

Non-ST segment elevation myocardial infarction in the elderly

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Ischemic heart disease constitutes the leading cause of death in Western countries. The general incidence of acute coronary syndromes (ACS), especially non-ST segment elevation myocardial infarction (NSTEMI), is growing. Advanced age is both a strong risk factor for ACS and an independent predictor of poorer clinical outcomes. Management of this entity is often complex in the elderly, while special attention should be focused on comorbidities and geriatric conditions. This article aims to review clinical presentation, identification and management of NSTEMI in the elderly population.

Keywords

Acute coronary syndrome; Elderly; Non-ST segment elevation myocardial infarction

1. Introduction

Ischemic heart disease constitutes the leading cause of death in Western countries. Advanced age is both a strong risk factor for acute coronary syndromes (ACS) and an independent predictor of poorer clinical outcomes [1]. Due to progressive ageing in our societies, the general incidence of ACS, especially non-ST segment elevation myocardial infarction (NSTEMI), is growing. This article aims to provide a systematic and updated review on this topic, as shown in Fig. 1.

2. Management of NSTEMI in the elderly

Current European Society of Cardiology guidelines recommend a prompt diagnosis and identification of NSTEMI patients in order to early initiate and provide the best treatment [2]. However, clinical presentation in the elderly is often atypical, thus high clinical suspicion is essential [2, 3]. The electrocardiogram still represents the first-line diagnosis tool in suspected ACS. A 12-lead electrocardiogram within the first 10 minutes of admission at emergency department/first contact in the pre-hospital setting is mandatory. A high level of clinical suspicion is required in patients presenting with signs or symptoms suggestive of ongoing myocardial ischemia or left bundle branch block [2]. Also, early measurement of cardiac troponin levels is recommended to identify patients with the highest risk. Importantly, however, interpretation of troponin levels in the elderly population may be challenging as concentrations may be different

between young and older individuals and comorbidities, such as renal impairment, are common in the elderly [4]. Thus, recently suggested rule-in and rule-out algorithms should be used with especial caution in this population. It is also of importance to remark that there should not be differences regarding management according to sex, since gender-bias has been identified, as elderly women usually receive lower invasive treatment, antiplatelet drugs, and other secondary prevention medications [5–8].

2.1 Risk assessment

Both ischaemic and haemorrhagic risk assessment are essential in management of elderly patients with NSTEMI. Quantitative assessment of ischaemic risk (using clinical scores) is superior to subjective clinical assessment. Accordingly, current European Society of Cardiology (ESC) guidelines recommend the utilization of validated prognosis scales [2]. The GRACE (*Global Registry of Acute Coronary Event*) score, which has been previously validated in the elderly population [9], provides not only in-hospital mortality risk, but also at 6 months, 1 year and 3 years follow-up. The combined risk of death or myocardial infarction (MI) at 1 year is also assessed [10].

Major bleeding events are also related to an increase in mortality rates in NSTEMI patients. Moreover, age is an independent risk factor for both ischemic and haemorrhagic complications. Several bleeding risk scores have been developed in order to identify patients at highest risk. The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) bleeding score combines demographic, clinical and laboratory variables, though, predictable values on elderly population are not as accurate as in younger patients [11]. ARC-HBR scale (Academic Research Consortium for High Bleeding Risk) has been recently proposed as a useful tool to identify high bleeding risk patients [12]. Nevertheless, nowadays their use still lacks a strong recommendation (IIb class level recommendation). On the other hand, other scales have been proposed to identify patients with worse outcomes in the elderly NSTEMI population, though they have not been found to independently predict events [13].

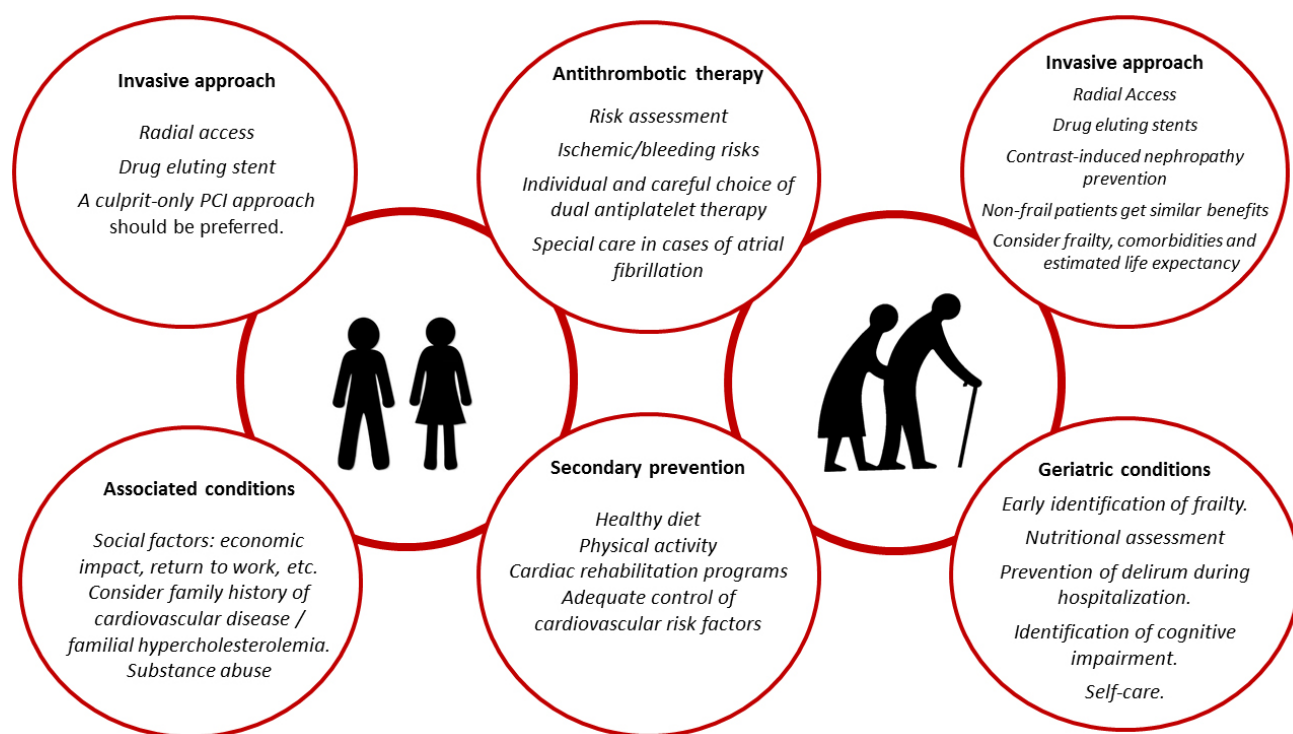


Fig. 1. Central illustration. Schematic representation of key components in management of non ST-elevation myocardial infarction in the elderly. Specific considerations regarding management of non STEMI elderly patients are remarked. Differences but also similarities with younger patients are presented. Concerning invasive approach, specific technical actions should be considered in order to provide greater benefits. Geriatric conditions should be early identified and treated. Elderly patients with NSTEMI should be treated as younger patients with regard to antithrombotic therapy or secondary prevention.

Frailty is defined as a loss of biological reserve, leading to an impaired response to stressor events [14]. It is closely related with high mortality and worse outcomes in different clinical settings. There are two main approaches to the characterization of frailty: (1) frailty as a phenotype of poor physical function (physical frailty), and (2) frailty as the consequence of an accumulation of deficits [14]. Physical frailty can be defined as the presence of three or more of: unintentional weight loss, weakness, poor endurance and energy, low physical activity level or slowness, according to Fried *et al.* [15]. On the other hand, FRAIL (Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight) scale is a simple-to-use tool that takes into consideration the following questions to the patient (adding one point to each of the following affirmative answers; frailty is diagnosed if 3 or more of the following criteria are met):

- 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 metres?
- At least 5 of the following: 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.

FRAIL scale is highly recommended due to its simplicity and easy to interpret in the acute setting, and has been already validated the setting of ACS in the elderly [16].

2.2 Dual antiplatelet therapy

Dual antiplatelet therapy (DAPT) is the cornerstone of medical treatment in all NSTEMI patients, as it provides a reduction in events, although at the expense of an increase in bleeding events [17]. Individual and careful choice of both the agent and dosage is highly recommended, particularly in the elderly, as physiological changes associated with ageing, like multi-organ function impairment and drug interactions, may lead to an increase bleeding risk [18]. The use of newer and more potent P2Y12 inhibitors are recommended unless contraindicated in all ACS patients together with aspirin, also in the elderly. DAPT is recommended for one year after the index event, regardless of treatment strategy, as shown in Table 1 [19]. As a novelty, current guidelines do not recommend routine pre-treatment with a P2Y12 inhibitor in patients in whom coronary anatomy is unknown, especially if an early coronary angiography is programmed [2].

Current guidelines also recommend prasugrel as the preferred P2Y12 receptor inhibitor for NSTEMI patients undergoing percutaneous coronary intervention (PCI) according to ISAR REACT 5 results [20]. However, regarding elderly patients, prasugrel showed an increased risk in fatal and life-

Table 1. Antiplatelet drugs. Initial and maintenance dosages according to current clinical guidelines.

ASA (acetylsalicylic acid)		Loading dose: 250–300 mg Maintenance dose: 87–100 mg/day
P2Y12 INHIBITOR	TICAGRELOR	Loading dose: 180 mg Maintenance dose: 90 mg twice/day
	PRASUGREL	Loading dose: 60 mg Maintenance dose: 10 mg once a day * Maintenance dose: 5 mg once a day if weight <60 kg or age >75 years
	CLOPIDOGREL	Loading dose: 300–600 mg Maintenance dose: 75 mg/day

*Prasugrel 10 mg/day is not eligible for patients ≥ 75 years old.

threatening bleedings compared to clopidogrel in ACS patients over 75 years [21]. Thus, prasugrel 10 mg/day is actually not eligible for ACS patients ≥ 75 years old. On the other hand, half-dose prasugrel (5 mg/day) has been considered to be not superior in reducing ischemic rates in those ACS patients undergoing PCI in the Elderly in the ACS 2 trial, and the ESC 2020 guidelines include such recommendation [22]. Conversely, ticagrelor has been progressively introduced in this population showing better results in patients carefully selected despite a theoretical high bleeding risk profile [23]. In a substudy of the LONGEVO-SCA registry, nearly one every six octogenarian patients with NSTEMI were discharged with DAPT including ticagrelor. These patients were younger, with lower ischemic and haemorrhagic risks and fewer comorbidities than those discharged with aspirin and clopidogrel [24]. Bleeding rates at 6 months were lower than expected, although most patients receiving ticagrelor had a high PRECISE-DAPT score [25].

Last, but not least, clopidogrel is usually the P2Y12 inhibitor most often prescribed in the elderly [26]. As a matter of fact, POPular-Age trial demonstrated that clopidogrel produced less bleeding events but comparable ischemic rates in NSTEMI patients >70 years old when compared with other potent P2Y12 inhibitors [27].

2.3 Anticoagulation

When NSTEMI is diagnosed, initiation of parenteral anticoagulation is recommended. In those patients remitted to PCI, unfractionated heparin is recommended. Low molecular weight heparin (LMWH) should be considered in those patients already pre-treated with LMWH. Alternatively, fondaparinux can be considered in cases of conservative treatment or transferral to a PCI hospital [2].

Atrial fibrillation (AF), deserves special attention in this clinical scenario due to its high prevalence in this patients. In NSTEMI patients with AF, direct oral anticoagulants (DOACs) are preferred over warfarin/acenocumarol, unless valvular AF [28]. The default strategy proposed by the last ESC guidelines includes triple therapy (combination of aspirin + clopidogrel + DOAC) up to 1 week after revascularization followed by single antiplatelet therapy plus oral anticoagulation for one year after the index event. This strategy can be modified according to ischemic and bleeding risks

profile, shortening or extending the duration of triple therapy accordingly [2]. On the other hand, and as later addressed in this paper, impact of geriatric syndromes in management of patients with atrial fibrillation and coronary disease, deserves special attention, as they actually impact on prognosis [29, 30]. In the elderly population, special attention should be paid on renal function and dosages should be modified accordingly.

3. Invasive strategy in non-ST elevation acute coronary syndrome.

The majority of elderly patients with NSTEMI should be treated with an invasive coronary angiography according to current ESC Guidelines [2]. An immediate invasive strategy or early invasive strategy is recommended in those patients with high or very high-risk criteria, respectively, as shown in Table 2.

Decision regarding invasive approach should be weighted after addressing the risks and benefits of myocardial revascularization. It also depends on comorbidities, cognitive status, functional impairment, frailty, and life expectancy. Of note, low rates of revascularization in the elderly population are continuously reported [31], though benefits of revascularization appear to be maintained at older ages as showed in several clinical trials [32, 33]. Table 3 (Ref. [34–37]) summarizes clinical studies regarding invasive vs conservative management in NSTEMI elderly patients. Interestingly, when taking frailty into consideration, benefits of an invasive strategy in NSTEMI elderly patients is less clear [37]. The MOSCA-frail is an ongoing clinical trial that will specifically address the benefits of an invasive strategy in frail elderly patients with NSTEMI [38].

Besides, there are some important technical aspects to consider when performing revascularization. First, radial artery access and drug eluting stents (DES) are highly recommended in the elderly, irrespective of clinical presentation or concomitant therapy [39]. In cases of high bleeding risk, DES and short duration of DAPT have been shown to be safe [40]. Regarding contrast-induced nephropathy (CIN), its incidence is much higher in the elderly population. The risk of this complication should be assessed in all patients providing an adequate hydration status before coronary angiography,

Table 2. Management according to risk criteria in NSTEMI. Adapted from 2020 ESC Guidelines (including level of recommendation).

Very high risk criteria	High risk criteria
<ul style="list-style-type: none"> • Haemodynamic instability/cardiogenic shock • Life-threatening arrhythmias • Recurrent/refractory chest pain despite medical treatment • Mechanical complications of MI • Acute heart failure 	<ul style="list-style-type: none"> • Established NSTEMI diagnosis • Dynamic new or presumably new contiguous ST/T segment changes (symptomatic or silent) • GRACE risk score >140 • Resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock • Transient ST-segment elevation
ST-segment depression >1 mm/6 leads + ST-segment elevation in aVR and/or V1.	
Immediate invasive coronary angiography (<2 h)	Early invasive strategy (<24 h)
IC	IA

GRACE, Global Registry of Acute Coronary Events; PCI, percutaneous coronary intervention; MI, myocardial infarction.

Table 3. Impact of invasive treatment in elderly patients with NSTEMI.

	Size (n)	Mean age (years)	Female sex (%)	Diabetes (%)	Previous stroke	Follow up	Results
After Eighty [34]	457	84.8	51%	17%	15%	1.5 years	Benefit of early invasive approach on the composite of myocardial infarction, need for urgent revascularization, stroke, and death.
MOSCA [35]	106	82	47%	46%	24%	2.5 years	No differences in the rate of: <ul style="list-style-type: none"> - All-cause mortality - Reinfarction - Readmission for cardiac cause
Italian Elderly ACS [36]	313	81.8	50%	40%	7.9%	1 year	No differences in the primary endpoint of mortality, myocardial infarction, disabling stroke and repeat hospital stay for cardiovascular causes or bleeding.
LONGEVO-SCA [37]	531	84.3	38.7%	39.9%	15.2%	6 months	Conservative strategy was associated with higher incidence of: <ul style="list-style-type: none"> - Cardiac death - Reinfarction - New revascularization

and special care should be taken in cases of chronic kidney disease [19]. Finally, but also of importance, proton pump inhibitors prescription should be considered [41].

Regarding surgical revascularization, 5–10% of NSTEMI patients require coronary artery bypass grafting (CABG) [42]. Although CABG surgery can be performed successfully, a careful patient selection is recommended. The surgical risk for these patients is only acceptable in the absence of comorbidities, especially renal dysfunction, cerebrovascular disease or poor clinical status [43]. Age itself is a risk factor for perioperative stroke after CABG [44] whilst computed tomography (CT) scan screening of atheroma in the ascending aorta may be considered when addressing best surgical strategy in this population [45].

4. Geriatric syndromes

Geriatric syndromes are multifactorial conditions identified more commonly in older adults [46] (Fig. 2). Due to its great impact on morbidity and mortality, assessment of frailty and other geriatric syndromes is essential [14]. Frailty has

been identified as a decisive issue in clinical decision-making. An integrative and interdisciplinary approach is mandatory, including physical and nutritional aspects in order to improve outcomes [18, 47]. As many as 10% of ≥65 years and 25–50% of ≥85 years patients admitted with ACS are frail. Frailty strongly associates worse events in the short and long-term in NSTEMI elderly patients [48–50]. Cardiac rehabilitation (CR) programs have proven to provide significant benefits after an ischemic event, though a low proportion of elderly patients are referred [51].

Likewise, malnutrition, present in up to one third of ACS elderly patients, associates worse prognosis [52]. Thus, strategies to prevent and improve nutrition status are of great importance.

Cognitive impairment also represents a marker of poor prognosis after an ACS [53]. Delirium, an acute disorder of attention and cognition, is also frequent after admission to cardiac intensive care units [54], associating poorer outcomes [55]. Accordingly, it is highly encouraged to implement measures to prevent delirium.

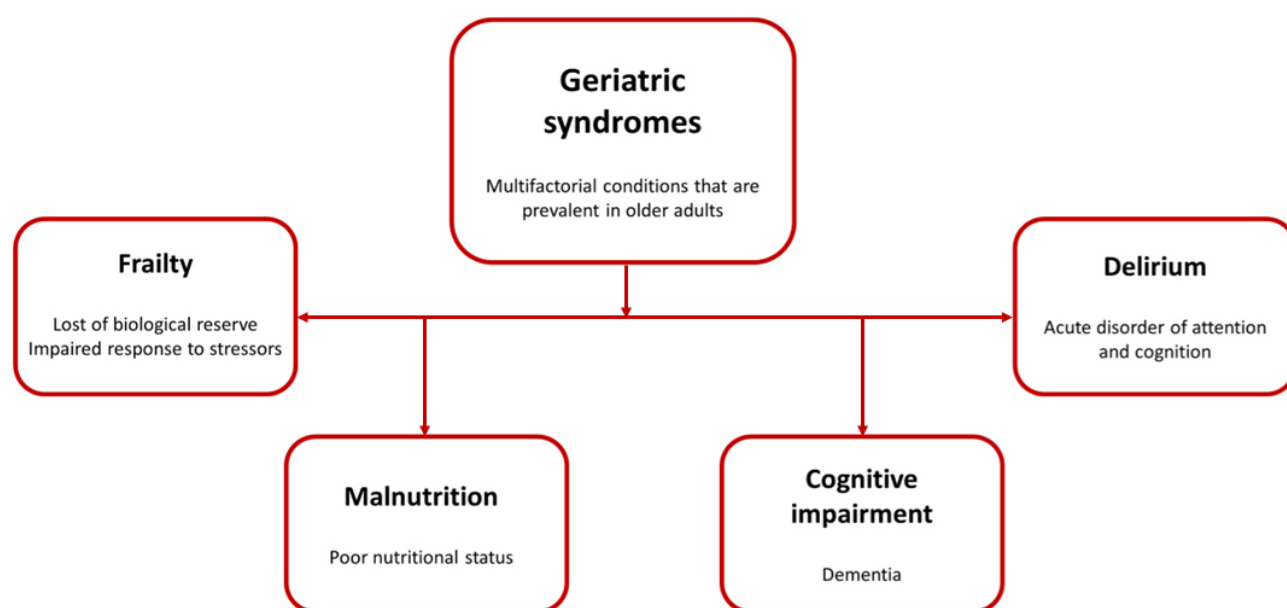


Fig. 2. Geriatric syndromes common in the elderly. Geriatric syndromes are multifactorial conditions that are prevalent in older adults. Due to its importance, frailty, malnutrition, cognitive impairment and delirium are highlighted.

Table 4. Secondary prevention. Adapted from current ESC Guidelines.

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish.
Physical activity	3.5–7 h moderately vigorous physical activity per week or 30–60 min most days.
Blood pressure	BP <140/90 mmHg. Angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor blockers in cases of intolerance to ACE inhibitors) are recommended, especially in patients with left ventricular dysfunction, diabetes or chronic kidney disease.
Diabetes	HbA1c: <7% (<53 mmol/mol). Sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor antagonist should be considered regarding their cardiovascular benefits in this scenario.
Low-density lipoprotein cholesterol (LDL-C)	Statins are recommended in all NSTEMI patients. Goal: $\geq 50\%$ LDL-C reduction from baseline and LDL-C <1.4 mmol/L (<55 mg/dL).
Cardiac rehabilitation	Enrolment in cardiac rehabilitation programmes is recommended.

5. Secondary prevention

Age is associated with high rates of recurrent cardiovascular events [56]. Secondary prevention should be highly encouraged in this population. Some of the recommendations in secondary prevention are summarized in Table 4.

Lipid-lowering therapies are essential after an ACS, and high-dose statins are highly encouraged in current guidelines. Different studies and meta-analysis have demonstrated that elderly patients do also benefit from this therapy, though registries show a low proportion of patients ≥ 80 years receiving this treatment after an ACS [57, 58]. In the IMPROVE-IT trial patients over 75 years who received intensive statin therapy after an ACS experienced a substantial reduction in a composite of cardiovascular events with no differences in terms of safety or tolerability [59]. In a meta-analysis including nine clinical trials including 19,569 patients between 62–82 years, statin therapy reduced all-cause mortality by 22% over five years and also other cardiovascular events [60]. Recently, Schubert *et al.* [61] demonstrated in a real-world set-

ting trial that lower lipid levels were associated with significant reductions in a combined primary outcome including cardiovascular mortality, myocardial infarct and stroke and also with significant reduction in HF admission rates or need for revascularization. As a matter of a fact, secondary prevention measures should be adapted to baseline specific conditions such as frailty or polypharmacy and risk of drug interaction [57]. Recommendations regarding angiotensin converting enzyme inhibitors, mineralocorticoid receptor antagonists and beta-blockers, do not differ from those in younger patients.

Enrolment in cardiac rehabilitation programmes provides better drug adherence and functional capacity in the elderly immediately after an ACS [51, 62]. Such great benefits also include better cardiovascular risk factors control, Mediterranean diet adherence and functional capacity improvement [47, 63].

6. Conclusions

Management of elderly patients with NSTEMI constitutes both a priority and a challenge for cardiologists nowadays. Assessment of ischemic and haemorrhagic risks is principal, as well as comorbidities and geriatric syndromes. Overall, robust elderly patients with ACS should be managed as their younger counterparts. Specific focused therapies, aimed to prevent functional decline, malnutrition or other geriatric conditions, should be implemented during hospitalization in all cases. In this complex clinical setting, a multidisciplinary approach is required to provide best treatment and prognosis.

Abbreviations

AF, atrial fibrillation; ACS, acute coronary syndrome; CIN, contrast-induced nephropathy; CR, cardiac rehabilitation; DAPT, dual antiplatelet therapy; DES, drug eluting stents; DOAC, direct oral anticoagulants; ESC, European Society of Cardiology; LMWH, low molecular weight heparin; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

Author contributions

CJM and PDV wrote this manuscript, prepared the figures and adapted Tables 2,4. PDV and FA wrote the manuscript and revised 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.

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