% *vs*. 3.1%, $P < 0.001$).[37] In the ASSENT-3 study, patients older than 64 years who received abciximab and half dose of unfractionated heparin (UFH) showed an increase in major bleeding and hemorrhagic stroke. In the GUSTO V study, the incidence of major bleeding and hemorrhagic stroke was significantly higher in patients ≥ 75 years who used this association,[38] suggesting that the combination of GP IIb-IIIa inhibitors and fibrinolytic therapy should not be used in the elderly. GP IIb-IIIa inhibitor use before PPCI should be restricted to the catheterization lab in patients presenting high thrombotic burden with low bleeding risk.

4.8 Anticoagulants

Meta-analysis of 21 small studies in patients with suspected STEMI showed a 25% reduction in mortality in patients receiving unfractionated heparin. For 1,000 patients treated, 35 deaths, 10 strokes and 19 events of pulmonary embolism would be prevented, with an increase in 10 major bleeding events. Fibrinolytic therapy was not used in these studies.[39] The EXTRACT-TIMI 25 study compared the use of different fibrinolytic agents in 20,506 patients and randomized for enoxaparin or unfractionated heparin.[40] Due to previous studies showing an increase in major bleeding in the elderly, this study used an adjusted dose of enoxaparin in this group of patients. UFH was administered to all patients assigned to this strategy with an iv bolus of 60 U/kg body weight (4000 U maximum) followed by an infusion of 12 U/kg per hour (maximum 1000 U/h) for at least 48 hours, with adjustment to an activated partial thromboplastin time of 1.5–2.0 control. Enoxaparin was given to patients ≤ 75 years as a 30 mg iv bolus followed by 1.0 mg/kg subcutaneously every 12 hours. For patients ≥ 75 years, a modified dosing regimen was tested with omission of the iv bolus and reduction of the maintenance dose to 0.75 mg/kg subcutaneously every 12

hours until hospital discharge or day 8. For patients of any age with an estimated creatinine clearance of < 30 mL/min, the dose was modified to 1.0 mg/kg every 24 hours. The incidence of hemorrhagic stroke was not different between the two groups. When the incidences of major bleeding and hemorrhagic stroke in the population over 75 years of age were evaluated, no statistical difference was observed.

4.9 Beta-blocker

Beta-blockers are used in STEMI to decrease oxygen demand, reduce heart rate, blood pressure and myocardial contractility. Its use reduces mortality in AMI, especially in elderly patients.[41] Two studies conducted before the reperfusion era showed benefits only in elderly patients. The combined data from these studies show a 5% reduction in mortality in younger and 23% in older patients ($P = 0.0005$).[42,43] The COMMIT-CCS study with 45,852 STEMI patients randomized within 24 hours of symptom onset, assessed the use of intravenous metoprolol or placebo.[26] There was no reduction in total mortality, reinfarction and cardiac arrest, but an excess of cardiogenic shock was observed in the metoprolol arm. In evaluating patients aged over 70 years, there was an increase in the combination of mortality and cardiogenic shock. Thus, the use of intravenous beta-blocker in the elderly should be restricted to stable Killip class 1 patients. Regarding oral beta-blocker use, most randomized trials excluded patients aged over 75 years. In an observational study in 58,165 patients aged over 65, beta-blocker was associated with lower hospital mortality with this decrease observed in all age groups.[44] Unlike intravenous beta-blocker use, oral beta blockers can be used in elderly patients with STEMI in the absence of contraindications. The dose must be titrated gradually.

4.10 Nitrates

Clinical studies demonstrate little benefit of nitrate use in STEMI. Meta-analysis of 22 studies did not show a statistically significant decrease in mortality (7.7% to 7.4%).[45] Nitrates can be administered to relieve angina and in patients with congestive heart failure. Any form of nitrates should be avoided in patients with systolic blood pressure below 90 mmHg, or those where there is drop equal to or greater than 30 mmHg in systolic blood pressure, or bradycardia, or tachycardia, or right ventricular infarction. Its use is contraindicated in patients who used phosphodiesterase-5 inhibitors for erectile dysfunction in the previous 48 hours, due to refractory hypotension risk. Because of its modest benefit, nitrates should be withdrawn when limiting the prescription of beta-blockers and angiotensin-converting enzyme (ACE) inhibitors; drugs with proven beneficial effects.

4.11 ACE inhibitors

The benefit of early use of ACE inhibitors in STEMI was evaluated in the GISSI[46] and ISIS-4[47] trials, which showed little reductions in 35 days mortality, with no effect on mortality in patients aged ≥ 70 years. Meta-analysis of several studies with more than one hundred thousand patients, found that those aged 55–74 years, with anterior wall STEMI and heart rate equal to, or greater than 80 beats/minute, were those who presented more benefit with the use of ACE inhibitors.[48] Retrospective analysis of 14,129 STEMI patients ≥ 65 years of age, showed mortality reduction at one year follow up.[49]

4.12 Statins

Evidence of statin use in ACS patients aged over 75 years is scarce. However, there is no reason to suppose that the benefits observed with statins in the secondary prevention studies should not be extended to this group.

5 Conclusions

Despite the population where the incidence of MI is highest and risk is greatest, the elderly are way underrepresented in major clinical trials from which most practice guidelines derive their recommendations, and thus the latter are usually derived from extrapolations from younger and healthier individuals. Major co-morbidities and the aging process, *per se*, exert a great impact in clinical decision making and the response to therapy. Chronological age is less important than assessment of frailty, general health status, and the particular wishes of the patient and family. The lack of substantial evidence and the complicating impact of frailty and co-morbidities make clinical decisions often very difficult. Whatever evidence there is from clinical trials performed in younger, healthier individuals should be taken into account together with a thorough geriatric assessment of the patient, weighing the risks and benefits of procedures that can be lifesaving, but that can carry substantial risks. No treatment should be denied to elderly individuals based on their age. Rather, a thorough consideration of the potential pros and cons should be discussed with the patient and family. Perhaps in no other scenario is clinical decision making more difficult and a true scientific art (based on scarce science and experienced clinical judgment) than in the elderly, especially the frail patient with co-morbidities, who has often (if not always) been excluded from clinical trials.

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