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Review

Non-ST Elevation Myocardial Infarction in the Elderly. Antithrombotic Therapy and Beyond

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Abstract

Non-ST segment elevation myocardial infarction (NSTEMI) is the most frequent type of acute coronary syndrome in the elderly. Antithrombotic therapy is the cornerstone of pharmacological therapy in the setting of an acute ischemic event, a clinical scenario in which thrombotic and bleeding risks ought to be considered, particularly in older patients. In this article, specific aspects of antithrombotic therapy in elderly patients with NSTEMI are reviewed, including pharmacokinetic and pharmacodynamic characteristics and different clinical situations. The role of frailty and other common geriatric conditions, that are associated with worse prognosis in elderly patients with cardiovascular disease, is also addressed.

Keywords: elderly; acute coronary syndrome; non-ST segment elevation myocardial infarction; antithrombotic therapy; frailty

1. Introduction

Non-ST segment elevation myocardial infarction (NSTEMI) is the most frequent type of acute coronary syndrome (ACS) in older patients, those over 75 years old, who constitute the main focus of this review [1,2]. Antithrombotic therapy is the cornerstone of pharmacological therapy in patients with ACS since it is associated with a significant reduction in ischemic events, although at the expense of an increased risk of bleeding, especially in the elderly [1,2]. In this setting, and according to current recommendations, a comprehensive assessment of ischemic and hemorrhagic risks should be carefully performed. This is a complex clinical scenario, in which it is important to assess and consider the role and prognostic impact of comorbidities and geriatric conditions, common in the elderly population. Fig. 1 summarizes the main concepts addressed in the text.

2. Pharmacology of Antithrombotic Agents: Focus on the Elderly

The risk of atherothrombotic and bleeding events is higher in elderly patients with ACS compared to younger subjects, which poses important challenges at the time of selecting the most appropriate antithrombotic regimens [3,4]. In addition, pharmacological responsiveness, clinical efficacy and drug interactions might be altered by age-related conditions such as hemostatic alterations (decreased fibrinolysis, increased clotting, endothelial dysfunction, heightened platelet reactivity), changes in pharmacokinetics (diminished absorption, alterations in hepatic metabolism—e.g., reduced cytochrome P450 (CYP) activity-, changes in renal clearance leading to reduced elimination…), comorbidities and polypharmacy (increasing the risk of drug interactions) [5].

The most frequently used oral antiplatelet agents in ACS patients are aspirin and $P2Y_{12}$ antagonists (clopidogrel, prasugrel, and ticagrelor), either alone or in combination as dual antiplatelet therapy (Table 1).

Aspirin is an irreversible inhibitor of the platelet cyclooxygenase-1 enzyme with a potentially increased pharmacodynamic sensitivity in older patients, although this phenomenon has not been fully established [6,7]. Of

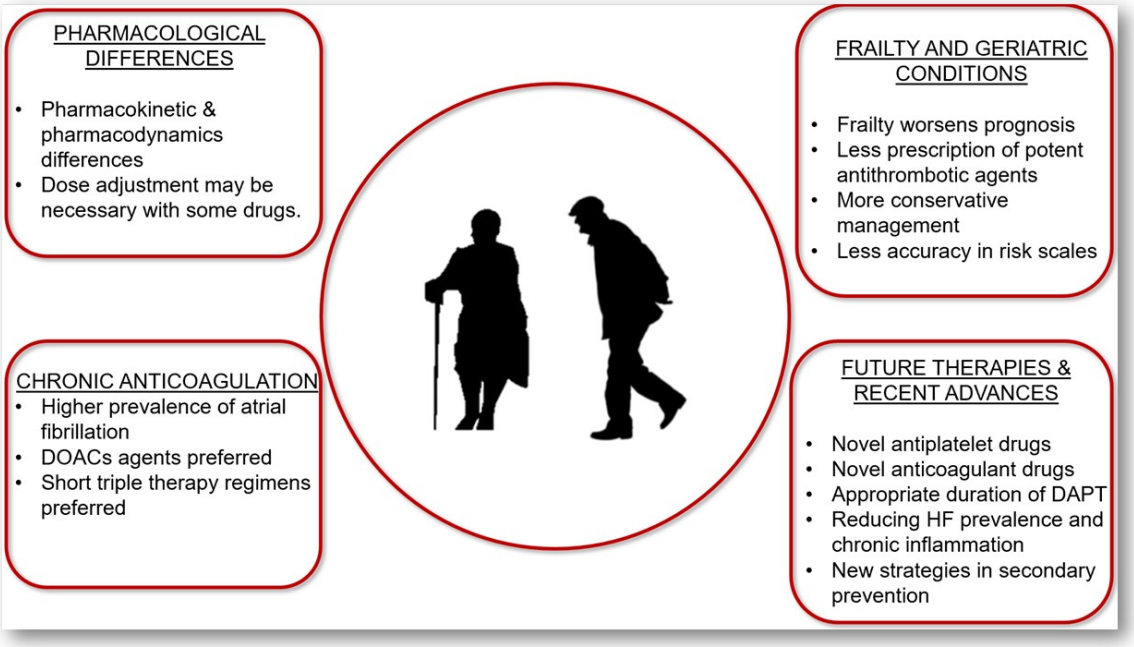

Fig. 1. Update on antithrombotic therapy in the elderly with non-ST segment elevation acute myocardial infarction. DOACs, direct oral anticoagulant agents; DAPT, dual antiplatelet therapy; HF, heart failure.

note, the higher vulnerability of older patients to gastrointestinal disturbances (due sometimes to chronic abuse of non-steroidal anti-inflammatory agents) may prompt physicians to pay a special attention to elderly patients receiving antiplatelet therapy in order to prevent gastrointestinal bleeding. Clopidogrel is still the most widely used $P2Y_{12}$ inhibitor in older patients probably due to its lower risk of bleeding compared to prasugrel or ticagrelor [8]. However, clopidogrel has broad variability in response and the prevalence of poor responsiveness is higher among older subjects [9]. On the other hand, clopidogrel appears to be a reasonable alternative to ticagrelor in NSTEMI elderly patients $\geq$70 years according to the individual ischemic and bleeding risk profile, since it was associated with lesser bleeding rates without an increase in the combined endpoint of all-cause death, myocardial infarction, stroke and bleeding in the POPular AGE trial [10].

With regards to prasugrel, an increasingly higher risk of bleeding among patients over 75 years was found in TRITON-TIMI 38 trial based on a regimen of prasugrel 10 mg once daily (o.d.). This effect has in part been attributed to an augmented exposure to its active metabolite [11,12]. Then, a reduced dose of prasugrel (5 mg o.d.) is recommended in patients $\geq$75 years of age, which has a slightly more potent platelet inhibitory effect compared to clopidogrel [13]. However, the clinical benefit of this regimen has not been well proven yet. In particular, the ELDERLY ACS-2 trial investigated the clinical efficacy of half-dose prasugrel (5 mg o-d) in an elderly ACS population ($\geq$74 years). Of note, this trial was stopped prematurely due to futility as the half-dose prasugrel regimen was not superior to regular-dose clopidogrel, showing no differences in ischemic events but a numerically higher rate of bleeding events [14]. Conversely, no dose adjustment because of age is needed for ticagrelor as the benefits of this drug compared to clopidogrel were maintained in all age subgroups in the pivotal PLATO trial [15].

Finally, platelet function tests have been proposed as a tool to guide antithrombotic therapy adjustments in high-risk bleeding groups such as elderly patients after an ACS. However, in a randomized clinical trial, a platelet function monitoring strategy was not associated with fewer bleeding or ischemic events in this subgroup [16].

Currently, there are two groups of parenteral antiplatelet agents available in ACS patients: glycoprotein IIb/IIIa inhibitors (GPIs) and cangrelor, a $P2Y_{12}$ receptor antagonist (Table 2). These are used almost exclusively in the setting of percutaneous coronary intervention (PCI). GPIs are the most potent antiplatelet agents in the armamentarium, among them tirofiban and eptifibatide are currently available for clinical use. Noteworthy, both drugs require dose adjustment in patients with impaired renal function [3]. No specific dose-adjustment for GPIs according exclusively to age is recommended, although careful selection of patients is mandatory because excessive in bleeding rates with GPIs have been observed in older patients [17]. Cangrelor, an intravenous $P2Y_{12}$ inhibitor, has no hepatic or renal metabolism and a short half-life so no age-related pharmacological issues have been reported to date [18].

Parenteral anticoagulation is also an important part of the initial therapeutic management of NSTEMI patients, especially those undergoing PCI [1]. The pharmacological

Table 1. Pharmacological properties of the most commonly used oral antiplatelet agents in acute coronary syndromes.

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Group	COX-1 inhibitor	$P2Y_{12}$ inhibitor: thienopyridine	$P2Y_{12}$ inhibitor: thienopyridine	$P2Y_{12}$ inhibitor: CPTP
Direct action	Yes	No	No	Yes*
Receptor blockade	Irreversible	Irreversible	Irreversible	Reversible
Onset of action**	15–30min	2–6 h	30 min–4 h	30 min–2 h
Offset of action	3–7 days	5–10 days	7–10 days	3–5 days
Drug interactions (CYP system)	No	Yes	No	Yes
Considerations in elderly patients	No	Increased rate of poor response	If $\geq$75 years, dose reduction to 5mg o.d.	No

COX, cyclooxygenase; CPTP, cyclopentyltriazolopyrimidine; CYP, cytochrome P450.

*Although ticagrelor is direct-acting, approximately 30–40% of its antiplatelet effectiveness is due to an active metabolite (AR-C124910XX). **It may vary according to clinical setting.

features of the most frequently used parenteral anticoagulant agents are presented in Table 3. Unfractionated heparin is the only agent that can be used in patients with severe renal impairment, while enoxaparin (a low-molecular-weight heparin) and bivalirudin (a direct thrombin-inhibitor) require dose adjustment below certain levels of creatinine clearance (CrCl). Fondaparinux is contraindicated if CrCl $<$20 mL/min. Importantly, a reduction in subcutaneous dosing of enoxaparin for patients aged $\geq$75 years from 1 to 0.75 mg/kg (without initial bolus) is recommended, whereas the other parenteral anticoagulant agents do not require a specific age-related dose adjustment [3,5].

3. Antithrombotic Treatment in an Elderly Patient with ACS and Indication for Oral Anticoagulation

Atrial fibrillation (AF) affects up to one third of patients with coronary artery disease, especially in the elderly [1]. In elderly patients with AF, anticoagulation is indicated, with direct oral anticoagulants (DOACs) constituting the treatment of choice [19,20]. Table 4 summarizes standard doses for DOACs. When specific criteria are present, adjusted doses must be prescribed.

However, a high percentage of elderly patients with AF do not receive or receive inadequate doses of anticoagulant therapies. This inappropriate use of a reduced dose has been associated with age itself, concomitant use of antiplatelet therapy, subjective perceptions of the physician and the overestimation of the bleeding risk [21–24]. The results of DOACs trials in patients with indication (indications) of chronic anticoagulation and dual antiplatelet therapy are summarized in Table 5. When DOACs cannot be used (e.g., mechanical prosthetic valves) vitamin K antagonists plus antiplatelet regimens based on clopidogrel is indicated [1,25]. According to current guidelines, it is recommended to shorten the triple therapy (anticoagulant + aspirin + clopidogrel) as much as possible, from 1 week to 1 month depending on patient's risk profile [1,26–29].

4. Role of Frailty, Comorbidity and Other Ageing Related Variables on Risk Prediction and Antithrombotic Management in Elderly Patients with NSTEMI

Dual antiplatelet therapy (DAPT) is recommended for 12 months after an ACS but duration may vary depending on ischemic and bleeding risks, comorbidities, or need for chronic anticoagulation [1,27]. Thus, an individualized approach on a case-to-case basis is crucial in order to provide the optimal antithrombotic strategy and its duration for each patient [2]. In this setting, the assessment of comorbidities and a comprehensive geriatric assessment is also of great importance [30]. Besides, most recommended bleeding risk stratification tools come from studies where patients at older ages are clearly underrepresented [31,32]. The PRECISE DAPT score is recommended for guiding intensity and duration of DAPT after an ACS [1]. However, patients older than 75 years (more than 90%) are frequently at the highest risk category because age accounts for more than half of points needed for reaching this high-risk category. In addition, most of these patients are at high risk for ischemic events, since the prevalence of diabetes, multivessel disease or prior coronary intervention is high. Therefore, the use of this tool has been suggested to be adapted with different thresholds in older patients [24]. On the other hand, and according to the *Academic Research Consortium*, age $\geq$75 years, but also frequent comorbidities in the elderly like anemia or chronic kidney disease (CKD), constitutes a minor risk factor for bleeding risk. Of note, in this scale high bleeding risk is defined when at least 1 major or 2 minor factors are present [3]. Fig. 2 outlines the complex balance of ischemic and bleeding risks in this population.

Frailty is an age-associated clinical syndrome characterized by a decrease in physiological reserve that entails an increased vulnerability to stressors. In cardiovascular disease, frailty has been associated with worse clinical outcomes and higher morbidity and mortality in all clinical scenarios, in both acute and chronic settings [33]. The awareness of its importance has led to the statement of specific

Table 2. Pharmacological properties of currently approved parenteral antiplatelet agents.

	Cangrelor	Abciximab	Tirofiban	Eptifibatide
Group	$P2Y_{12}$ inhibitor	GPI	GPI	GPI
Molecular structure	ATP analog	Fab of a monoclonal antibody	Non-peptide synthetic molecule	Synthetic cyclic heptapeptide
Reversibility	Yes	Yes*	Yes	Yes
Plasmatic half-life	3–6 min	Biphasic: <10 min and ~30 min	~2 hours	~2.5 hours
Duration of antiplatelet effect after discontinuation	60–90 min	Platelet life-span	~4–8 horas	~4 horas
Renal adjustment	No	No Contraindicated in hemodialysis	Reduce infusion by 50% if CrCl <30 mL/min	Reduce infusion by 50% if CrCl 30–50 mL/min Contraindicated if CrCl <30 mL/min or hemodialysis
Considerations in elderly patients	No	Caution due to increased bleeding risk	Caution due to increased bleeding risk	Caution due to increased bleeding risk

ATP, adenosine triphosphate; CrCl, creatinine clearance; Fab, antigen-binding fragment; GPI, glycoprotein IIb/IIIa inhibitor. *Frequently reported as an irreversible agent due to its great affinity for the receptor.

Table 3. Pharmacological properties of parenteral anticoagulant agents used in acute coronary syndromes.

	Unfractionated heparin (UFH)	Enoxaparin	Fondaparinux	Bivalirudin
Target	IIa and Xa (IXa, XIa and XIIa to a lesser extent)	Xa (IIa to a lesser extent)	Xa	IIa
Route of administration	IV	IV, SC	SC	IV
Direct action	No*	No*	No*	Yes
Plasmatic half-life	60–90 min	4–5 h (SC)	25 min	25 min
Reversal agent	Protamine	Protamine (partial reversal: 40–70%)	No	No
Renal adjustment	No	Dose reduction if CrCl <30 mL/min Contraindicated if CrCl <15 mL/min	Contraindicated if CrCl <20 mL/min	Reduce infusion if CrCl 30–59 mL/min Contraindicated if CrCl <30 mL/min
Considerations in elderly patients	No	If ≥75 years, dose reduction to 0.75 mg/kg b.i.d. and no initial bolus	No	No

CrCl, creatinine clearance; IV, intravenous; SC, subcutaneous. *Need a cofactor: antithrombin III.

Table 4. Direct-acting anticoagulants standard and adjusted doses.

	Apixaban	Edoxaban	Dabigatran	Rivaroxaban
Standard doses	5 mg twice daily	60 mg once daily	150 mg twice daily	20 mg once daily
Reduced doses	2.5 mg twice daily if two or more criteria* Age ≥80 years Weight <60 kg Creatinine ≥1.5 mg/dL *Also if ClCr <30 mL/min	30 mg once daily if Weight <60 kg ClCr <50 mL/min * Concomitant use of P-gp inhibitors	110 mg twice daily Age >80 years	15 mg once daily ClCr <50 mL/min *

* According to Cockroft-Gault formula. ClCr, Creatinine clearance; P-gp, glycoprotein P.

Table 5. Main pivotal trials including patients with acute coronary syndrome and indication of anticoagulation with direct oral anticoagulants.

Clinical trial	Description	Primary outcome	Results
PIONEER AF-PCI	2124 patients. Safety comparison of 2 strategies of rivaroxaban (2.5 mg/15 mg) + DAPT vs triple therapy 12 months	Clinically relevant bleeding TIMI (safety)	Rivaroxaban therapy was associated with a significant decrease in bleeding compared to triple VKA therapy.
REDUAL-PCI	2725 patients. Safety of 2 doses of dabigatran (110 mg/12 h and 150 mg/12 h) vs standard triple VKA therapy 24 months	Clinically relevant bleeding ISTH (safety)	Dual therapy with dabigatran (with both doses) is safer than using triple therapy.
AUGUSTUS	4600 patients. Non-inferiority trial of Apixaban vs VKA combined with $P2Y_{12}$ inhibitor. To demonstrate superiority of single antiplatelet therapy with aspirin vs placebo. 6 months.	Clinically relevant bleeding ISTH (safety)	The rate of bleeding was lower with Apixaban than with VKA in triple therapy; in addition, a reduction in bleeding was observed with placebo vs Aspirin.
ENTRUST AF-PCI	1506 patients. Safety of Edoxaban + $P2Y_{12}$ vs triple therapy with VKA + $P2Y_{12}$ + Aspirin 12 months.	Clinically relevant bleeding ISTH (safety)	Edoxaban demonstrated non-inferiority for bleeding compared to VKA therapy.

DAPT, dual antiplatelet therapy; VKA, vitamin K antagonists; TIMI, Thrombolysis in Myocardial Infarction; ISTH, International Society on Thrombosis and Haemostasis.

recommendations in order to achieve a prompt identification. In elderly with ACS, the FRAIL scale (Table 6) has been shown to identify patients with worse prognosis [33]. The role of frailty, comorbidity and other geriatric assessment for predicting bleeding risk in patients with ACS has also been assessed, with several studies showing an association between frailty and higher incidence of bleeding [34,35]. On the other hand, data from the LONGEVO-SCA registry show that only comorbidity according to Charlson index was significantly associated with bleeding, while the contribution of the geriatric assessment was modest [36,37]. Likewise, a substudy from the FRASER registry found that frailty did not improve the prediction of bleeding over the PRECISE DAPT and PARIS bleeding risk scores [38].

Some comorbidities such as CKD, or anemia are frequent in this population, associating higher rates of morbidity and mortality, and lesser referral to invasive management [30,39]. Besides, CKD is a well identified risk factor for development of contrast-induced acute kidney injury in patients undergoing invasive approach [2,30]. Cancer is the second leading cause of mortality in these patients, and shares common risk factors with coronary artery disease. Its prevalence is higher in the elderly and adversely impacts prognosis. Therefore, a multidisciplinary approach is of great importance [40].

Gender differences have also been identified in the management and prognosis of elderly patients with ACS. Women are more likely to be older, frailer and with higher burden of cardiovascular risk factors [30,41]. Atypical presentation and delayed diagnosis are also more frequent, and women are treated conservatively more often than men [41]. Moreover, in octogenarians with NSTEMI, female sex has been associated with worse short-term prognosis [42].

Finally, ethical considerations due to ageism may arise in a progressively elderly, more comorbid ACS population. Thus, it is essential to carefully choose best clinical management, also considering patient's preferences and goals [43].

5. Frailty and Invasive Strategy in Elderly Patients with ACS

Age itself is not a contraindication for PCI, since PCI has demonstrated to significantly decrease short and long-term mortality and morbidity in elderly patients with STEMI [2,26].

However, decision-making is far more complex in NSTEMI. It is well-known that frailty worsens the prognosis [30,32,44–50]. However, whether this means that frail patients should be managed differently remains unknown.

The European guidelines on NSTEMI recommend for older people the same diagnostic and intervention strategies as for younger patients, including radial approach in PCI and the use of drug eluting stents [1]. In this regard, the implantation of a latest-generation drug-eluting stent might allow for the indication of short periods of dual antiplatelet therapy. So, age should not be a limitation. However, age is only the tip of the iceberg. Geriatric conditions, such as comorbidities and frailty, also play a role in the prognosis. Indeed, the guidelines recognize the absence of robust data on the management of frail patients and recommend an individual approach, balancing the potential benefit of treatments with their potential harm. The critical question

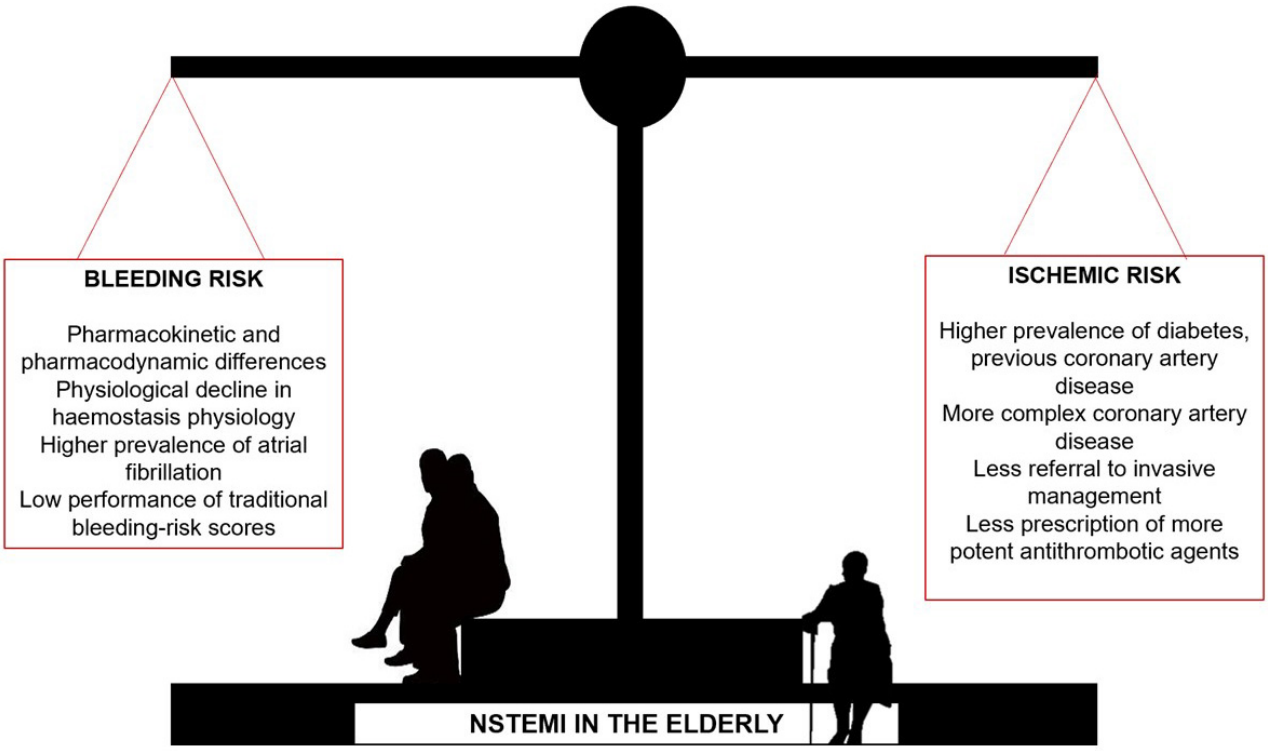

Fig. 2. Ischemic and bleeding risks in the elderly population with non-ST segment elevation acute myocardial infarction.

Table 6. FRAIL Scale (Frailty if 3 or more of the following 5 criteria are present).

Item	Assessment
Fatigue	Do you feel tired most of the time?
Resistance	By yourself and not using aids, do you have any difficulty walking up a flight of stairs without resting?
Ambulation	By yourself and not using aids, do you have any difficulty walking 100 m?
At least 5 of the following symptoms	Arthritis, diabetes, angina/infarction, hypertension, stroke, asthma, chronic bronchitis, emphysema, osteoporosis, colorectal cancer, skin cancer, depression and anxiety, dementia, leg ulcers
Weight loss	Weight loss >5% in the past year

is: Can an invasive strategy modify the poor prognosis that frailty confers?

The "After-eighty" trial compared invasive vs conservative strategies in patients older than 80 [51]. It should be noted that this study only focused on age. Comorbidities and frailty were not evaluated and were probably underrepresented. On the other hand, no patient received a coronary angiogram regardless of the clinical course in the conservative group. This management is very far from usual clinical practice. The results largely favored the invasive group for a composite endpoint (including death, myocardial infarction, urgent revascularization or stroke). The MOSCA trial meant a step further because it focused on age and comorbidities [52]. The inclusion criteria were NSTEMI, age older than 70, and at least two comorbidities. Patients were randomized to the invasive or conservative strategies in the conservative arm, but a coronary angiogram was permitted if recurrent ischemia. There were no differences for a primary endpoint consisting of the composite of death, reinfarction or readmission for a cardiac cause. However, the study was unpowered since it did not reach the estimated sample. In line with these results, registries of elderly patients with NSTEMI suggest that comorbidities and disability impair the potential benefit of in-hospital revascularization on outcomes [53,54]. The management (invasive or not) of frail elderly patients with NSTEMI has also been addressed in different registries [55,56]. The MOSCA-FRAIL clinical trial is the first trial including elderly (age older than 70 years) and frail (defined by four or more points in the Clinical Frailty Scale) patients with NSTEMI [57], randomized to invasive or conservative strategies (with crossover permitted if recurrent ischemia). The primary endpoint was the number of days alive out of hospital during the first year. Interestingly, invasive treatment in frail older patients was not associated with survival benefits [58].

Table 7 (Ref. [51,52,58]) summarizes the main characteristics of the clinical trials assessing the impact of an invasive strategy in elderly patients with NSTEMI.

Table 7. Main clinical trial assessing the impact of an invasive management in elderly patients with NSTEMI.

Study	Population (n)	Mean age (years)	Female sex (%)	Endpoint	Follow up	Frailty and comorbidity assessment
Tegn *et al.* [51] After Eighty (2016) [51]	457	84.8	51%	A composite of death, myocardial infarction, urgent revascularization or stroke	1.5 years	No assessment
Sanchis *et al.* [52] MOSCA (2016)	106	82	47%	Death, reinfarction, or readmission for cardiac causes.	2.5 years	No frailty assessment. Charlson comorbidity index
Sanchis *et al.* [58] MOSCA-FRAIL	167	86	38%	Number of days alive out of the hospital from discharge to 1 year follow-up.	1 year	Clinical Frailty Scale score $\geq$4 Comorbidity burden Polypharmacy

NSTEMI, non-ST segment elevation myocardial infarction.

Table 8. Recent pharmacologic advances in cardiovascular field and potential cardiovascular benefits in the elderly.

	Drug Class	Mechanism	Potential cardiovascular benefits in the elderly
Selatogrel	Antiplatelet sc	Reversibly-binding $P2Y_{12}$ inhibitor	Potential early, pre-hospital treatment in ACS, $\downarrow$ risk bleeding
Anfibatide	Antiplatelet iv	Platelet receptor GP Ib inhibitor	Antiplatelet effect without $\uparrow$ bleeding and thrombocytopenia
Asundexian	Anticoagulant	Oral activated coagulation factor XIa inhibitor	$\downarrow$ Bleeding compared with apixaban in AF patients
Cardiovascular polypill	Aspirin + ACE inhibitor + statin	Multiple	$\uparrow$ adherence $\rightarrow \downarrow$ CV death, MI, stroke or urgent revascularization

ACE, angiotensin-converting enzyme; ACS, acute coronary syndromes; AF, atrial fibrillation; CV, cardiovascular; GP, glycoprotein; iv, intravenous; MI, myocardial infarction; sc, subcutaneous. $\uparrow$: increase. $\downarrow$: reduce.

6. Recent Advances and Future Directions in Antithrombotic Treatment

Although the death rates among elderly patients with ACS have declined significantly, considerable opportunities for improvement remain. Table 8 summarizes the recent advances and their potential benefit in elderly patients with ACS.

Novel antiplatelet drugs have been recently developed; some explore new pharmacological targets, while others seek to refine existing drugs. Selatogrel (ClinicalTrials.gov Identifier: NCT04957719) is a novel subcutaneous reversibly-binding $P2Y_{12}$ inhibitor, that is being tested in phase III studies. However, its future use in elderly patients is uncertain [59]. The appropriate duration of DAPT after PCI is currently under research. Several studies have suggested that a regimen based one-month of DAPT after PCI may mitigate bleeding risk without compromising safety, compared with longer durations [60,61]. Due to the excess of bleeding risk in the ACS elderly population, this population could benefit most from this approach.

Bleeding events are related to adverse outcomes in elderly patients with ACS. Reducing the bleeding rates, especially in patients under chronic anticoagulation, may significantly impact on survival [62].

Asundexian, a recently introduced oral anticoagulant agent that inhibits the activated coagulation factor Xia, might reduce thrombosis with minimal effect on haemostasis. Although larger clinical trials are needed, its promising results with very low rates of bleeding, are encouraging and could lead to improve prognosis of elderly patients with ACS and AF [63,64].

In lights to decrease the high rates of recurrent ischemic events, patient adherence to secondary prevention treatment is crucial. However, adherence rates in the elderly population are low due to the impact of comorbidities or polypharmacy, among others. The SECURE trial showed that in elderly patients admitted for ACS, the use of the cardiovascular polypill was associated with a significantly lower risk of major adverse cardiovascular events [65]. Lastly, a new generation of cholesterol-lowering drugs based on genetic transcription such as inclisiran may reduce the burden of cardiovascular disease [66].

Cardiac rehabilitation programs are essential after an ACS, especially in frail elderly patients, in whom a multidimensional approach is encouraged, aimed to decrease frailty and physical disability [67].

7. Conclusions

The management of NSTEMI in the elderly still represents a clinical challenge. Several factors, including frailty and comorbidities, which adversely impact prognosis, must be taken into account when choosing the correct antithrom-

botic therapy and referring to invasive management. Although new therapies are been tested with potential cardiovascular benefits in the elderly, randomized clinical trials specifically focused on this population are needed.

Author Contributions

PD-V: conception, design. PD-V, CJ-M, JLF, PC-G, CB, SG-B, AA-S, JS and MM-S: acquisition, analysis and interpretation of data. All authors have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

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Conflict of Interest

JL Ferreiro reports: (a) speaker fees from Eli Lilly Co, Daiichi Sankyo, Inc., AstraZeneca, Roche Diagnostics, Pfizer, Abbott, Ferrer, Rovi, Boehringer Ingelheim, Bristol-Myers Squibb and Terumo; (b) consulting fees from AstraZeneca, Eli Lilly Co., Ferrer, Boston Scientific, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Bristol-Myers Squibb and Biotronik; (c) research grant from AstraZeneca. The author declares no conflict of interest. Manuel Martínez-Sellés is serving as one of the Editorial Board members and 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 Pietro Scicchitano.

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