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Antithrombotic strategies in elderly patients with acute coronary syndrome

Traitements antithrombotiques chez les patients âgés avec un syndrome coronaire aigu

Abbreviated title: Elderly and antithrombotics

Abbreviated title: Patients âgés et antithrombotiques

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Jean-Guillaume Dillinger[a,*], Marc Laine[b,c,d], Sara Bouajila[a], Franck Paganelli[b,c], Patrick Henry[a], Laurent Bonello[b,c,d]

[a] *Department of Cardiology, Hôpital Lariboisière, AP-HP, Inserm U-942, Université de Paris, 75010 Paris, France*

[b] *Mediterranean Association for Research and Studies in Cardiology (MARS Cardio); Centre for Cardiovascular and Nutrition Research, AP-HM, Aix-Marseille University, INSERM 1263, INRA 1260, 13015 Marseille, France*

[c] *Cardiology Department, Hôpital Nord, 13015 Marseille, France*

[d] *Mediterranean Association for Research and Studies in Cardiology (MARS Cardio), 13015 Marseille, France*

* Corresponding author at: Department of Cardiology, Hôpital Lariboisière, 2 Rue Ambroise Paré, 75010 Paris, France.

E-mail address: jean-guillaume.dillinger@aphp.fr (J.-G. Dillinger).

Jean-Guillaume Dillinger and Marc Laine contributed equally to the manuscript as joint first authors.

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Summary

Elderly patients represent a growing proportion of the acute coronary syndrome population in Western countries. However, their frequent atypical symptoms at presentation often lead to delays in management and to misdiagnosis. Furthermore, their prognosis is poorer than that of younger patients because of physiological changes in platelet function, haemostasis and fibrinolysis, but also a higher proportion of comorbidities and frailty, both of which increase the risk of recurrent thrombotic and bleeding events. This complex situation, with ischaemic and haemorrhagic risk factors often being intertwined, may lead to confusion about the required treatment strategy, sometimes resulting in inadequate management or even to therapeutic nihilism. It is therefore critical to provide a comprehensive overview of our understanding of the pathophysiological processes underlying acute coronary syndrome in elderly patients, and to summarize the results from the latest clinical trials to help decision making for these high-risk patients.

Résumé

Les patients âgés représentent une proportion croissante des patients admis pour un syndrome coronarien aigu dans les pays développés. Cependant, leurs symptômes atypiques lors de l'événement entraînent souvent des retards de prise en charge et des diagnostics erronés. De plus, leur pronostic est plus mauvais que celui des patients plus jeunes en raison des modifications physiologiques liées au vieillissement de la fonction plaquettaire, de l'hémostase et de la fibrinolyse, mais également à cause de comorbidités plus fréquentes et d'une fragilité qui augmentent à la fois le risque d'événements thrombotiques et hémorragiques. Cette situation complexe, avec des facteurs de risque ischémiques et hémorragiques souvent imbriqués, peut conduire à une confusion dans la stratégie du traitement antithrombotique, pouvant aboutir à une prise en charge inadéquate voire à un nihilisme thérapeutique. Il est donc essentiel d'avoir une compréhension globale des processus physiopathologiques sous-jacents au cours du syndrome coronarien aigu chez les patients âgés. Cette revue résume les principes physiopathologiques de la thrombose chez les patients âgés, les résultats des derniers essais cliniques ainsi que les recommandations pour aider à une meilleure prise de décision pour ces patients âgés à haut risque.

KEYWORDS

Elderly;

Acute coronary syndrome;

Antiplatelet;

Ischaemic;

Bleeding;

MOTS CLÉS

Sujet âgé ;

Syndrome coronaire aigu ;

Antiagrégant plaquettaire ;

Ischémie ;

Saignement ;

Abbreviations: ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CI, confidence interval; DAPT, dual antiplatelet therapy; GPI, glycoprotein IIb/IIIa inhibitor; HR, hazard ratio; MACE, major adverse cardiovascular events; NOAC, non-vitamin K antagonist oral anticoagulant; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; UFH, unfractionated heparin; VKA, vitamin K antagonist.

Background

Acute coronary syndrome (ACS) is an important health issue that contributes considerably to global mortality and morbidity in men and women worldwide [1, 2]. Recent advances in percutaneous coronary intervention (PCI) and antithrombotic treatment have helped to improve the prognosis of patients with ACS. Over the past 10 to 15 years, registries and cohort studies on ACS have shown a large decrease in mortality, which is currently estimated at around 5–10% in the first year following the index event [3, 4]. However, some efforts are still needed in specific high-risk populations, such as those with diabetes, women and elderly patients, to subsequently reduce mortality after ACS.

Elderly patients are usually defined as having a chronological age of ≥ 65 years [5]. However, there is no medical or biological evidence to support this definition. In developed countries, the limit is often set at 75 years or even 80 years. In the present review, we will use the threshold of ≥ 75 years to define elderly patients consistently with recent guidelines [6-8]. Elderly patients represent a growing proportion of the ACS population, although are often underdiagnosed because of atypical symptoms at presentation. Moreover, elderly patients have a high prevalence of comorbidities, such as hypertension, diabetes, chronic kidney disease, anaemia, etc., leading to a higher risk of bleeding and ischaemic events compared with younger patients. Therefore, elderly patients are also often undertreated as a result of higher vulnerability to complications with conservative or invasive strategies, in part explaining the increased morbidity and mortality attributable to ACS in this population.

Antithrombotic treatment is a key issue in the ACS setting, as platelet activation and coagulation are important pathogenic factors in the process of atherothrombosis. As a result of a narrow risk-benefit balance in elderly patients, antithrombotic treatment requires specific attention. This review summarizes current evidence regarding antithrombotic treatment in elderly patients with ACS, and offers age-specific management strategies in situations where a knowledge gap remains.

Platelet function and coagulation in elderly patients

Platelet function

Despite the fact that platelet count decreases moderately with age, an increase in platelet responsiveness is observed in elderly patients, resulting in an increased thrombotic risk [9, 10]. It has been established

since 1975 that adenosine diphosphate-induced platelet aggregation increases with age. This finding is also observed using other platelet agonists, such as collagen, epinephrine and arachidonic acid [11]. The concentration of adenosine diphosphate required to induce platelet aggregation has also been shown to decrease with age [12]. Besides, age is associated with a decrease in the number of platelet receptors for prostaglandin I2 and in the plasmatic concentration of prostaglandin I2, which plays a key role in the platelet inhibitory signalling pathway [13, 14]. Age-related endothelial dysfunction is also strongly correlated to reduced bioavailability of nitric oxide – one of the most potent platelet inhibitors [15-18]. Moreover, intraplatelet production of reactive oxygen species increases with age, leading to the inactivation of nitric oxide as a result of oxidative reactions [19-23]. Thus, through oxidative stress, reactive oxygen species are responsible for an increased level of platelet activation [24, 25].

Coagulation

Aging is associated with a procoagulant state. Indeed, the procoagulant factors VII, VIII, IX, X, XII, von Willebrand factor, prekallikrein and high-molecular-weight kininogen have been shown to increase with age [26-33]. Reflecting this activation of the coagulation cascade, the level of D-dimers increases with age [34]. In addition to this procoagulant state, aging is frequently associated with a proinflammatory state, with C-reactive protein and interleukin-6 concentrations being increased in elderly patients [35]. Through its proclotting effects, this proinflammatory state promotes thrombotic events, such as ACS, and worsens their prognosis [36, 37]. This propensity for inflammation in elderly patients is mainly the result of a mechanism of immunosenescence [38]. Regarding fibrinolytic factors, the expression of plasminogen activator inhibitor-1, which is known to have antifibrinolytic properties, is increased in elderly patients, therefore shifting again the haemostatic balance in favour of thrombosis [39].

Ischaemic and bleeding risks in elderly patients

Ischaemic risk

As described above, elderly patients have several haemostatic, coagulant and fibrinolytic alterations that may favour the occurrence of ischaemic events (Central illustration). Previous large registries have shown that patients aged ≥ 75 years represent about 25% of cases of ST-segment elevation myocardial infarction

(STEMI) and 40% of cases of non-STEMI (NSTEMI) [40-43]. Beyond the higher prevalence of thrombotic events in this high-risk population, coronary artery disease encountered in elderly subjects is more complex (calcified, multivessel disease, involvement of the left main artery) than in younger patients [44]. Furthermore, factors such as a proinflammatory state worsen the prognosis of those patients presenting with ACS. The mortality rate is 3 times higher in elderly patients presenting with ACS, and in-hospital mortality increases by 75% for each additional decade [45, 46]. In a recent registry, the 1-year mortality rates of patients presenting with NSTEMI aged 80–84, 85–89 and > 90 years were 23.6%, 33.6% and 45.5%, respectively [47].

The risk of major adverse cardiovascular events (MACE) can be stratified using scores integrating clinical data available at the patient's bedside and routine laboratory tests. The Thrombolysis In Myocardial Infarction (TIMI) risk score was developed from the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) study and TIMI 11B trials including patients with unstable angina and NSTEMI [48, 49]; it includes seven items, each counting as 1 point: age ≥ 65 years; aspirin consumption in the previous 7 days; two anginal episodes (or more) in the last 24 hours; previous coronary stenosis of ≥ 50%; ST-segment deviation on the electrocardiogram at presentation; the presence of at least three risk factors for coronary artery disease; and elevated cardiac biomarkers [50]. The TIMI risk score predicts the risk of all-cause mortality, new or recurrent myocardial infarction (MI) or revascularization required by severe recurrent ischaemia at 14 days. By including age as one of its items, the TIMI risk score highlights the increased risk of ischaemic recurrences and, more broadly, of MACE in elderly patients.

The simpler TIMI risk index is used in patients with STEMI to determine their mortality risk outside hospital or on arrival at the hospital. The TIMI risk index is defined as (heart rate×[age/10]²) divided by systolic pressure. This simple score composed of three items is strongly correlated to prognosis, and underscores the key role of age in determining outcome after ACS [51].

The Global Registry of Acute Coronary Events (GRACE) score is correlated with in-hospital mortality, 6-month mortality and recurrent myocardial infarction or mortality at 6 and 12 months [52-54]. Age is one of the eight items used to calculate this score, emphasizing the strong correlation between age and MACE over the course of ACS.

Several lines of evidence highlight the critical need for up-to-date care of elderly patients presenting with an ACS to alleviate the burden of ischaemic recurrences and mortality in this high-risk population, implying optimal medical therapy and an invasive strategy (i.e. coronary angiography and PCI if required), including in patients aged > 90 years [55, 56]. However, an invasive strategy, although overall beneficial, is associated with an increased risk of bleeding events in elderly patients [57]. It is therefore of the utmost importance to identify both ischaemic and bleeding risk factors to provide a tailored antithrombotic strategy in this high-risk population [58, 59].

Bleeding risk

Bleeding is a dramatic complication because of the underlying cause (such as intracranial haemorrhage, haemorrhagic shock, etc.), because of the adverse events related to blood transfusion (septic, immunological reaction, etc.) and because of the discontinuation of dual antiplatelet therapy (DAPT) that it may require, and the increased risk of thrombotic recurrences inherent to this interruption. The occurrence of bleeding in patients with ACS has been widely correlated to the risk of death and recurrent myocardial infarction. Because not all bleeding events have the same impact on prognosis, it is important to classify them accurately in daily practice. The Bleeding Academic Research Consortium (BARC) classification is used most widely to classify the severity of bleeding (Table 1) [60].

In the ADAPT-DES study, including 8582 “all comers” who underwent successful PCI with a drug-eluting stent, postdischarge bleeding occurred in 6.2% of patients, and bleeding was strongly associated with mortality (13% vs 3.2% in patients without bleeding; $P < 0.0001$) [61]. In a registry of 8000 patients, Valle et al. found that postdischarge bleeding increased the risk of myocardial infarction or death after PCI (hazard ratio [HR] 3.09, 95% confidence interval [CI] 2.41–3.96) [62]. Interestingly, the risk of death following BARC 3c bleeding in patients with ACS was higher than that associated with recurrent myocardial infarction [63].

Bleeding is frequent in elderly patients with ACS (Central illustration). In the SENIOR trial that randomized 1200 patients aged ≥ 75 years (mean age 81 years) between a drug-eluting stent and a bare-metal stent, the rate of BARC 3 or BARC 5 bleeding at 1 year was 3.5% [64]. Therefore, it is critical to determine the bleeding risk of patients to adjust the antithrombotic strategy accordingly. The HAS-BLED

score allows for a detailed assessment of the patient bleeding risk; however, it was validated in patients with atrial fibrillation and not in the setting of ACS [65]. Therefore, the use of the HAS-BLED score is not recommended for the assessment of bleeding risk in elderly patients with ACS.

Six risk scores have been developed to predict bleeding risk in patients treated with antiplatelet agents: REduction of Atherothrombosis for Continued Health (REACH); the Dutch acetylsalicylic acid (ASA) score; DAPT; Patterns of non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS); PREdicting bleeding Complications in patients undergoing stent Implantation and SubsequEnt Dual AntiPlatelet Therapy (PRECISE-DAPT); and BLEEding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome (BleeMACS) [58, 59, 66-69]. Of note, advanced age is the only item found in each scoring system. These data underline that elderly subjects are both at higher risk of ischaemic/thrombotic event, but also at higher risk of bleeding, which complicates their management and reinforces the importance of a personalized treatment strategy. The power of discrimination of these scores is relatively modest, none of them having an area under the curve > 0.70 in their validation tests. Recently, the Academic Research Consortium (ARC) established a consensus paper defining high bleeding risk as a BARC 3 or BARC 5 bleeding risk ≥ 4% at 1 year or a risk of intracranial haemorrhage ≥ 1% at 1 year [70]. Major and minor criteria are detailed in the document: a major criterion confers a 1-year BARC 3 or BARC 5 bleeding risk of ≥ 4% or a 1-year risk of intracranial haemorrhage of ≥ 1%, whereas minor criteria are associated with a 1-year BARC 3 or BARC 5 bleeding risk of < 4% (Table 2). Taken separately, age ≥ 75 years is considered as a minor criterion. However, age is frequently associated with the presence of comorbidities, such as chronic kidney disease, anaemia, stroke history and malignancy, all increasing the risk of bleeding [70]. In this consensus document, experts consider patients to be at high risk of bleeding under DAPT if at least one major criterion or two minor criteria are met. Physicians can rely on these criteria to determine the bleeding risk of elderly patients in the setting of ACS. These criteria are part of the new European Society of Cardiology NSTEMI guidelines [6]. Regarding the duration of DAPT, the DAPT score helps to identify patients eligible for prolonged dual therapy (i.e. up to 30 months) for whom thrombotic risk outweighs the risk of bleedings [59]. On the other hand, the PRECISE-DAPT score identifies patients in whom DAPT can be shortened to 3–6 months because of a very high risk of bleeding [58]. Importantly, unlike the PRECISE-DAPT score used at the

time of PCI, the DAPT score is calculated after 12 months of DAPT [71]. The criteria used in the calculation of these scores are listed in Table 3. The use of the DAPT and PRECISE-DAPT scores to determine the duration of DAPT is recommended in international guidelines, and should be considered in elderly patients with ACS as for younger patients [6, 72].

Antithrombotic treatment

Aspirin

Aspirin is a cornerstone antithrombotic treatment in the setting of ACS. Convincing evidence of the effectiveness of aspirin in myocardial infarction in addition to fibrinolysis was demonstrated in 1988 by the Second International Study of Infarct Survival (ISIS-2), in which the benefits of aspirin and streptokinase were seen to be additive [73]. Similarly, in patients with NSTEMI, several studies including patients with unstable angina in the era before PCI showed that aspirin was associated with a significant reduction in myocardial infarction or death. However, a limited number of elderly patients were enrolled in these old trials.

International guidelines recommend the administration of a bolus of aspirin (150–300 mg) in patients with ACS, including elderly patients, to ensure complete inhibition of thromboxane A2-dependent platelet aggregation. A meta-analysis suggested that aspirin administration was associated with a highly significant reduction in MACE of up to 46% over 2 years of follow-up [74]. Aspirin is also strongly recommended for long-term secondary prevention of coronary artery disease and ischaemic stroke. However, no specific studies on aspirin in this setting have been performed in elderly patients, and no data on bleeding rates regarding age are available.

The gastrointestinal side effects of aspirin are well known and increase with dose. Current evidence supports a daily dose of 75/100 mg for the long-term prevention of ischaemic events in patients with ACS or stable coronary artery disease [74-76]. These reduced doses should be used in elderly patients to minimize the gastrointestinal side effects of aspirin.

Clopidogrel

DAPT with aspirin and a P2Y12 inhibitor is currently recommended in ACS [6, 7]. Clopidogrel was the first

P2Y12 inhibitor to show a reduction in recurrent ischaemic events in patients with ACS [77, 78]. No difference was observed between younger and older patients, with a threshold established at 65 years. Similar results concerning the effectiveness of clopidogrel regardless of age were reported in the COMMIT trial, including patients with STEMI and fibrinolytic therapy [79]. However, it is now well established that the clopidogrel response is highly variable, and many components of this variability have been identified [80, 81]. Age has been shown to be a strong and independent factor for high on-treatment platelet reactivity, in addition to other factors, such as diabetes or genetic traits – mainly cytochrome P450 2C19*2 [82]. However, the safety profile of clopidogrel in terms of bleeding events makes it interesting in elderly patients with ACS known to be at high bleeding risk.

New P2Y12 inhibitors

Prasugrel and ticagrelor have been shown to be superior to clopidogrel in reducing ischaemic events in patients with ACS. Elderly patients are more vulnerable to the adverse effects of antithrombotic therapies, and more potent P2Y12 inhibitors should be used after careful estimation of the risk-benefit balance in this population. Prasugrel was evaluated in the TRITON-TIMI 38 trial that included ACS patients scheduled for an invasive strategy [83]. Recurrent cardiovascular events were significantly reduced by 19% in patients treated with prasugrel compared with in those treated with clopidogrel. However, this benefit was not demonstrated in three prespecified subgroups, including patients with previous stroke or transient ischaemic attack, patients aged ≥ 75 years and those weighing < 60 kg. Therefore, prasugrel 10 mg is usually not recommended in patients aged ≥ 75 years. Prasugrel 5 mg seems to be a more appropriate dosage to obtain satisfactory platelet inhibition in elderly patients [84]. However, the benefit of this reduced dose has not been clinically proven in patients with ACS [85].

Ticagrelor, a reversibly binding P2Y12 inhibitor, was shown to reduce the primary composite endpoint of cardiovascular death, myocardial infarction and stroke by 16% compared with clopidogrel in the PLATO trial [86]. No significant difference was observed between young and old patients regarding ischaemic or bleeding events [87]. Current guidelines recommend the use of prasugrel or ticagrelor over clopidogrel in patients without contraindications or an excessive risk of bleeding [6, 7, 88, 89]. Prasugrel and ticagrelor should not be used in patients with a previous haemorrhagic stroke, those on a long-term oral

anticoagulant or patients with moderate-to-severe liver disease. It should also be noted that prasugrel and ticagrelor have not been studied in adjunction to fibrinolysis, and are therefore not recommended in this setting. Of note, it is not recommended to administer routine pretreatment with a P2Y12 inhibitor in patients with NSTEMI in whom the coronary artery is unknown and early invasive management is planned [6]. This rule seems particularly true in elderly patients in whom the bleeding risk is increased.

Recent guidelines mentioned that prasugrel should be considered in preference to ticagrelor in patients with NSTEMI who proceed to PCI. In the ISAR-REACT 5 trial, 4018 patients with ACS (NSTEMI and STEMI) scheduled to have an invasive evaluation were included. The antithrombotic strategy with prasugrel was superior to that with ticagrelor in terms of the occurrence of death, myocardial infarction and stroke, without any increase in bleeding complications. However, a reduced maintenance dose of prasugrel 5 mg daily was recommended in patients aged ≥ 75 years (13.7% of the population). In summary, prasugrel 5 mg (dosage not available in France) or ticagrelor should be used in elderly patients with a high ischaemic risk (especially after PCI) after careful evaluation of the bleeding risk.

Glycoprotein IIb/IIIa inhibitors

In accordance with the increased risk of major bleeding complications with the use of glycoprotein IIb/IIIa inhibitors (GPIs), this treatment should be limited to bailout situations or thrombotic complications during PCI. The bleeding risk related to GPIs is particularly increased in elderly patients [90]. Therefore, GPIs should be used with caution in this population. Moreover, as impaired renal function is frequent in elderly patients, careful dose adjustment should be considered to prevent bleeding.

Anticoagulation

Anticoagulation is used during ACS to inhibit thrombin generation and therefore decrease thrombus-related events. In patients with STEMI treated with primary PCI, unfractionated heparin (UFH) should be used as a first-line anticoagulant agent, according to previous clinical trials that failed to demonstrate the superiority of other anticoagulant agents over UFH. For example, bivalirudin, a direct thrombin inhibitor, was studied extensively in several trials that included thousands of patients with ACS (STEMI, NSTEMI or unstable angina). The reduction in bleeding risk initially observed with this agent compared with UFH

combined with a GPI was not observed in recent randomized clinical trials that compared bivalirudin with UFH without a GPI [91-93]. Furthermore, bivalirudin is associated with an increased risk of MACE compared with UFH [93]. In the randomized ATOLL trial, low-molecular-weight heparin failed to demonstrate its superiority compared with UFH regarding ischaemic endpoint in a randomized clinical trial that included 910 patients with primary PCI [94]. However, enoxaparin seems to be superior to UFH in reducing mortality and bleeding outcomes [95]. Importantly, fondaparinux is not recommended for primary PCI (class III) [7]. Besides, in patients with STEMI treated with fibrinolysis, low-molecular-weight heparin is recommended over UFH because of a net clinical benefit in favour of enoxaparin [7, 96]. The low-molecular-weight heparin dose should be adjusted according to body weight and renal function, which is particularly relevant in elderly patients (Table 4). In the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT)-TIMI 25 trial, a lower dose of enoxaparin (subcutaneous dose of 75 IU/kg without intravenous bolus) was given to patients aged ≥ 75 years, and appears to be helpful in reducing the bleeding risk without jeopardizing its antithrombotic efficacy [97].

Fondaparinux was found to be superior to UFH in patients with STEMI treated with streptokinase [98, 99]. In the large OASIS-5 trial of patients with NSTEMI, this anticoagulant treatment was also shown to be particularly safe, and to reduce major bleeding while maintaining efficacy; it is therefore the first-line anticoagulant agent for patients with NSTEMI [6, 100]. The safety profile of low-dose fondaparinux is particularly interesting in elderly patients presenting with NSTEMI. In all cases, anticoagulation should be as short as possible, except if another indication requires longer treatment duration. Furthermore, we believe that physicians should use the anticoagulant that they are used to, and should avoid the switch from one anticoagulant agent to another, as recommended [94].

Thrombolysis

Fibrinolytic therapy is the recommended reperfusion strategy when primary PCI cannot be performed in time. The largest absolute benefit is seen among patients at the highest ischaemic risk, including elderly subjects, and when treatment is offered < 2 hours after symptom onset. However, fibrinolytic therapy is associated with a significant excess of intracranial haemorrhage (1%). The most recent data coming from the STREAM trial showed that prehospital fibrinolysis followed by an early PCI strategy was associated

with a similar outcome to transferring for primary PCI patients with STEMI presenting within 3 hours after symptoms onset and who could not undergo primary PCI within 1 hour after initial medical contact [101]. Fibrinolysis with a half dose of tenecteplase was performed in the study, and is currently recommended in patients aged ≥ 75 years. Because of the excess in bleeding risk after fibrinolysis, enoxaparin doses should be reduced, and new P2Y12 inhibitors should not be administered in this setting.

Optimization of antithrombotic therapy

Evaluation of platelet function

The availability of different P2Y12 receptor inhibitors has enabled physicians to offer individualized antithrombotic treatment, which may include escalation or de-escalation of antiplatelet agents (Central illustration). Several studies have shown that platelet function testing or genetic testing can identify patients with high platelet reactivity on clopidogrel or aspirin, which reflects an increased risk of ischaemic events [102, 103]. However, in the ARCTIC trial, platelet function monitoring with adjustment of antiplatelet therapy for coronary stenting failed to show a significant reduction in the composite ischaemic endpoint of death, myocardial infarction, stroke or urgent revascularization [104]. Similarly, tailoring antiplatelet therapy in elderly patients with ACS was evaluated in the ANTARCTIC trial [105]. Patients were randomized to receive oral prasugrel 5 mg daily with dose or drug adjustment in case of inadequate response (monitoring group) or oral prasugrel 5 mg daily with no monitoring or treatment adjustment. The primary endpoint, including ischaemic and bleeding events, did not differ significantly between groups. In the TROPICAL-ACS study, guided de-escalation of antiplatelet treatment was non-inferior to standard treatment in terms of ischaemic but also bleeding events [106]. Therefore, routine use of platelet function evaluation is currently not recommended, including in elderly patients. Platelet function evaluation or genetic testing may be considered as optional tools for treatment guidance in very selected cases.

Measures to reduce the bleeding risk in elderly subjects

Pretreatment with P2Y12 inhibitors in patients undergoing PCI

Among patients scheduled for PCI, including those with NSTEMI, pretreatment with thienopyridines has

been shown to be associated with a significant excess of bleeding, with no reduction in cardiovascular death or ischaemic events [107]. This result was updated with pretreatment with prasugrel in the randomized ACCOAST trial [108]. For ticagrelor, optimal timing of administration (pretreatment or treatment after PCI) was not properly evaluated in patients with ACS. Moreover, type 2 myocardial infarction is frequent in elderly patients, which may lead to different management compared with type 1 myocardial infarction [109, 110]. Therefore, the administration of P2Y12 receptor inhibitors is not recommended in elderly subjects, until the diagnosis of ACS has been confirmed angiographically [6].

Use of proton pump inhibitors

The routine use of proton pump inhibitors in patients with antiplatelet and anticoagulant treatment has been shown to decrease gastroduodenal bleedings [111]. Guidelines recommend administration of gastroprotective agents to older patients (aged > 65 years) and to those with a high risk of gastrointestinal bleedings on antiplatelet agents [112-114]. Therefore, proton pump inhibitors are highly recommended in elderly patients treated with aspirin or DAPT [8].

De-escalation of antiplatelet treatment after ACS

Given the first-line use of more potent P2Y12 receptor inhibitors, and the reduction in thrombotic risk over time after ACS, strategies of de-escalation of antiplatelet therapy seem particularly interesting in elderly patients. In the setting of ACS, the TOPIC trial suggests that downgrading from a new P2Y12 receptor inhibitor to clopidogrel in patients with ACS treated with DAPT after 1 month may reduce bleeding complications, without excess of recurrent ischaemic events, which were similar in both groups. In the same way, in the HOST-REDUCE-POLYTECH-ACS trial, 2238 patients with ACS receiving PCI were randomly assigned to a de-escalation group (10 mg prasugrel for 1 month followed by 5 mg) or a conventional group. The study demonstrated a significant reduction in bleeding events in the de-escalation group [115]. Another de-escalation strategy of stopping aspirin in high-risk PCI patients treated with DAPT with ticagrelor was evaluated in the TWILIGHT study [116]. After 3 months of DAPT with ticagrelor and aspirin, ticagrelor as monotherapy was associated with a lower incidence of clinically relevant bleedings than the conventional strategy, without an increase in ischaemic events. Therefore, de-

escalation strategies could be interesting in patients at high risk of bleedings, such as elderly patients.

Duration of DAPT

In patients with ACS, DAPT is usually recommended for 1 year, but individual decision making and reassessment is required according to changes in ischaemic or bleeding risk over time. Prolonged DAPT for 30 months could be preferred in patients at high ischaemic risk. However in the DAPT trial, prolonged DAPT with clopidogrel did not change the ischaemic and safety endpoints in the subgroup of elderly patients [71]. In the PEGASUS trial, no benefit of prolonged therapy with ticagrelor 60 or 90 mg twice daily was observed in elderly patients who had a myocardial infarction 1–3 years before randomization, in terms of reduction in ischaemic events: HR 0.77, 95% CI 0.59–1.01 for ticagrelor 60 mg twice daily, and HR 1.02, 95% CI 0.80–1.30 for ticagrelor 90 mg twice daily, compared with placebo [117]. This lack of benefit was associated with a 2.5–3-fold increase in bleeding risk in elderly patients.

Management of elderly patients requiring long-term oral anticoagulation

The need for chronic anticoagulation is a key issue in elderly patients. The first question that the clinician must ask is whether there is justification for long-term anticoagulation. Some situations are indisputable, such as atrial fibrillation, mechanical prosthetic valve and recent pulmonary embolism [118-120]. Some situations are less formal, such as anticoagulation after transcatheter aortic valve replacement to prevent valvular haemodynamic deterioration [121] or long-term prevention of venous thromboembolism [120]. These frequent comorbidities in elderly patients with ACS complicate the antithrombotic strategy [122]. The most recent data come from randomized studies evaluating antithrombotic strategy in patients with atrial fibrillation. Prevalence of atrial fibrillation ranges from 5% to 20% in patients aged > 75 years [123, 124]. After ACS, DAPT is required, especially when PCI with stent implantation is performed. However, the antiplatelet treatment does not offer sufficient protection against systemic embolism and stroke, and anticoagulation should be continued, leading to the concept of triple antithrombotic therapy. Since the WOEST trial, which compared triple therapy (vitamin K antagonist [VKA}), clopidogrel and aspirin) with clopidogrel and a VKA, de-escalation with early interruption of aspirin has been proposed to decrease the bleeding risk [125]. Indeed, the WOEST trial demonstrated a decrease in the rate of bleeding events in the

clopidogrel and VKA group: 19.4% vs 44.4% (HR 0.36, 95% CI 0.26–0.50; $P < 0{\cdot}0001$) [125]. Interestingly, the rate of secondary ischaemic events was decreased in the double therapy group compared with the triple therapy group: 11.1% vs 17.6% (HR 0.60, 95% CI 0.38–0.94; $P = 0.025$).

Several studies have been performed to assess each non-VKA oral anticoagulant (NOAC) – dabigatran, rivaroxaban, apixaban and edoxaban – in this setting [126-129]. These trials support the better safety of a dual antithrombotic strategy (NOAC and clopidogrel) compared with the combination of antiplatelet agent(s) with a VKA regarding bleeding and thrombotic events [130]. Triple antithrombotic therapy should therefore be avoided and, if prescribed, the duration should be as short as possible (1 month) in elderly patients because of the extremely high bleeding risk of this combination. In this setting, double therapy should be the rule, and triple therapy the exception, dedicated to patients with a high thrombotic risk and a low bleeding risk. Importantly, NOACs should be preferred over VKAs unless contraindicated (e.g. severe chronic kidney disease) [131]. When dabigatran is used in combination with an antiplatelet agent, the dose of 110 mg twice daily should be used in elderly patients, whereas rivaroxaban 15 mg is recommended [131]. The recommended dose of apixaban in combination with antiplatelet agents is 5 mg twice daily, except in patients with two of the these criteria – age > 80 years, creatinine > 133 μmol/L or weight < 60 kg – in whom apixaban 2.5 mg twice daily should be considered [131]. In patients requiring long-term oral anticoagulation, the most recent guidelines recommended as a default strategy a very short triple therapy (in hospital and up to 1 week) followed by a double therapy including an oral anticoagulant and single antiplatelet therapy [6]. Triple therapy can be prolonged for 1 month after ACS in patients at high ischaemic risk, but not in those at high bleeding risk, including elderly patients.

Finally, continuation of anticoagulant treatment combined with an antiplatelet agent after 1 year exposes patients to a 50% increase in bleeding events [132]. Therefore, anticoagulation with discontinuation of the antiplatelet agent at 1 year (or even 6 months) should be used in most elderly patients to decrease the bleeding risk (HR 0.64, 95% CI 0.46–0.91), as demonstrated in the AFIRE trial [133].

Conclusions

A growing number of patients with ACS are older than 75 years; their prognosis is worse than younger patients because of higher comorbidities and increased recurrent bleeding and thrombotic events. A careful evaluation of both ischaemic and bleeding risks is necessary in this high-risk population, and antithrombotic treatment should be adjusted based on an individualized and often collegial strategy, taking into account age, comorbidities and frailty, as well as patient preference. The optimization of antiplatelet therapy should be assessed in a dynamic process according to the occurrence of adverse events during follow-up.

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Figure legend

Central illustration. Antithrombotic strategies in patients with acute coronary syndrome. ACS: acute coronary syndrome; ADP: adenosine diphosphate; CAD: coronary artery disease; CRP: C-reactive protein; IL-6; interleukin-6; DAPT: dual antiplatelet therapy; GRACE: Global Registry of Acute Coronary Events; NSTEMI: non-ST-segment elevation myocardial infarction; PAI-1: plasminogen activator inhibitor-1; PCI: percutaneous coronary intervention; PG12: prostaglandin 12; PPI: proton pump inhibitor; PRECISE-DAPT: PREdicting bleeding Complications in patients undergoing stent Implantation and SubsequEnt Dual AntiPlatelet Therapy; REACH: REduction of Atherothrombosis for Continued Health; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction; Vwf: von Willebrand factor.

Table 1 Bleeding Academic Research Consortium bleeding classification.

BARC bleeding classification	Description
Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek treatment from a healthcare professional; may lead to self-discontinuation of treatment
Type 2	Bleeding that leads to non-surgical medical intervention/evaluation by a healthcare professional or hospitalization
Type 3a	Overt bleeding and transfusion Overt bleeding + Hb drop of 3–5 g/dL
Type 3b	Cardiac tamponade Overt bleeding + Hb drop of ≥ 5 g/dL Bleeding requiring surgical intervention (excluding dental, nasal, skin or haemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial haemorrhage (excluding microbleeds or haemorrhagic transformation) Intraocular bleeding compromising vision
Type 4	CABG-related bleeding within 48 hours
Type 5	Probable or definite fatal bleeding

BARC: Bleeding Academic Research Consortium; CABG: coronary artery bypass graft; Hb: haemoglobin.

Table 2 Minor and major criteria for high bleeding risk at the time of percutaneous coronary intervention according to the Academic Research Consortium consensus document.

Minor	Major
Age ≥ 75 years	Long-term oral anticoagulation
	Platelet count < 100,000 mL
Hb = 11–12.9 g/dL (male), 11–11.9 g/dL (female)	Hb < 11 g/dL
	Chronic bleeding diathesis
Moderate CKD (crCl 30–59 mL/min)	Severe or end-stage CKD (crCl < 30 mL/min)
	Liver cirrhosis with portal hypertension
Spontaneous bleeding requiring transfusion or hospitalization in the past 12 months (not meeting major criterion)	Spontaneous bleeding requiring transfusion or hospitalization in the past 6 months or any time if recurrent
	Active malignancy within the past 12 months excluding non-melanoma skin cancer
Use of NSAIDs or steroids (long term)	Major surgery or major trauma within 30 days before PCI
	Non-deferrable major surgery on DAPT
Ischaemic stroke history (not meeting major criterion)	Moderate or severe ischaemic stroke (NIHSS score ≥ 5) within the past 6 months
	Previous spontaneous ICH (any time)
	Previous traumatic ICH within the past 12 months
	Presence of brain arteriovenous malformation

CKD: chronic kidney disease; crCl: creatine clearance; DAPT: dual antiplatelet therapy; Hb: haemoglobin; ICH: intracranial haemorrhage; NIHSS: National Institutes of Health Stroke Scale; NSAID: non-steroidal anti-inflammatory drug; PCI: percutaneous coronary intervention.

Table 3 PRECISE-DAPT and DAPT scores.

	PRECISE-DAPT score	DAPT score
DAPT duration and cut-off values	3–6 months DAPT if score ≥ 25	30 months DAPT if score ≥ 2
	12–24 months DAPT if score < 25	12 months DAPT if score < 2
Criteria for calculation	Age	Age
	White blood cell count	Cigarette smoking
	Haemoglobin	Diabetes mellitus
	Creatinine clearance	MI at presentation
	Previous bleeding	Previous PCI or myocardial infarction
		Paclitaxel-eluting stent
		Stent diameter < 3 mm
		LVEF < 30% or CHF
		Vein graft stent

CHF: congestive heart failure; DAPT: Dual AntiPlatelet Therapy; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; PRECISE-DAPT: PREdicting bleeding Complications in patients undergoing stent Implantation and SubsequEnt Dual AntiPlatelet Therapy.

Table 4 Dose adjustment of antithrombotic treatments in elderly patients.

Antithrombotic drug	Recommendations		
	Normal dose	Age-related reduced dose	Specific contraindications
Aspirin	LD 150–300 mg; MD 75 mg	No dose adjustment	Intolerance to aspirin Active peptic ulcer
Clopidogrel	LD 300–600 mg; MD 75 mg	No dose adjustment	NA
Prasugrel	LD 60 mg; MD 10 mg	5 mg if ≥ 75 years	Previous stroke Dose reduction for low body weight (< 60 kg): 5 mg
Ticagrelor	LD 180 mg; MD 90 mg b.i.d.	No dose adjustment	Strong CYP3A4 inhibitors Oral anticoagulant agent
UFH	Primary PCI: 70 IU/kg IV bolus Fibrinolysis: 60 IU/kg IV bolus (max 4000 IU) then 12 IU/kg/h for 24–48 hours (max 1000 IU/h) Adapted for aPTT 1.5–2.0	No dose adjustment	Type 2 heparin induced thrombocytopaenia
Enoxaparin	Primary PCI: 0.5 mg/kg IV Fibrinolysis: 0.75 mg/kg b.i.d. SC (max 75 mg)	No dose adjustment	eGFR < 15 mL/min/1.73 m^2
Fondaparinux	2.5 mg SC once daily	No dose adjustment	eGFR < 20 mL/min/1.73 m^2
Thrombolysis (tenecteplase)	30 mg if < 60 kg	Reduce to half dose if ≥ 75 years	Previous ICH or stroke of unknown origin at anytime

35 mg if 60–70 kg	Ischaemic stroke < 6 months
40 mg if 70–80 kg	CNS damage or neoplasms or arteriovenous malformation
45 mg if 80–90 kg	Recent major trauma/surgery/head injury (< 1 month)
50 mg if ≥ 90 mg	GI bleeding < 1 month
	Aortic dissection
	Non-compressible puncture < 24 hours
	Known bleeding disorder (excluding menses)

aPTT: activated partial thromboplastin time; b.i.d.: twice a day; CNS: central nervous system; CYP3A4: cytochrome P450 3A4; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; ICH: intracranial haemorrhage; IV: intravenous; LD: loading dose; MD: maintenance dose (daily); NA: not applicable; PCI: percutaneous coronary intervention; SC: subcutaneous; UFH: unfractionated heparin.

Antithrombotic strategies in elderly patients with ACS

Elderly patients = Patients ≥ 75 years, ~ 25% of the STEMI population and ~ 40% of the NSTEMI population

Thrombosis specificity

- Platelet function
  - ↗ ADP-induced platelet aggregation
  - ↗ Arachidonic acid-induced platelet aggregation
  - ↘ PGI2 platelet receptors
  - ↗ Endothelial dysfunction
- Coagulation
  - ↗ Factors VII, VIII, IX, X, Vwf
  - ↗ Prekallikrein, kininogen
  - ↗ D-dimers
- Fibrinolysis
  - ↗ PAI-1
- Proinflammatory state
  - ↗ CRP and IL-6

Increased thrombotic risk

- Complex CAD
- Activated coagulation
- Inflammatory state
- Age = item of the TIMI risk score or GRACE score

→ Mortality X3 after ACS in elderly patients

Increased bleeding risk

- Presence of comorbidities
- Chronic kidney disease
- Anaemia
- Malignancy
- Stroke
- Frailty
- Age = item of the REACH, DAPT, PRECISE DAPT score

→ Bleeding risk ~ 3.5%/year after ACS in elderly patients

Antithrombotic treatment options

Acute phase

- Low-dose aspirin with PPIs
- Avoid P2Y12 inhibitor pretreatment in patients with NSTEMI
- Prefer primary PCI to fibrinolysis (half-dose) in patients with STEMI
- Shorten curative anticoagulation duration

Follow-up

- De-escalation of dual antiplatelet therapy after ACS
- Shorten duration of DAPT in patients with high bleeding risk
- Avoid triple antithrombotic therapy if anti-coagulation is required
- Anticoagulation alone after 1 year if anti-coagulation is required

→ Individualized antithrombotic treatment

Elderly patients = high ischemic and bleeding risk

Antithrombotic treatment = individualized strategy and dynamic reassessment process