

Management strategy of non-ST segment elevation acute coronary syndromes in octogenarians: a call for a personalized approach

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The rate of octogenarians among patients with non-ST segment elevation acute coronary syndrome (NSTEMACS) will continue to increase in the coming years due to population aging. Routine invasive management of NSTEMACS has shown long-term benefit in general population but evidence-based recommendations in this subset of patients remain scarce. The decision-making process in elderly patients should take into account several geriatric factors including frailty, comorbidities, dependency, cognitive impairment, malnutrition, and polymedication. Chronological age is a poor marker of the biological situation in octogenarians and heterogeneity is common. Recent studies support an invasive strategy in most octogenarians. However, observational data suggest that significant comorbidities seem to be related to futility of an invasive approach whereas the risk-benefit balance in frail patients might favor revascularization. Further studies are needed to define a tailored approach in each octogenarian with NSTEMACS through a better assessment and quantification of frailty, comorbidities and ischemic risk.

Keywords

Octogenarians; Non-ST elevation acute coronary syndrome; Frailty; Comorbidities; Elderly

1. Introduction

The steep rise of life expectancy in the past century has dramatically shifted the population pyramid, and the number of people aged 80 or older is projected to keep growing. The health burden of this aging population is a major concern worldwide. Coronary artery disease (CAD) stands as the leading cause of death in the elderly [1–4]: patients older than 77 account for a third of patients with acute myocardial infarction [3, 5, 6]. Large randomized trials have showed a long-term benefit of routine invasive management in patients with non-ST segment elevation acute coronary syndrome (NSTEMACS), but the mean age in these trials was around 65 years and few octogenarians were included, raising concerns about the external validity of these results when applied to older patients [7, 8]. This scarcity of evidence may account for the marked differences seen in clinical management

of elderly patients with NSTEMACS across countries [9]. Several factors associated with NSTEMACS morbi-mortality are common in octogenarians (Fig. 1). Age is not only a powerful risk factor for CAD but also an independent prognostic marker for cardiovascular complications after an acute coronary syndrome [10]. Furthermore, NSTEMACS in octogenarians frequently has an atypical clinical presentation and includes symptoms as dyspnea, syncope, or malaise [11, 12]. In addition, the higher prevalence of bundle branch blocks and intraventricular conduction disorders in the elderly may contribute to diagnostic uncertainty [13]. Issues of accessibility to health services by older patients also contribute to diagnostic delay. Moreover, octogenarians usually display more complex CAD and reduced cardiac reserve leading to an increase in NSTEMACS-related and procedural complications [5, 10]. Comorbidity and frailty, common in octogenarians, are independently associated with worse outcomes, including rehospitalizations and death for noncardiac causes [14–17] and are the main factors that explain that the patients at higher risk receive invasive treatment less frequently, the so-called risk-treatment paradox [18]. This review intends to give a detailed insight into the peculiarities of octogenarians with NSTEMACS.

2. Frailty and comorbidities

Age plays a major role in the morbidity and mortality of patients with NSTEMACS and is included in all risk assessment scores [19, 20]. However, even among octogenarians, risk profiles can be enormously heterogeneous particularly with regards to frailty and comorbidity. Therefore, comprehensive geriatric assessment is essential in these patients [21].

Frailty can be characterized as a phenotype of poor physical function and vulnerability preceding dependency [22]. It leads to longer hospital stay, greater use of resources, higher risk of delirium [23] and increased risk of both procedural and pharmacological complications [10, 19, 24]. Frailty is also associated with female sex. Octogenarian women with

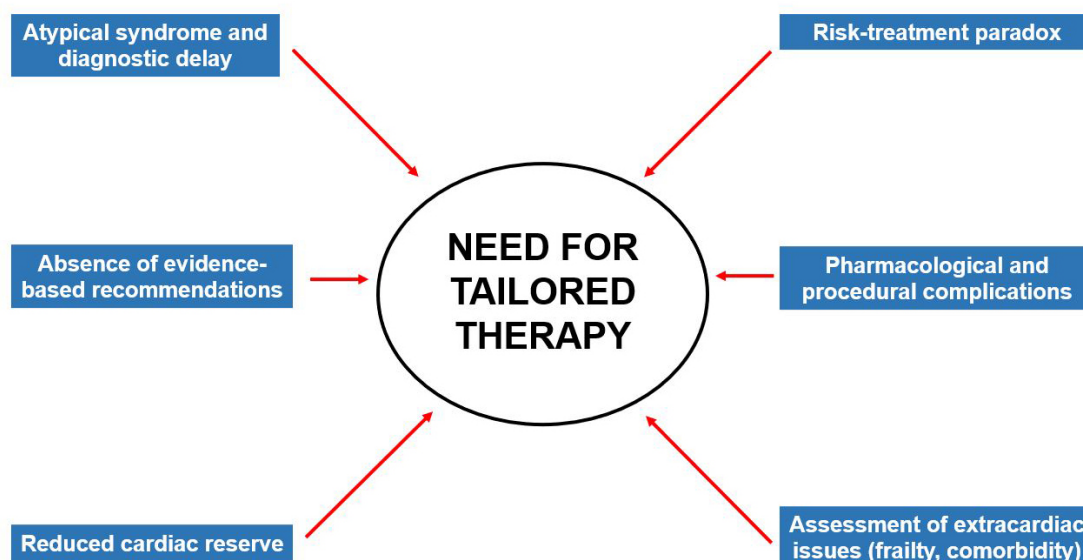


Fig. 1. Distinctive features of octogenarians with non-ST segment elevation acute coronary syndrome. A personalized approach is essential to address the heterogeneity in this subset of patients.

NSTEACS present frailty and readmissions more frequently than men [25] and undergo coronary angiography less frequently than men despite their worse prognosis [26]. Although its impact on prognosis is well documented, frailty is still very rarely assessed when planning the management of NSTEACS in octogenarians [27]. Different scales have been developed to this end. Scales focused on physical frailty are based on symptoms like slowness, weakness, unintentional weight loss, low energy, or low physical activity. The most widely used measure of physical frailty is the Fried scale [28]. A different approach is to consider frailty as an accumulation of deficits (multidimensional frailty) including comorbidities, disabilities, symptoms, and laboratory results associated with poor outcomes [21]. Frailty assessment is important, as frailty might influence management, risk stratification, and prognosis [22]. Frailty should be assessed both in the acute and chronic settings [29]. Ideally, frailty should be measured in the community, so that the evaluation could be available when the patient experiences an acute event [21]. In patients admitted with NSTEACS, frailty evaluation at admission is better done with simple scales that do not involve physical tests [21, 27]. The most recommended scales in this scenario are the Clinical Frailty Scale and the “FRAIL” Scale [30] that have shown a consistent association with short-term and mid-term mortality and with conservative treatment [31–36]. The Edmonton Frail Scale is also independently associated with mortality and is a better risk predictor than chronological age [37]. Furthermore, frailty can also be measured including not only clinical items but also biomarkers such as reduced blood levels of albumin, vitamin D and cystatin C derived from malnutrition [38] or an increased C-reactive protein [39]. The Green score, which includes laboratory determinations, is more complex to measure but it has

also demonstrated to be a better risk predictor than the Fried Criteria in elderly patients with NSTEACS [40–42]. Moreover, the claims-based frailty index has been created to facilitate the study of frailty from epidemiologic and population health perspectives. It is calculated by an addition of several frailty-associated variables (impaired mobility, falls, musculoskeletal problems, cognitive impairment, heart failure, stroke, admission in the previous 6 months...) obtained from administrative data [43, 44].

Different scales have also been developed to assess comorbidity, the most common being the Charlson Comorbidity Index [45]. Another simplified comorbidity index comprising 6 conditions (renal failure, anemia, diabetes, peripheral artery disease, cerebrovascular disease and chronic lung disease) has been shown to provide a useful risk stratification in elderly patients with NSTEACS [46]. In any case, each illness should be carefully evaluated individually as their severity, prognostic impact, and influence in management could be very different.

3. Pharmacological considerations

Age-dependent decline in muscle mass, renal function and volume of distribution alters pharmacokinetics. Octogenarians receive optimal medical therapy less frequently than younger patients due to concerns for side effects, bleeding risk [47], and procedural complications [24, 47]. Meticulous dosing adjustment is needed, and may sometimes be particularly challenging in very old patients and in those with multiple comorbidities, in which evidence-based recommendations are scarce.

Observational data suggest that dosing errors with antithrombotic therapy are more frequent in vulnerable patients leading to a higher risk of bleeding [48]. The Platelet

Inhibition and Patient Outcomes (PLATO) trial demonstrated mortality and ischemic events reduction in the ticagrelor arm against clopidogrel, without a significant increase in major bleeding across all subgroups [49]. However, in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) trial, ischemic benefit in the prasugrel group was coupled with an increase in major bleeding, so a reduced-dose of prasugrel was suggested for specific subgroups like octogenarians [50]. In a real-world registry of patients with NSTEMACS, the duration but not the type of dual antiplatelet therapy was associated with a higher rate of bleeding without differences between clopidogrel and ticagrelor after adjustment for confounders [51]. In contrast, results from the SWEDEHEART registry showed higher mortality and major bleeding in elderly patients treated with ticagrelor [52]. Different approaches have been suggested, including a more cautious risk profile definition, shortening dual antiplatelet therapy duration, using ticagrelor monotherapy or de-escalation from ticagrelor/prasugrel to clopidogrel, since ischemic risk prevails in the first month whereas bleeding risk becomes more important within long-term [53].

The treatment of cardiovascular risk factors is another key issue. A high-dose statin regimen is known to provide greater protection, but its effectiveness in octogenarians has been challenged [54]. Conversely, observational data including 634 elderly patients suggested that a high-dose statin regimen achieved a greater benefit than in younger controls and that major side effects did not depend on the statin dose or type [55]. The addition of ezetimibe to simvastatin monotherapy conferred prognostic benefit without safety issues in a clinical trial including elderly patients [56]. Current guidelines recommend the use of statin therapy in octogenarians with NSTEMACS considering a low-dose in case of renal impairment or potential for drug interactions [57].

Octogenarians with diabetes mellitus usually display long-term disease and established target organ damage that may limit benefits from sodium glucose co-transporter 2 inhibitors and glucagon like peptid-1 receptor agonists, but they are recommended nonetheless to reduce the burden of cardiovascular disease, unless contraindicated [58]. Risk of hypoglycemia is increased in this subgroup, and its consequences more severe, so strict glycemic control should be avoided [58]. Therefore, sulfonylureas and meglitinides are particularly discouraged in this subset of patients, due to their absence of cardiovascular benefit and higher risk of hypoglycemia [57]. Dipeptidyl peptidase-4 inhibitors have proven to be safe in the elderly irrespective of renal impairment except for saxagliptin, which was associated with higher risk of heart failure [59].

There is a general recommendation for cautious introduction of ACE inhibitors and β -blockers, with more lenient dosing targets than the standard heart failure therapy [60]. Enrolment in cardiac rehabilitation programs provides sub-

stantial benefits in the elderly after an NSTEMACS [29]. A trial in elderly patients randomized to cardiac rehabilitation during 1 year versus clinical follow-up, improved cardiovascular risk factors control, Mediterranean diet adherence, and functional capacity [61].

Suboptimal secondary prevention is a common problem in octogenarians [62], but the scarce clinical trial data available and observational evidence strongly support the use of optimal medical therapy in robust octogenarians.

4. Evidence regarding management

The current recommendations arise mainly from a meta-analysis of the FRagmin and Fast Revascularisation during Instability in Coronary artery disease (FRISC) II, Randomized Intervention Trial of unstable Angina (RITA)-3 and Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trials, comparing routine invasive strategy with selective invasive strategy [63]. The FRISC II trial was a prospective randomized multicenter study including 2457 patients with a median age of 66 years. There was a significant decrease in myocardial infarction and non-significantly lower mortality in the routine invasive arm after 6 months [64]. The sustained benefit up to 5 years in FRISC-II was mainly related to myocardial infarction, whereas the mortality benefit decreased, especially in elderly patients [65]. The RITA-3 randomized 1810 patients with a mean age of 62 years, the ones in the intervention group underwent revascularization within the first 72 hours. After 4 months the difference between both groups was mainly driven by a significant decrease of refractory angina in the intervention arm [66]. In contrast with FRISC II, the benefit at 5 years follow-up was also due to a long-term reduction in mortality, especially in high-risk patients [67]. ICTUS randomized 1200 patients with a median age of 62 years and could not demonstrate superiority of the invasive approach, though rehospitalizations were significantly lower in that group [68]. These apparent inconsistencies might be related to differences in design, concomitant medical treatment, timing of angiography, and patients' characteristics. Meta-analysis of these and other trials showed that a routine invasive strategy does not reduce all-cause mortality in NSTEMACS but decreases the risk of reinfarction and rehospitalizations, especially in high-risk patients, at the cost of increased bleeding and periprocedural complications [69–73]. However, most trials were conducted before key improvements in NSTEMACS management such as new antiplatelet drugs, the widespread use of radial access and modern drug-eluting stents. Indeed, recent observational studies found clear prognostic benefit from invasive strategy [74, 75]. Therefore, guidelines recommend routine invasive strategy for all patients irrespective of age, except for those deemed to be at a very low risk, where a selective invasive strategy is accepted [20, 76]. Observational studies also support an invasive approach, but are burdened by an unavoidable selection bias, as octogenarians who undergo conservative management are more likely to be frail and have

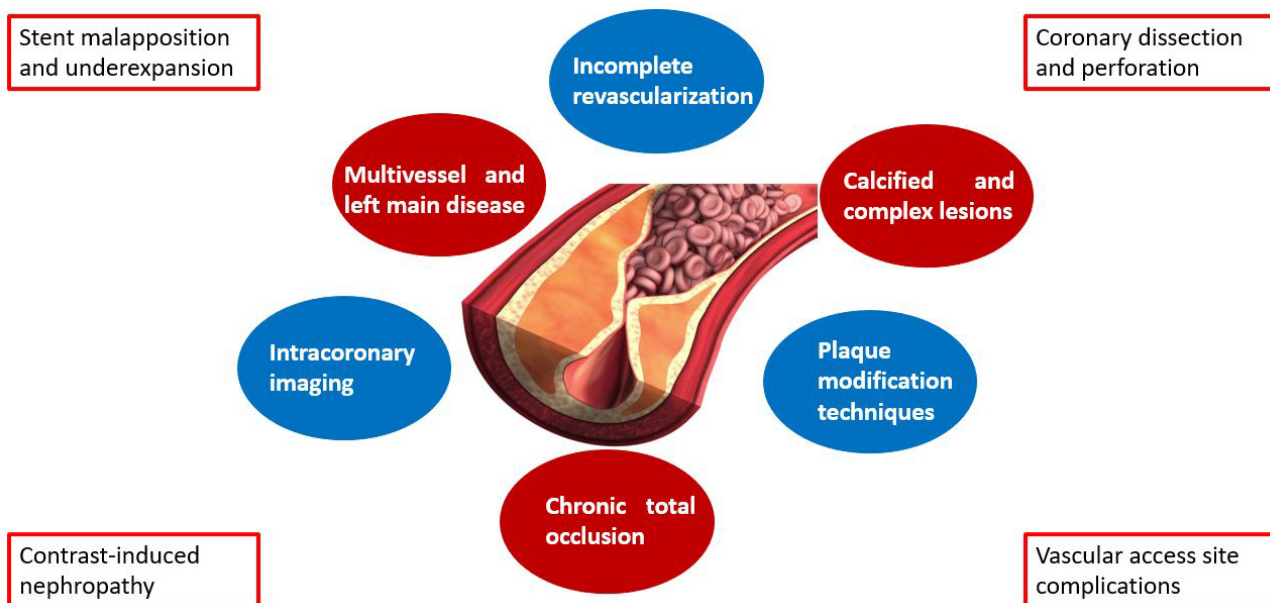


Fig. 2. Main features and risks of percutaneous coronary intervention in octogenarians with non-ST segment elevation acute coronary syndrome. Most octogenarians display multivessel and complex disease with tortuosity and vascular calcification that increase the need of advanced techniques.

severe comorbidities. Nevertheless, over the past decade the shift towards invasive management of NSTEMI in octogenarians has come hand in hand with a decrease in mortality [3, 77–80]. In-hospital mortality has fallen for all age subgroups, with the largest absolute reduction seen among the elderly [81]. Although octogenarians undergo invasive management less frequently, when revascularization is performed it is associated with a survival benefit [74, 75]. A propensity score analysis comparing an invasive strategy with conservative treatment in octogenarians with non-ST elevation myocardial infarction was associated with a 32% decrease in mortality [82]. Percutaneous revascularization was feasible in frail patients and was associated to a significant reduction of rehospitalizations and mortality [83]. Older adults seem to benefit significantly from invasive treatment at the cost of an increased incidence of bleeding complications, which were particularly high in patients with comorbidity, and a similar rate of procedural complications between frail and non-frail patients [84–86]. The inherent greater risk of complications does not directly entail absence of benefit from an invasive approach. Perhaps counter-intuitively, greater frailty without significant comorbidities has been shown to be associated with greater clinical and survival benefit from an invasive approach in NSTEMI [83, 87]. On the other hand, comorbidities can result in futility if the prognosis, clinical implications or functional repercussions of a previous condition are more limiting than the NSTEMI itself [88]. Another observational study with propensity-score matching showed a decrease in mortality associated with in-hospital revascularization in elderly patients with NSTEMI, although the benefit of revascularization was progressively reduced as the comorbidity burden increased [89]. Renal failure, peripheral

artery disease, and chronic lung disease are the comorbidities with the most detrimental effects on revascularization benefits [89]. Other comorbidities as diabetes [90], anemia [91] and chronic kidney disease also have significant influence on the outcome of patients with acute coronary syndromes, particularly in the case of the elderly, and related to their frailty status [92]. The association with prognosis is stronger in frail patients for diabetes [93] and in robust patients for anemia [94] and kidney disease [95]. Renal impairment, left ventricular systolic dysfunction and mitral regurgitation are other markers of poor prognosis in octogenarians [96, 97].

Procedural complications have dramatically decreased with the widespread use of the radial access, which should also be preferred in the elderly even though the rate of access site crossover is superior in patients over 75 years [98, 99]. Another frequent complication with prognosis impact is contrast-induced nephropathy. Previous renal impairment, diabetes mellitus, frailty and age are among the most important risk factors. Minimizing the volume of contrast together with pre- and post-procedural hydration is recommended to prevent this entity [20].

More than 50% of octogenarians with acute coronary syndrome display multivessel disease, which is associated with worse outcomes [18]. The results of several randomized trials support complete revascularization in ST-elevation myocardial infarction [100–102]. Subgroup analysis suggested greater benefit in those older than 65 years in the Complete versus Lesion-only Primary PCI trial (CvLPRIT) [100]. Complete revascularization was also associated with better results in a prospective registry analysis of >21000 patients with acute coronary syndrome [103], although once again octogenarians were barely included. A culprit-only strategy

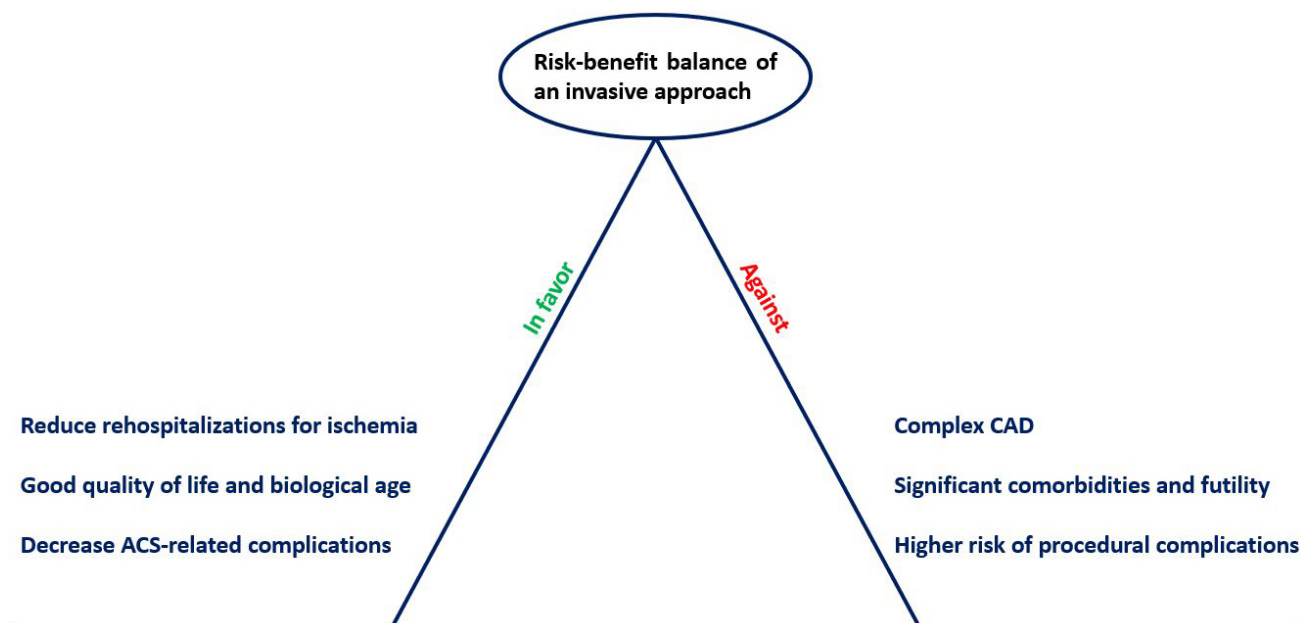


Fig. 3. Risk-benefit balance of invasive management in octogenarians with non-ST segment elevation acute coronary syndrome. ACS, Acute coronary syndrome; CAD, Coronary artery disease.

could make sense for the elderly to shorten hospital stay and antiplatelet treatment duration, but mainly to reduce procedural complications related to the greater challenge of treating complex multivessel CAD. Vessel tortuosity and vascular calcification hamper optimal apposition, increase the need of advanced techniques for lesion preparation such as rotational atherectomy and lead to higher incidence of inadequate stenting and periprocedural complications (Fig. 2) [104]. In this setting, the Functional versus Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease (FIRE) trial will provide evidence on whether a specific revascularization strategy may improve outcomes among the elderly presenting with a myocardial infarction and multivessel disease [105].

Cardiac surgery has been classically avoided in octogenarians due to comorbidity and frailty concerns and the inherent risk of cardiopulmonary bypass. However, there has been a three-fold increase in elderly patients undergoing coronary artery bypass grafting in the last decades [106]. A propensity-score matched observational study compared 7-years outcomes of 941 patients undergoing percutaneous coronary intervention with 441 matched patients treated with surgery. In this study percutaneous coronary intervention was an independent predictor of mortality, and surgery reduced more clearly the risk of death in octogenarians, patients with left main or three-vessel disease, and those with previous heart failure or renal impairment [107]. A series of 101 octogenarians receiving bypass grafting presented a survival rate of 91% in the first year [108]. Mechanical ventilation times and intensive care unit stay lengths are expected to be longer and may in some cases be unacceptable in risk-benefit terms

[108], so frailty assessment has important implications for the postoperative course [109]. Several studies have proved feasibility of bypass grafting in the elderly bearing in mind that shorter cardiopulmonary bypass or off-pump surgery may prevent postoperative morbidity. Nonetheless, a recent meta-analysis did not find off-pump grafting to be superior in older patients [110].

Octogenarians are by definition a high-risk group, but evidence from randomized clinical trials regarding invasive approach is recent and still scarce. A meta-analysis showed that invasive strategy was associated with a 30% reduction in the 5-year composite of cardiovascular death or myocardial infarction in patients >65 years [63]. However, this benefit cannot be assumed to translate to octogenarians. Three randomized clinical trials provide most information regarding invasive strategy in octogenarians with NSTEMI/ACS. The Italian Elderly ACS included 313 patients over 75 years and showed no difference in a combined primary endpoint of death, myocardial infarction, disabling stroke, and repeat hospital stay for cardiovascular causes or severe bleeding. The crossover between both groups was noteworthy, since patients in the conservative arm experienced significantly more recurrent ischemic events prompting revascularization and 45% patients in the invasive arm did not undergo revascularization. Also, frailty and comorbidities scales were not even recorded [111]. CoMORBilidades en el Síndrome Coronario Agudo (MOSCA) trial included 106 patients >70 years with at least two of the following comorbidities: renal failure, neurological disease with residual deficit, dementia, anemia, chronic pulmonary disease or peripheral artery disease. The main endpoint was the composite of all-cause mortality, re-

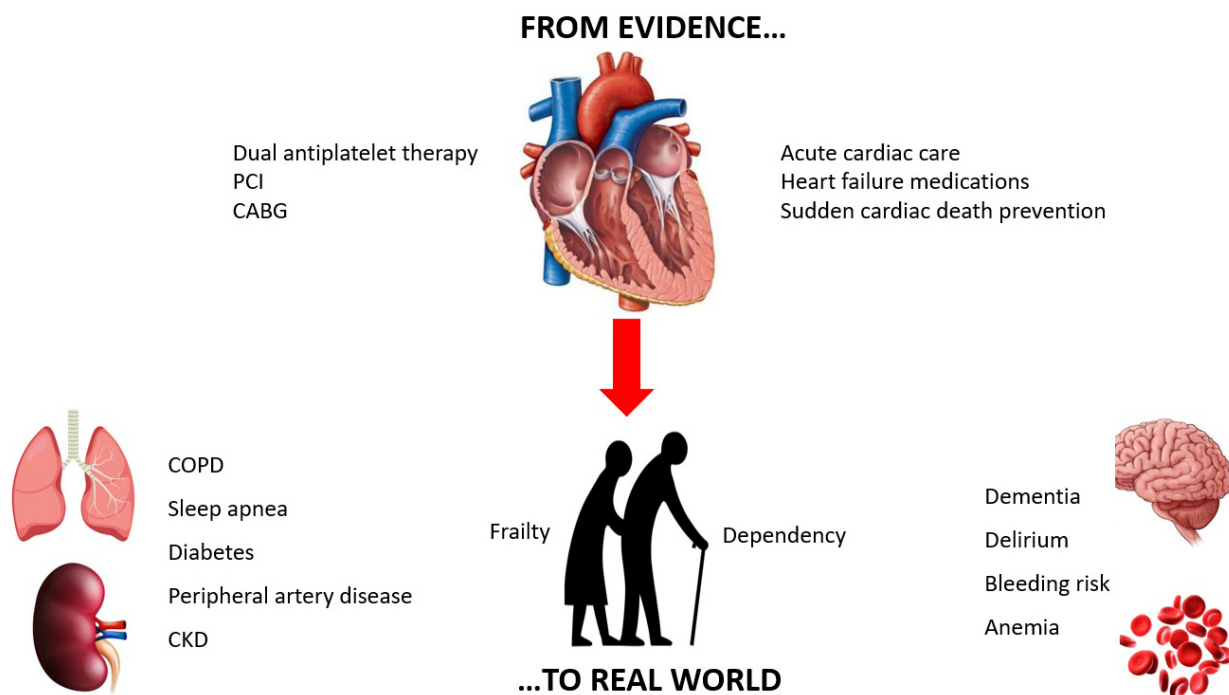


Fig. 4. A call for a personalized approach in octogenarians with non-ST segment elevation acute coronary syndrome. CABG, Coronary artery bypass grafting; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; PCI, Percutaneous coronary intervention.

infarction and readmission for cardiac cause (postdischarge revascularization or heart failure), without significant differences during follow up. Again, a high rate of crossover (20%) was recorded [88]. The After-Eighty study included 457 octogenarians and its primary outcome was a composite of myocardial infarction, need for urgent revascularization, stroke, and death. The invasive strategy was superior to the conservative one. Of the four components, myocardial infarction and the need for urgent revascularization reached statistical significance whereas stroke and death from any cause did not. Efficacy of the invasive strategy was diluted with increasing age and the two strategies did not differ in terms of bleeding complications. No patient underwent coronary angiography in the conservative arm. Furthermore, only 23% of the potential candidates for inclusion were finally randomized, suggesting a bias toward lower-risk patients [112]. Two ongoing randomized clinical trials will bring light to this field: MOSCA-FRAIL performed in patients >70 years and frailty defined by a category ≥ 4 in the Clinical Frailty Scale [113] and SENIOR-RITA in patients >75 years [114].

5. Discussion

Octogenarians comprise a subset of patients with great heterogeneity in terms of life expectancy and quality of life (Fig. 3) [20, 76]. Indeed, there is a growing commitment to discriminate chronological from biological age, and as long as the quantification of comorbidities and frailty continues to improve, the design of future trials will allow for more representative elderly patients and practice-changing results. So far, investigators still find enrollment and design challenges

limiting sample size and resulting in a high proportion of low-risk patients [46].

Although there is a complex interaction and overlap between comorbidities, frailty and age, frail patients without comorbidity seem to be good candidates for invasive management and revascularization, even assuming a higher risk of complications [75, 87], in contrast with patients presenting relevant extracardiac diseases, where an invasive management benefit could be diluted as the comorbidity burden increases [88, 89].

Interventional management in the elderly is steadily increasing, even after adjusting for comorbidities. Current evidence points towards an invasive strategy benefit and both percutaneous coronary intervention and coronary bypass grafting seem feasible and safe. Secondary prevention measures and neurohormonal treatment should not be taken for granted. The duration and type of antiplatelet therapy is crucial, leaving room to improve the balance of ischemic and hemorrhagic risks. The assessment, prevention and treatment of other specific risks, including delirium, heart failure, or decompensation of other conditions are equally important. Invasive and conservative managements should not be approached as two separate and static strategies. In fact, some elderly patients might benefit from an initial conservative approach open to a subsequent invasive management depending on clinical course (recurrent angina, ventricular arrhythmias, heart failure). Guideline-directed management cannot replace clinical judgement and personalized medicine, especially in this complex scenario (Fig. 4).

6. Conclusions

A growing proportion of octogenarians present with NSTEMACS and treatment strategy should be based on biological age, frailty and comorbidities. Frail patients might benefit from revascularization, although they have a higher rate of complications. Assessment of risk-benefit balance is needed as some comorbidities could be associated with futility. However, an initial conservative management might be an option in some patients that can be changed due to clinical reasons. Further evidence is required to solve this conundrum, but only tailored strategies can tackle heterogeneity.

Author contributions

SÁZ and AAG performed the bibliographic research. JMS designed and wrote the manuscript. JMS and MMS created the tables and figures. SÁZ, AAG and MMS reviewed the manuscript. All authors contributed to editorial changes. All authors read and approved the final version.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. Manuel Martínez-Sellés is serving as one of the Guest editors of this journal. We declare that Manuel Martínez-Sellés had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Leonardo De Luca.

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