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Invasive strategy in elderly patients with acute coronary syndrome in 2018: close to the truth?

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Abstract

Elderly population constitutes an increasingly larger proportion of patients admitted for acute coronary syndromes (ACS). The optimal management of ACS in these patients is still a challenge due to their clinical peculiarities and the paucity of specific data, and they have been traditionally managed more conservatively mainly based on subjective criteria. In ST-segment elevation acute myocardial infarction urgent reperfusion is the standard of care and there is no upper age limit. In non-ST segment elevation acute myocardial infarction evidence is controversial, incomplete and mainly focused on chronological age. While a strict conservative strategy should be avoided, routine invasive strategy may reduce the occurrence of myocardial infarction and need for revascularization at follow-up with no established benefit in terms of mortality. Clinical characteristics associated with aging, such as comorbidities and frailty, further discriminate patient's risk beyond age. Evidence is scarce, but it suggests that these features may modulate the benefit of invasive strategy in this population. Ongoing trials should clarify the optimal management of ACS based on these parameters.

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1 Introduction

Elderly population constitutes an increasingly larger proportion of patients admitted for acute coronary syndromes (ACS) due to the rise in life expectancy. In European registries on non-ST-elevation acute coronary syndromes (NSTE-ACS), the proportion of patients > 75 years was 27%–34%.[1,2] In a recent USA registry, myocardial infarction (MI) prevalence in patients > 75 years was 17.5% for men and 11.0% for women.[3] Elderly population poses a diagnostic and therapeutic challenge due to its clinical peculiarities (*i.e.*, comorbidities, frailty, higher risk of complications, *etc*.) and the paucity of specific evidence.[4]

Invasive strategy in ACS is an evidence-based approach that it has led to a significant improvement in outcomes over the past decades.[5–7] Patients with ST-segment elevation myocardial infarction (STEMI) require an urgent reperfusion therapy.[5] Additionally, most patients with NSTE-ACS benefit from an invasive management.[6] However, elderly patients have been traditionally managed more conservatively, it is mainly based on physicians' subjective criteria. For instance, coronary angiography was performed in 67% of patients < 70 years of age compared with 33% in patients over 80 years in the GRACE registry.[8]

Over the past years, a significant increase in percutaneous coronary intervention (PCI) among elderly has been consistently described in population-based registries.[9–11] This temporal trend has been associated to a decrease in the mortality rate, mostly observed in patients treated with invasive strategy. Nevertheless, elderly patients are still less likely to undergo early angiography after an ACS.[12]

2 Is the elderly patient different?

Clinical practice guidelines recommend invasive strategy in STEMI and most of NSTE-ACS patients based on a large body of evidence.[5,6] We may wonder if there is a case for treating elderly patient differently from the general population. ACS diagnosis often poses a challenge in the elderly due to more frequency of atypical symptoms, baseline electrocardiogram changes, elevated basal troponin levels [being a dilemma the diagnosis of myocardial infarction (MI) in some cases] and higher rates of type 2 MI (due to myocardial oxygen supply-demand mismatch).[4] Age is an independent risk factor for thrombotic and bleeding risk, as well as PCI complications.[2,7,13–16] Clinical peculiarities of

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elderly patients, such as comorbidities, polypharmacy, frailty, cognitive status and socioeconomic features, can influence the response to treatments and they have impact on prognosis.[4] Older patients also tend to have more complex coronary disease and this is probably the cause of a lower rate of successful revascularization.[17,18] Finally, wide observational registries show that this population is currently being treated differently than younger patients.[12] Thus, it is warranted a detailed analysis of the evidence available in this subgroup separately from the general population.

3 What do we know?

3.1 STEMI

Urgent reperfusion is the standard of care in STEMI, using primary PCI and thrombolysis when the first is not timely available. Clinical guidelines point out that there is no upper age limit regarding urgent reperfusion in STEMI.[5] Therefore, invasive strategy is warranted in this setting. However, there are some pitfalls that must be noted. Elderly patients are at particular high risk of bleeding related to antithrombotic therapies and PCI access site. This may be overcome by adjusting antithrombotic dose when necessary, avoiding unnecessary thrombolysis (or adjusting dosage), choosing lower bleeding risk antiplatelet drugs, limiting multiple combinations of antiplatelet and anticoagulant therapies, and favoring radial access in PCI.[4,5]

Primary PCI must be the treatment of choice in these patients. A pooled analysis of three randomized clinical trials comparing primary PCI and thrombolysis in the elderly, showed a benefit of the first in terms of death, re-infarction, or disabling stroke.[19] However, thrombolysis is still recommended for older patients when primary PCI is not available.[5] The STREAM trial showed that there are no significant differences in the composite endpoint of death, shock, heart failure or reinfarction between primary PCI and fibrinolysis in patients presenting within three hours of symptom onset with delay to PCI more than one hour after first medical contact. However, a higher rate of intracranial bleeding was observed in the thrombolysis group. A protocol amendment was made after trial initiation due to an excess of intracranial bleeding in > 75 years, reducing by 50% the dosage of tenecteplase. Additionally, > 75–year–old patients did not receive enoxaparin intravenous bolus nor clopidogrel loading dose.[20]

3.2 NSTE-ACS

European clinical practice guidelines on NSTE-ACS state that elderly patients should be considered for an invasive strategy, and emphasize the need for a detailed clinical evaluation including comorbidities, life expectancy, quality of life, frailty and patient preferences, in order to individualize the risks and benefits.[5,6] However, no specific recommendations are available to guide therapeutic decisions based on these parameters. Moreover, guidelines stress that elderly patients are underrepresented in randomized clinical trials and that they are less likely to receive an invasive strategy compared to younger individuals.[6]

A meta-analysis of patient-pooled data from the FRISC II-ICTUS-RITA-3 studies suggested the benefit of routine invasive strategy in patients > 75 years, which may even benefit more than younger patients.[21] However, these trials were not specifically designed for elderly patients.

There are two randomized clinical trials focused on the management of NSTE-ACS elderly patients (Table 1). Savonito, *et al*.[22] in the Italian-ACS trial included 313 NSTE-ACS patients ≥ 75 years and they found no significant benefit of the routine invasive strategy in a composite primary endpoint (all-cause mortality, non-fatal MI, disabling stroke, repeat cardiovascular hospitalization or severe bleeding), when compared to selective invasive strategy consisting of initial medical therapy and coronary angiography only if significant recurrent ischemia (29% of the patients in this group underwent coronary angiography). It should be noted that this study was underpowered for the primary endpoint. In the subgroup analysis, patients with troponin elevation benefit from a routine invasive strategy. Additionally, a significant reduction in the primary endpoint was observed in a sensitivity analysis according to the treatment received.[23] However, we must be cautious with the interpretation of subanalysis of a negative trial.

On the other hand, the After Eighty trial (457 NSTE-ACS patients ≥ 80 years) showed a significant benefit of routine invasive strategy in the composite primary endpoint of MI, need for urgent revascularization, stroke and death, compared to conservative strategy.[24] MI and need for urgent revascularization were the components of the composite endpoint that showed significant benefit individually. No significant differences were detected regarding to bleeding. It must be pointed out that only 457 patients were included out of 4187 screened: 53% met exclusion criteria (mainly short life expectancy), and only 23% of candidates for inclusion were randomized (main reason for not inclusion was logistic reasons). Therefore, selection bias may be an issue in this trial and the included population may not reflect the whole spectrum of elderly patients. Moreover, coronary angiography was not performed in any of the patients assigned to the conservative group. Thus, this was a strict

Table 1. Comparison of randomized clinical trials including elderly patients in NSTE-ACS.

Trial (year)	*n*	Inclusion criteria	Mean age, yrs	Percent of crossover conservative arm	Primary endpoint & Follow up	Invasive strategy effect HR (95% CI)	Total mortality	
							RIS	CS
Italian ACS elderly[22] (2012)	313	NSTE-ACS, age ≥ 75 yrs, together with ischemic ECG changes and/or elevated troponin.	82.5	28.9%	Composite of all-cause mortality, nonfatal MI, disabling stroke, repeat hospital stay for cardiovascular causes or severe bleeding. Follow-up: one year	0.80 (0.53–1.19) $P = 0.26$	19 (12.3%)	22 (13.8%)
After Eighty[24] (2016)	457	NSTE-ACS, age ≥ 80 yrs.	84.7	0	Composite of MI, need for urgent revascularization, stroke, and death. Follow-up: median 1.53 yrs	0.48 (0.37–0.63) $P < 0.0001$	57 (25%)	62 (27%)
MOSCA[34] (2016)	106	NSTEMI, age ≥ 70 yrs, and at least two significant comorbidities.	82	20%	Composite of all-cause mortality, recurrent MI and readmission for cardiac cause. Follow-up: median 2.5 yrs	0.77 (0.48–1.24) $P = 0.29$	22 (42.3%)	26 (48.1%)

Data are presented as median or *n* (%). ACS: acute coronary syndromes; CI: confidence interval; CS: conservative strategy; HR: hazard ratio (routine invasive *vs.* conservative strategy); MI: myocardial infarction; NSTE-ACS: non-ST-elevation acute coronary syndromes; NSTEMI: non-ST-elevation myocardial infarction; RIS: routine invasive strategy.

conservative group and it does not reflect a selective invasive strategy, which may have provided better results in this subgroup.[24]

These contradictory results may reflect the differences in the design of both trials: selective invasive strategy in the Italian-ACS and pure conservative strategy in the After Eighty. Consequently, the conservative strategy must be avoided in the elderly due to a higher risk of MI and need for urgent revascularization; however, no conclusive data can be drawn regarding to a selective invasive strategy.

Recently, Garg, *et al.*[25] published a meta-analysis of randomized clinical trials comparing routine invasive strategy (RIS) with selective invasive strategy (SIS). It included four studies with 1887 patients (mean age 79 years) followed-up for a mean period of 36 months. It is to note that a total of 63% and 30% of patients underwent revascularization in the RIS and SIS groups, respectively. RIS was associated with a significantly decreased risk of the composite end point of death or MI (OR = 0.65; 95% CI: 0.51–0.83; $P < 0.001$), MI (OR = 0.51; 95% CI: 0.40–0.66; $P < 0.001$), and need for revascularization (OR = 0.31; 95% CI: 0.11–0.91; $P = 0.03$). However, no significant differences in all-cause death, cardiovascular death or major bleeding were found between both strategies.

To summarize, current evidence supports the use of a RIS in elderly in order to reduce the occurrence of MI and need for revascularization at follow-up, and there is no established benefit in terms of mortality. It is to note that the RIS did not increase the risk of major bleedings, probably because antithrombotic drugs were equally used in both strategies and also the reduction in access-site complications driven by the expansion of the radial approach. Last but not least, we have to keep in mind that randomized clinical trials focused on elderly population included a highly selected population (10.9% of screened patients in After Eighty trial and 48.5% of patients assessed for eligibility after signed consent in the Italian-ACS trial), which limits the generalization of the results in the whole spectrum of elderly patients.

Observational studies, despite their methodological limitations, may reflect an evidence closer to the real-life population. In this line of though, population-based registries have evaluated the temporal trends in PCI in the elderly and its relationship with outcomes. In a nationwide US analysis including more than six million of hospitalizations from 1998 to 2013, data showed a significant increase in PCI among patients over 70 years, and these was associated with a decrease in the mortality rate and length of stay in the group receiving PCI compared to patients treated conservatively.[9] Similar findings have been reported over the last years in Europe.[11] Further evidence is necessary including a wide spectrum of elderly patients closer to the "daily-practice" population.

4 Close to the truth?

Currently, invasive management of elderly population still raises several concerns. The mentioned limitations of

the available evidence do not allow to establish firm recommendations in this group of patients. Moreover, future trial designs must take into account inclusion criteria beyond age (such as comorbidities and frailty) and other relevant endpoints in this population (such as quality of life or institutionalization). This wider approach may clarify the more convenient management of an individual elderly patient.

Chronological age itself is not a true reflection of the patient status. On the one hand, age limit for "elderly" definition are heterogeneous and arbitrary, and it becomes obsolete when demographic circumstances vary. On the other hand, clinical characteristics associated with aging, such as comorbidities and frailty, further discriminate patient's risk beyond age.[26–28] The previously mentioned trials focused on age for inclusion. Comorbidities and frailty not only were not taken into account for the inclusion but also some of them were actually considered exclusion criteria.

Comorbidities are frequent in elderly population, and they have a negative prognostic impact in non-STEMI patients.[29] Nevertheless, comorbidity burden defined by the Charlson Comorbidity Index (CCI) is associated with readmissions after PCI.[30] Certain comorbidities, such as renal failure or anemia, confer a higher risk of PCI complications.[31] Therefore, the benefit of invasive strategy in elderly comorbid patients is not established, and these patients are often managed conservatively.[32]

Chuang, *et al*.[33] studied a cohort of 3057 (median follow-up of nine years) admitted with non-STEMI. They classified included patients in three groups based on CCI: low risk (CCI ≤ 1), medium risk (CCI 2–3) and high risk (CCI ≥ 4). Patients in high risk were less likely to receive invasive management (47%) than medium (68%) and low risk patients (81%). After statistical adjustment, the invasive management was associated with a significant reduction in one-year overall-mortality in the "low-risk" and "medium-risk" groups (HR = 0.38, 95% CI: 0.26–0.56; HR = 0.46, 95% CI: 0.32–0.67); but not in the "high-risk" group (HR = 1.02, 95% CI: 0.67–1.56).

Sanchis, *et al*.[34] conducted the first randomized clinical trial comparing routine invasive *vs.* conservative strategy (selective invasive strategy) in comorbid elderly patients with non-STEMI (Table 1). They included 106 patients over 70 years and comorbidities were a requisite for inclusion. Comorbidities were defined by at least two of the following: peripheral artery disease, cerebral vascular disease, dementia, chronic pulmonary disease, chronic renal failure or anemia. The invasive strategy did not improve outcomes in terms of mortality or ischemic events at long term follow-up (2.5 years). However, a significant benefit was observed in a non-prespecified sub-analysis at three months, which disappeared at long term. The small sample size and statistical power limit the conclusions of the study and they may be the cause of the lack of long-term benefit. Nevertheless, it also seems plausible that while PCI may improve short term outcomes, comorbidities may outweigh its long-term benefit. Further investigation is warranted in this setting.

Frailty is a condition characterized by a loss of biological reserve, which leads to impaired response to stressor events.[35] It reflects biological age beyond chronological age. Among elderly admitted with ACS, 10% of > 65 years and 25%–50% of > of 85 are considered frail.[36] Frailty has been identified as a strong independent predictor of in-hospital, 30-day and long-term mortality in elderly patients presenting NSTEMI.[37,38] Furthermore, data suggest that frailty captures most of the prognostic information provided by geriatric conditions after acute coronary syndromes, beyond comorbidities or cognitive impairment.[39–41]

A recent meta-analysis evaluated data from 8773 ACS patients participating in nine individual cohort studies and one RCT in which frailty had been evaluated during admission. The median prevalence of frailty and pre-frailty was 31.5% and 35.4%, respectively. Frail patients were significantly older (mean age: 74.6 *vs.* 69.8 years). Mortality was higher in frail patients. Regarding therapeutic management, frailty patients were less likely to receive coronary angiography, PCI (when angiography was made) or complete revascularization (when PCI performed).[36] These data confirm that this high-risk subgroup is being treated more conservatively and further investigation is warranted to clarify the proper management of these patients.

The LONGEVO-SCA registry included a cohort of 531 unselected elderly patients (≥ 80 years) with NSTE-ACS in which a geriatric assessment was performed during admission. 27.3% of patients were frail, but prevalence was increased up to 40.3% in patients treated conservatively. Conservative strategy was associated with a higher incidence of the primary endpoint (cardiac death, reinfarction or new revascularization at six months). Interestingly, frailty modified the association between therapeutic strategy and outcomes: in non-frail patients, a conservative management was strongly associated with worse outcomes; whereas no significant association was observed in frail patients.[42] Conversely, in a small size registry, PCI predicted a better outcome in frail patients with NSTE-ACS.[43]

To date, no prospective trial has focused on frailty as a guide to therapeutic decisions in ACS. The invasive and conservative strategies in elderly frail patients with non-STEMI (MOSCA-FRAIL) trial is currently recruiting non-STEMI patients older than 70 years and frail who are randomized to a routine invasive *vs.* conservative (selective

invasive) strategy.[44] The primary outcome is number of days alive out of the hospital during the first year and major cardiovascular events at 1-year follow-up.

Finally, the clinical peculiarities of the elderly population may decrease the importance of traditional hard endpoints (death, MI…) in favor of symptoms and quality of life (QoL) when making therapeutic decisions. A sub-analysis of the After Eighty trial found no relevant differences in one-year change of QoL between both initial strategies.[45] However, this included only a subgroup of the trial patients, and the results may not reflect the actual impact of invasive strategy in this endpoint. Several observational studies have pointed out the benefit of an invasive strategy in elderly patients in terms of QoL,[46–49] whereas others have shown little overall benefit with a trend of less impact in the elderly.[50] Heterogeneity of QoL tests, difficulties in its application in this population, and patient selection bias, may limit drawing solid conclusions derived from observational evidence. Further investigation should include QoL and derived endpoints as a measure of outcomes.

5 Conclusions

Elderly patients constitute a unique population group in which both the ischemic and complications risk are increased. The optimal management of ACS in these patients is still a challenge due to their clinical peculiarities and the paucity of specific data. In STEMI, there is no upper age limit regarding urgent reperfusion and primary PCI must be the standard of care. In NSTE-ACS, a strict conservative strategy must be avoided; whereas the use of a routine invasive strategy may reduce the occurrence of MI and need for revascularization at follow-up, with no established benefit in terms of mortality. However, the evidence in this field is derived from a highly selected population and it does not take into account relevant parameters beyond age. Comorbidity and frailty are key features that further discriminate patient's risk beyond age. Evidence on the impact of comorbidity and frailty in management of ACS is scarce. Ongoing trials should clarify the optimal management of ACS based on these parameters.

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