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Treatment of non-ST-segment elevation myocardial infarction in the elderly: the SENIOR-RITA trial

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Non-ST-segment elevation myocardial infarction is the prevalent form of infarction, especially in the elderly population. Compared with ST-segment elevation myocardial infarction, the culprit coronary artery lesion is not always traceable, and only a proportion of cases undergoing coronary angiography result in revascularization. At present, there is no evidence that a systematically invasive strategy has better outcomes, especially lower mortality, than a conservative approach. The SENIOR-RITA trial was the largest study in this regard, having randomized 1518 patients aged ≥75 years to invasive vs. conservative strategy with follow-up up to more than 4 years. Frail patients with cognitive impairment and comorbidities were not excluded. The results showed no differences between the two strategies in terms of primary endpoint (composite of cardiovascular death and infarction) or mortality, but a significant reduction in the risk of infarction and subsequent revascularization. These results confirm those of the previous meta-analysis of studies devoted to elderly patients and should be considered in terms of intervention strategy rather than revascularization efficacy. Subsequent antithrombotic therapies need to consider the frailty of these patients and their high haemorrhagic risk, with the increasing trend towards less aggressive and prolonged therapies than in the past.

Introduction: the complexity of non-ST-segment elevation myocardial infarction

Non-ST-segment elevation myocardial infarction (NSTEMI) has well-defined characteristics within the framework of acute coronary syndromes (ACS). Since the earliest prospective definitions of the syndrome, compared with patients with ST-segment elevation myocardial infarction (STEMI), those with NSTEMI have been characterized as being older, with a higher prevalence of long-term risk determinants, such as diabetes and renal failure, previous infarction, and revascularizations, and with more extensive coronary artery disease.[1] These differential characteristics persist even in the octogenarian population, as demonstrated by comparative data of patients with STEMI and NSTEMI recruited in studies devoted to elderly patients with ACS[2,3] (*Table 1*). For these reasons, in the long term, NSTEMI has thus far been considered a worse prognosis syndrome than STEMI.[1] Many of the aforementioned features are independent predictors of mortality that, added to advanced age, make it more difficult to improve survival following a targeted therapeutic intervention such as revascularization.

Another aspect that makes the validation of an invasive strategy more complex in NSTEMI than in STEMI is the less clear evidence of a culprit and treatable coronary lesion. In NSTEMI, thrombolysis does not resolve the clinical picture, and the demonstration of superiority of revascularization, compared to medical therapy, has also been very problematic: while for every 100 coronary

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Table 1 Comparison of the characteristics of patients with either ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction enrolled in the Elderly ACS 2 trial[2]

	STEMI ($n = 595$)	NSTEACS ($n = 848$)	P
Diabetes	151 (25.4)	269 (31.7)	0.009
Hypertension	426 (71.6)	694 (81.8)	<0.001
Hypercholesterolaemia	228 (38.3)	416 (49.1)	<0.001
Smoking	63 (10.6)	68 (8.0)	0.094
Chronic obstructive pulmonary disease	23 (3.9)	64 (7.5)	0.004
eGFR[a] at admission (mL/min/1.73 m^2)	55 (43-67)	55 (42-68)	0.781
Previous cardiovascular events			
Myocardial infarction	52 (8.7)	222 (26.2)	<0.001
Coronary angioplasty	62 (10.4)	202 (23.8)	<0.001
Coronary artery bypass	22 (3.7)	106 (12.5)	<0.001
Peripheral arterial disease	36 (6.1)	89 (10.5)	0.003
Left ventricular ejection fraction	45 (40-55)	50 (45-55)	<0.001
Three-vessel coronary disease	141 (23.8)	291 (34.4)	
Left main disease	16 (2.7)	83 (9.8)	<0.001

[a]eGFR, estimated glomerular filtration rate (Cockroft-Gault formula).

arteries in STEMI at least 90 result in immediate revascularization, in NSTEMI only about half of the patients undergoing coronary angiography will receive revascularization, and this is also the case in the most recent studies, 49.9% in the recent SENIOR-RITA (Older Patients with Non-ST-Segment Elevation Myocardial Infarction Randomized Interventional Treatment) trial.[4] For these reasons, the path towards demonstrating superiority of an early invasive strategy with angiography and, where feasible, revascularization in the elderly patients with NSTEMI, which began in 2008 with the Italian Elderly ACS trial,[5] has been very complex[6] (*Figure 1*).[5,7-13] A recent *individual patient data* (IPD) meta-analysis[14] of 1479 patients with NSTEMI ACS (median age 84 years, 89% with elevated baseline troponin values) enrolled in six randomized trials conducted between 2008 and 2021 did not demonstrate a significant reduction in the combined endpoint of death and myocardial infarction (MI) at 1 year with the invasive vs. conservative strategy [hazard ratio (HR) 0.87; 95% confidence interval (CI) 0.63-1.22; $P = 0.43$]. The only significantly reduced endpoints were MI (HR 0.65; 95% CI 0.44-0.87; $P = 0.006$) and the need for urgent revascularization (HR 0.41; 95% CI 0.18-0.95; $P = 0.037$), with no differences in mortality.

The SENIOR-RITA trial

The SENIOR-RITA trial[4] conducted in the UK between 2016 and 2023 and discontinued slightly earlier than planned with 1668 patients, partly due to the intervening pandemic that inevitably slowed enrolment at the 48 participating centres, should be placed in this context. Approximately one-fifth of the 6977 eligible patients were randomized, with a total of 1518 participants; the mean age, proportion of women, and proportion of invasively treated cases were almost overlapping between the randomized patients and those eligible but not randomized for various reasons.

The study has many commendable aspects:

- It enrolled only patients with Type 1 NSTEMI, eliminating the background noise of NSTEMI secondary to haemodynamic, hypertensive, or arrhythmic (Type 2) causes.
- It did not exclude frail patients and those with comorbidities or cognitive impairment from enrolment, conducting in all patients an important multifunctional assessment that will be assets for subsequent analyses of the prospective impact of these conditions, prevalent in elderly patients.
- It did not exclude patients with an indication for anticoagulant therapy who constituted ~23% of the population (12.5% of the total on triple therapy with aspirin, a $P2Y_{12}$ receptor blocker, and oral anticoagulant).
- Eighty-nine per cent of procedures were conducted with radial access with procedural complications in <1% of patients.

Time intervals between admission and percutaneous revascularization, with a median of 5 days, or bypass surgery, with a median of 18 days, were longer than the current guidelines, which recommend an invasive approach within 24-48 h.

The results, summarized in *Figure 2*, show that only the risks of re-infarction and subsequent revascularization were significantly reduced with the invasive approach, confirming the data from the previous meta-analysis.[14] When the patients from this study are integrated into an *updated IPD meta-analysis*, which has been preannounced by the principal investigator of the study, it will make the evidence that a systematically invasive strategy does not reduce mortality in elderly patients with NSTEMI even more solid. It is possible that a reduction in mortality is an unsuitable target for studies in very elderly populations: in the SENIOR-RITA trial, the primary composite endpoint of cardiovascular death and non-fatal infarction shows a very favourable trend with the invasive approach in patients aged <80 years (HR 0.70, 95% CI 0.46-1.07) compared with a decidedly neutral outcome in those aged ≥80 years (HR 1.01, 95% CI 0.81-1.27). For the above reasons, this conclusion does not necessarily relate to revascularization, but rather to a strategy that implies a probability of revascularization in ~50% of cases. The outcome of patients who actually do revascularization in the acute phase should be evaluated in an exploratory manner. The latter aspect is somewhat challenged by the surprising results of the FIRE (Functional Assessment in Elderly MI Patients with Multivessel Disease) study.[3,13]

The challenge of the FIRE study

The FIRE study, published in 2023,[13] randomized 1445 patients aged ≥75 years (mean age 80 years) with ACS

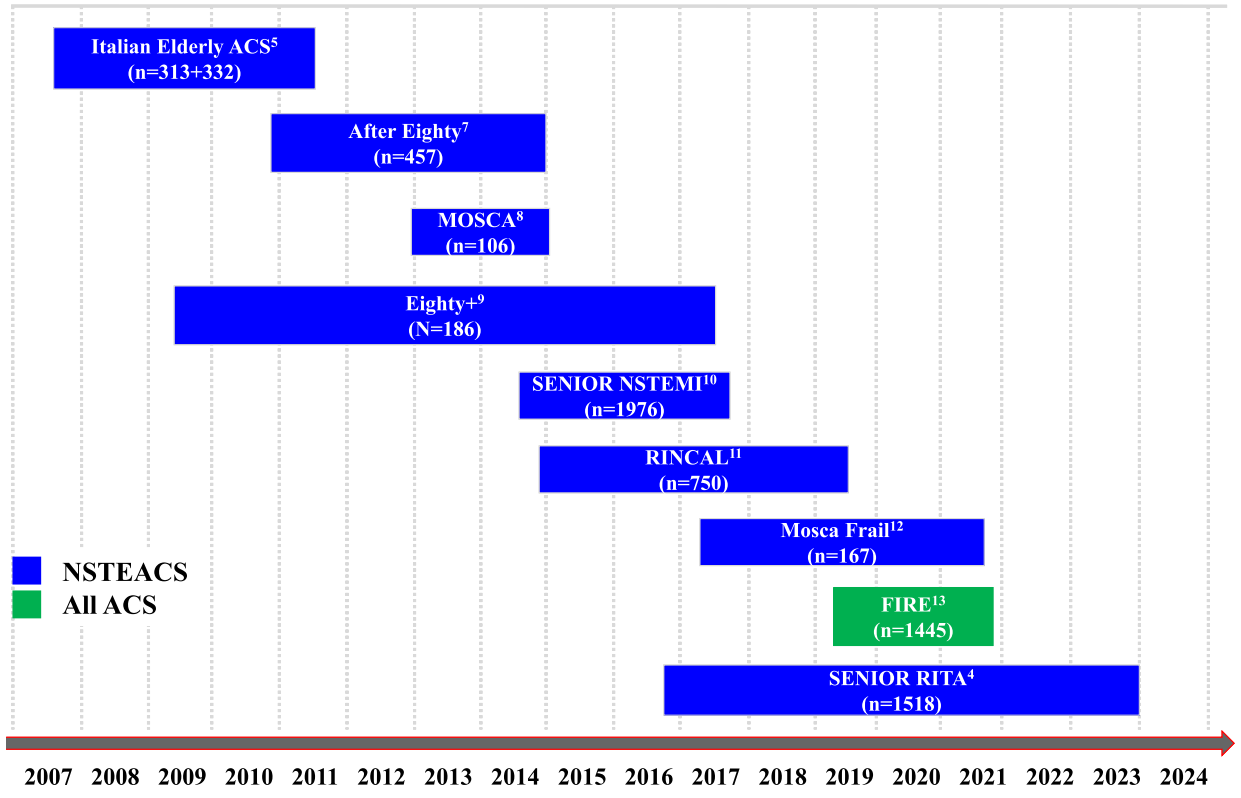

Figure 1 Graphical representation of the timing and sample size of clinical trials comparing treatment strategies in elderly patients with non-ST-segment elevation myocardial infarction acute coronary syndrome.

and multivessel coronary artery disease to receive complete revascularization, guided by physiologic assessment, or revascularization of the culprit artery alone. Thus, the starting point of this study is after coronary angiography, having excluded patients without technical indication for revascularization and those with single-vessel disease. Of the participants, 36.5% were women, and 35.2% had STEMI. One-year cardiovascular mortality in patients with NSTEMI was ~6%,[3] overlapping with that in the SENIOR-RITA trial.

At 1 year, the combined primary endpoint of death, infarction, stroke, and revascularization occurred in 15.7% of patients with complete revascularization and 21.0% of those with revascularization of the culprit vessel only (HR, 0.73; 95% CI, 0.57-0.93; $P = 0.01$), but the endpoints of death and infarction (8.9 vs. 13.5%; HR, 0.64; 95% CI, 0.47-0.88) and even all-cause mortality (9.2 vs. 12.8%; HR 0.70; 95% CI 0.51-0.96) and cardiovascular mortality (5.0 vs. 7.7%; HR 0.64, 95% CI 0.42-0.97) were significantly lower in the group with complete revascularization. Data in patients with NSTEMI (64.8% of the population) were as positive as in the overall study, with HR 0.61 (0.41-0.91) for the composite endpoint, 0.73 (0.49-1.09) for overall mortality, 0.66 (0.39-1.13) for cardiovascular mortality, and 0.57 (0.31-1.05) for MI, with all *P* for interaction negative towards the STEMI group.[3] The conclusion of this study is that complete revascularization significantly improves outcome, including 1-year mortality, in patients with ACS aged ≥75 years with multivessel disease: admittedly, there is a lack of a control group that does not undergo revascularization, which is certainly not applicable in the STEMI setting. In an IPD meta-analysis restricted to patients aged ≥75 years of all trials that compared multivessel revascularization of the culprit vessel alone in STEMI, the benefit was lost over time, becoming non-significant after the 4-year[15] follow-up in the SENIOR-RITA trial precisely, a benefit moreover not expected in the ninth decade of life. However, the preliminary step to access the benefits of revascularization remains coronary angiography, which was not included in the conservative arm of the SENIOR-RITA trial.

The change of perspective in antiplatelet therapy after acute coronary syndromes in the elderly

The elderly patients and bleeding risk

The elderly patients have a high bleeding risk (HBR).[6,16] In patients with ACS, bleeding risk is calculated using the PRECISE-DAPT score[17] or the criteria established by the Academic Research Consortium (ARC).[18] Age represents one of the five variables on which the PRECISE-DAPT is constructed and has a significant weight in the calculation. In addition, although age ≥75 years is considered a minor criterion in the ARC definition,[18] elderly patients very frequently have an additional minor criterion (mainly renal failure or anaemia) that

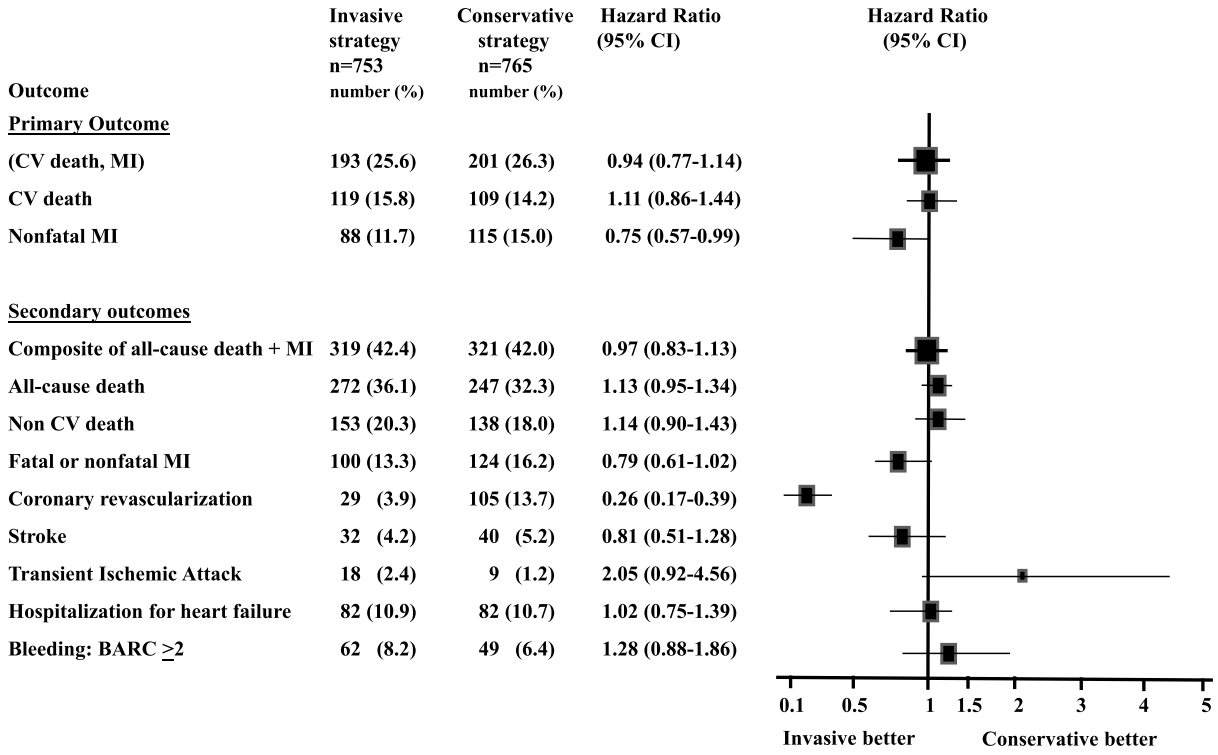

Figure 2 Primary and key secondary outcomes of the SENIOR-RITA trial. CV, cardiovascular; MI, myocardial infarction; BARC, Bleeding Academic Research Consortium; CI, confidence interval.

puts them in the category of HBR. In a study by our group,[19] moreover, conducted in a patient population selected for enrolment in a clinical trial and not on anticoagulant therapy, more than two-thirds of patients were classified as HBR according to the ARC criteria.

Guideline recommendations and recent evidence

The most recent European Society of Cardiology (ESC) guidelines recommend abbreviated dual antiplatelet therapy (DAPT) (albeit with IIb recommendation for 1-month DAPT) followed by single antiplatelet therapy in HBR patients.[20] Regarding the elderly patients, although defined as 'at special risk of bleeding for antithrombotic therapy in the acute and long-term phase', no specific recommendation is given, but it is recommended that the treatment strategy and medications be chosen taking into account the individual patient's ischaemic and haemorrhagic risk and according to the presence of comorbidity, frailty, and cognitive function.

In a recent meta-analysis,[21] data were collected from randomized trials conducted on the duration of DAPT in patients undergoing coronary angioplasty, focusing on 9006 HBR patients. The study showed that a shortened duration strategy ('abbreviated DAPT') of 1–3 months was associated with a significant reduction in cardiovascular mortality and bleeding without increasing the risk of ischaemic events compared with at least 6 months of DAPT.

In a recent consensus paper,[22] although the issue of the elderly patients is not specifically addressed, the proposed 'default strategy' in the HBR patients is an initial 1-month DAPT, combining aspirin with clopidogrel or ticagrelor, with a de-escalation to single antiplatelet therapy with aspirin or clopidogrel or ticagrelor. The proposed treatment strategy was compared with a standard 12-month DAPT, and the results were presented in an IPD meta-analysis:[23] considering globally the data of 24. 096 patients (both ACS and chronic coronary syndromes), the composite endpoint of all-cause mortality, MI, and stroke did not differ, using ticagrelor or clopidogrel as monotherapy, from those obtained with DAPT (HR 0.93, 95% CI 0.79–1.09; $P = 0.005$ for non-inferiority) with similar results observed in ACS patients who constituted 60% of the case series. On the other hand, $P2Y_{12}$ receptor inhibitor monotherapy had a lower haemorrhagic risk than DAPT (HR 0.49, 95% CI 0.39–0.63; $P < 0.001$). In the studies included in that meta-analysis, patients aged ≥75 years were modestly represented, but no interaction between efficacy or safety endpoints for those aged ≥65 or <65 years was observed in subgroup analyses. A more recent IPD meta-analysis comparing standard 12-month DAPT (aspirin and ticagrelor in 86% of patients), but limited to patients treated only with ticagrelor in the monotherapy group,[24] showed that, compared with 12-month DAPT, de-escalation to ticagrelor alone did not increase ischaemic risk while reducing haemorrhagic risk especially in patients with ACS. Also for this analysis, patients aged ≥75 years were a minority. However, considering the ACS patients classified as HBR (12.5% of the entire case series), major bleeding [Bleeding Academic Research Consortium (BARC) 3 or 5] was 1.8%

in the ticagrelor monotherapy group and 4.8% in the group treated with 12-month DAPT (consisting of aspirin + ticagrelor in all patients). These data show how a DAPT based on the combination of ticagrelor and aspirin for 12 months can be harmful in HBR patients.

Studies comparing antiplatelet strategies in the elderly patients

There is little evidence derived from studies comparing different antiplatelet strategies performed specifically in the elderly patients with ACS.[25] The Elderly ACS 2 trial,[26] conducted between 2012 and 2017, randomized 1443 patients (median age 80 years) with ACS treated with PCI to a 12-month DAPT with aspirin and clopidogrel vs. aspirin and 'low-dose' prasugrel (5 mg) according to Food and Drug Administration (FDA) indications: both ischaemic and haemorrhagic events occurred in non-significantly different rates in the two groups. A *post hoc* analysis of this study, which considered not only the first event but all events that occurred in the enrolled population, showed a lower incidence of ischaemic events in the first month with 'low-dose' prasugrel, while haemorrhagic events were significantly lower in the clopidogrel group.[27] In the POPular AGE study (clopidogrel vs. ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome),[28] which enrolled 1002 patients with NSTEMI ACS (mean age 77 years), a DAPT with aspirin and clopidogrel significantly reduced the risk of bleeding compared with patients treated with DAPT with aspirin and ticagrelor, with no differences between the two groups in thrombotic events. In that study, about half of patients treated with ticagrelor discontinued therapy due to side effects: moreover, 20% of patients were also on anticoagulant therapy, a percentage repeated in the SENIOR-RITA trial. Finally, the observational SWEDEHEART data[29] confirmed these observations in 14 005 elderly patients (median age 85 years, 58% treated with PCI): after statistical adjustment, the use of ticagrelor was found to be associated with an increased risk of bleeding and mortality compared with clopidogrel. All these observations appear to be in contrast to the analysis conducted on the elderly population included in the PLATO (PLATelet inhibition and patient Outcomes)[30] study, which had shown that the efficacy of ticagrelor in reducing the primary endpoint of cardiovascular death, MI, and stroke compared with clopidogrel was not significantly different in patients aged <75 years compared with those aged ≥75 years (although in the latter, the incidence of events in the two groups was almost similar, 17.2 vs. 18.3%). Moreover, in an analysis of the same study targeting patients with NSTEACS undergoing revascularization in the acute phase, the efficacy of ticagrelor vs. clopidogrel was found to be influenced by age, with a beneficial effect in patients aged <65 years (HR 0.59; CI 95% 0.41–0.95) but not beneficial in those aged ≥65 years (HR 1.17; CI 95% 0.85–1.61; *P* for interaction = 0.01), a finding published in the appendix of the paper.[31]

Overall, the decreasing need for a powerful and prolonged DAPT after angioplasty in ACS can likely be attributed to the evolution of interventional treatment due to improved material technology and increased operator experience, combined with an increased focus on secondary prevention goals.[32] The SENIOR-RITA procedural safety data point in the same direction. The conclusions from the albeit few observations discussed above are that the elderly patients with ACS should be considered at HBR and that antiplatelet treatment should initially consist of a DAPT using aspirin combined with a more potent inhibitor than clopidogrel (5 mg prasugrel in our experience), of short duration (likely 1 month), followed by either DAPT with clopidogrel[25] or monotherapy with a $P2Y_{12}$ receptor inhibitor, such as ticagrelor[21] or clopidogrel.[33] However, to reach evidence-based conclusions, further specific studies in the elderly ACS population and comparing these different antiplatelet strategies are needed, not to mention the possibility of continuation of aspirin alone, which has so far not been tested in comparison with $P2Y_{12}$ inhibitor monotherapy.

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Data availability

No new data were generated or analysed in support of this research.

Disclaimer

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