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Antithrombotic treatment tailoring and risk score evaluation in elderly patients diagnosed with an acute coronary syndrome

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Abstract

Age is an important prognostic factor in the outcome of acute coronary syndromes (ACS). A substantial percentage of patients who experience ACS is more than 75 years old, and they represent the fastest-growing segment of the population treated in this setting. These patients present different patterns of responses to pharmacotherapy, namely, a higher ischemic and bleeding risk than do patients under 75 years of age. Our aim was to identify whether the currently available ACS ischemic and bleeding risk scores, which has been validated for the general population, may also apply to the elderly population. The second aim was to determine whether the elderly benefit more from a specific pharmacological regimen, keeping in mind the numerous molecules of antiplatelet and antithrombotic drugs, all validated in the general population. We concluded that the GRACE (Global Registry of Acute Coronary Events) risk score has been extensively validated in the elderly. However, the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) bleeding score has a moderate correlation with outcomes in the elderly. Until now, there have not been head-to-head scores that quantify the ischemic versus hemorrhagic risk or scores that use the same end point and timeline (e.g., ischemic death rate versus bleeding death rate at one month). We also recommend that the frailty score be considered or integrated into the current existing scores to better quantify the overall patient risk. With regard to medical treatment, based on the subgroup analysis, we identified the drugs that have the least adverse effects in the elderly while maintaining optimal efficacy.

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1 Introduction

Age is an important prognostic factor in the outcome of acute coronary syndromes (ACS).[1] Older patients present a higher cardiovascular risk, including higher rates of myocardial infarction, refractory angina pectoris, endothelial dysfunction, and valvular heart disease.[2–5] Elderly patients are defined as patients over 75 years of age in the vast majority of trials and most references cited in this document. In an ACS setting, this group of patients is at high risk for myocardial infarction complications, such as re-infarction, stroke, heart failure, and arrhythmias. Bleeding in the context of antithrombotic therapies and other adverse events related to treatment are common in this group.[6,7] A substantial percentage of non-ST-elevated myocardial infarction (NSTEMI) and ST-elevated myocardial infarction (STEMI) patients is elderly, and this group represents the fastest-growing segment of the population treated in this setting.[8–11]

Elderly patients tend to have atypical symptoms, including fatigue, nausea, syncope, and atypical chest pain, and are less likely to receive optimal medical and interventional treatment (up to 30% of STEMI patients).[12,13] This situation leads to delayed ACS diagnosis and treatment.[14] Therefore, it is key to maintain a high index of suspicion for myocardial infarction in elderly patients who present with

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atypical complaints, as well as to pay specific attention to the proper dosing of antithrombotic therapies, particularly in relation to renal function. There is a net benefit in this group of patients of medical versus no medical treatment and percutaneous coronary interventions (PCI) versus a conservative strategy. The benefit is also conserved in the setting of thrombolysis, as the absolute mortality reduction in patients older than 75 years is similar to that of patients less than 55 years old.[15,16]

We will review the antiplatelet and anticoagulant drugs used in ACS in the overall populations, particularly in elderly patients. The aim of this paper is to better stratify treatment strategies and evaluate which scores are more pertinent to this population for treatment purposes to facilitate judgment during everyday practice.

2 Antiplatelet treatment (overview of antiplatelet drugs in Table 1)

Once administered, aspirin suppresses thromboxane A2 production during the platelet's lifespan. A large meta-analysis of 287 studies, which included 135,000 patients in comparisons of antiplatelet therapy versus control and 77,000 patients in comparisons of different antiplatelet regimens, showed that aspirin use results in a substantial reduction in vascular events. The study also indicated that a 75–150 mg regimen is sufficient to produce rapid and complete inhibition of thromboxane-mediated platelet aggregation versus higher regimens.[17] Aspirin allergy is no longer considered an impediment to PCI, as rapid protocols are available for desensitization.[18]

Clopidogrel irreversibly inactivates platelet $P2Y_{12}$ receptors for five days. It requires oxidation by the hepatic cytochrome P450 (CYP) system to generate an active metabolite, as 85% of the prodrug is hydrolyzed by esterases into an inactive form, which leaves only 15% available for transformation to the active metabolite. Clopidogrel plus aspirin is superior to aspirin alone in the NSTEMI setting and reduces subsequent cardiovascular events.[19] Clopidogrel suboptimal platelet inhibition is responsible for up to 2% of stent thrombosis, as patients may manifest as hypo- and hyper-responders.[20] In the case of thrombolysis, no loading dose is recommended for patients over 75 years old.[21] Clopidogrel must be administered even in STEMI patients not receiving reperfusion therapy, as mortality is significantly reduced by the association of heparin and clopidogrel.[22]

Prasugrel is a potent adenozine diphosphate (ADP)-receptor blocker that reaches its loading dose effect in 30 min. In the TRITON-TIMI trial, prasugrel (60 mg loading dose/10 mg maintenance dose) was compared to clopidogrel (300 mg loading dose/75 mg maintenance dose) in 13,608 patients scheduled for PCI in the context of moderate- to high-risk ACS. Overall, prasugrel significantly reduced the rates of ischemic events at the cost of an increased risk of major bleeding. There was no significant mortality in either group.

Post hoc subgroup analyses identified subgroups that exhibited less clinical efficacy and higher bleeding rates than the overall cohort: patients who had a previous stroke or transient ischemic attack had net harm from prasugrel [hazard ratio (HR): 1.54; 95% confidence interval (CI): 1.02–2.32; $P = 0.04$], patients 75 years of age or older had no net benefit from prasugrel (HR: 0.99; 95% CI: 0.81–1.21; $P = 0.92$), and patients who weighed less than 60 kg had no net benefit from prasugrel (HR: 1.03; 95% CI: 0.69–1.53; $P = 0.89$).[23] With this concern in mind, the 2012 ESC STEMI guideline notes that in patients with a body weight < 60 kg, a maintenance dose of 5 mg is recommended, and in patients > 75 years, prasugrel is generally not recommended; however, a dose of 5 mg should be used if treatment is deemed necessary.[24] The dosage of prasugrel 5 mg administered daily after PCI in patients > 75 years old was also validated by the Food and Drug Administration and the European Medicines Agency, as a lower dose of prasugrel in these subgroups reduced the risk of bleeding while maintaining efficacy.[25] To assess whether platelet function monitoring with treatment adjustment in elderly patients stented for an acute coronary syndrome has a role, the ANTARCTIC trial randomized 877 patients on prasugrel 5 mg once daily to an active group ($n = 442$) versus a conventional group ($n = 435$, no monitoring or treatment adjustment). The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, urgent revascularization, and Bleeding Academic Research Consortium (BARC)-defined bleeding complications (types 2, 3, or 5) at the 12-month follow-up. The primary endpoint occurred in 28% of patients in the monitoring group versus 28% of patients in the conventional group (HR: 1.003, 95% CI: 0.78–1.29; $P = 0.98$), with no difference in bleeding events between the two groups. Overall, there was no role for platelet function monitoring in this high-risk group of patients.[26] In a conservative treatment strategy of unstable angina or NSTEMI, 7243 patients < 75 years old (77.7%) and 2083 patients > 75 years old (22.3%) were randomly assigned to receive prasugrel or clopidogrel [loading dose of 30 mg of prasugrel or 300 mg of clopidogrel followed by blinded maintenance of 10 mg prasugrel (5 mg for patients > 75 years old or who weighed < 60 kg) or 75 mg of clopidogrel]. Aspirin 75–100 mg was also admin-

Table 1. Antiagregant treatment in acute coronary syndromes.

Drugs	Salicylate	Thienopyridine	Thienopyridine	Triazolopyrimidine	ATP analogue	GPIIb/IIIa inhibitors		
	Aspirin	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Abciximab (REOPRO)	Eptifibatide (INTEGRILIN)	Tirofiban (AGGRASTAT)
Indications	Primary prevention. Secondary prevention, invasive or conservatory strategy for STEMI/NSTEMI	Invasive or conservatory strategy for STEMI/NSTEMI if prasugrel or ticagrelor not available or if oral anticoagulation required	Invasive strategy for STEMI/NSTEMI	Invasive strategy for STEMI/ invasive or conservatory strategy for NSTEMI	Invasive strategy for STEMI/ NSTEMI	Invasive strategy for STEMI/NSTEMI, indicated in bailout situations/large thrombus burden		
Pretreatment (before cath lab)	In STEMI: yes In NSTEMI: yes	In STEMI: yes In NSTEMI: Unknown (both before or during PCI accepted)	In STEMI: no In NSTEMI: no	In STEMI: no In NSTEMI: Unknown (both before or during PCI accepted)	In NSTEMI: Unknown (both before or after PCI accepted)	Never before PCI		
Mechanism	COX1-irreversible inactivation	ADP-induced platelet activation inhibition by $P2Y_{12}$ irreversible receptor inactivation	ADP-induced platelet activation inhibition by $P2Y_{12}$ irreversible receptor inactivation	P2Y12 reversible receptor inactivation	ATP analogue, reversible	GPIIb/IIIa inhibitors (fibrinogen inhibition)		
Pharmacokinetics								
Loading dose effect	15–30 min	IE after 4–7 days if 75 mg/day IE after 3–6 h if 300 mg (peak in 24–48 h) Peak in 2 h after 600 mg	30 min	30 min	2 min	Peak in 2 h after bolus	Peak in 2 h after bolus	Peak in 2 h after bolus
Duration of loading dose	10 days	4–8 days: 5 days the average	5–10 days	3–4 days	1–2 h	48 h	4–8 h	4–8 h
Stop before major surgery	10 days	5 days	7 days	3–5 days	1 h	48 h	4–8 h	4–8 h
Plasma half life	20 min	30–60 min	30–60 min	6–12 h	5–10 min	10–30 min Affinity for receptor is moderate- high	2–3 h Affinity for receptor is low	2 h Affinity for receptor is moderate
Dosage								
Dosage in PCI strategy	Loading: 150–300 mg (*p.o.*) or 75–150 mg (*i.v.*) Maintenance: 75–100 mg/day	Loading: 300–600 mg (*p.o.*) Maintenance: 75 mg/day	Loading: 60 mg (*p.o.*) Maintenance: 10 mg/day	Loading: 180 mg (*p.o.*) Maintenance: 90 mg twice daily	Loading: 30 µg/kg (*i.v.*) Maintenance: 4 µg /kg per minute (*i.v.*)	Loading: 250 µg/kg (*i.v.*) Maintenance: 0.125µg/kg per minute (max. 10 mcg/min) (*i.v.*) for 12 h	Loading: 180 µg/kg (*i.v.*) Maintenance: 2 µg/kg per minute (*i.v.*) for 18 h	Loading: 25 µg/kg or 10 µg/kg (*i.v.*) Maintenance: 0.15 µg/kg per minute (*i.v.*) for 18 h

Table 1. Contin.

Drugs	Salicylate	Thienopyridine	Thienopyridine	Triazolopyrimidine	ATP analogue	GPIIb/IIIa inhibitors		
	Aspirin	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Abciximab (REOPRO)	Eptifibatide (INTEGRILIN)	Tirofiban (AGGRASTAT)
Dosage in conservative strategy	Same as above	Same as above	Not recommended (unknown anatomy)	Same as above	Not recommended	Not recommended	Not recommended	Not recommended
Dosage in thrombolysis	Same as above	Loading: 300 mg (oral) if < 75 yrs Maintenance: 75 mg/day	Not recommended (unknown anatomy)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Dosage in renal failure	No adjustement	No adjustement	eGFR < 15 mL/1.73 m^2 per minute: not recommended	eGFR < 15 mL/1.73 m^2 per minute: not recommended	eGFR < 15 mL/1.73 m^2 per minute: not recommended	No specific recommendation	eGFR: 30-50 mL/1.73 m^2 per minute: Loading: 180 µg/kg (*i.v.*), Maintenance: 1 µg/kg per minute (*i.v.*). eGFR < 30 mL/1.73 m^2 per minute: not recommended	eGFR: 15-29 mL/1.73 m^2 per minute: Loading: 25 µg/kg or 10 µg/kg (*i.v.*), Maintenance: 0.05 µg/kg/min (*i.v.*) eGFR < 15 mL/1.73 m^2 per minute: not recommended
Dosage in elderly (> 75 yrs)	Loading: same Maintenance: 75 mg/day (lowest dose effective)	No adjustement No loading if thrombolysis	Maintenance: 5mg/day. No role of platelet function testing.	No adjustement	No adjustement	Use with caution if >70 yrs	Use with caution if > 70 yrs	Use with caution if > 70 yrs
Trials	ISIS-2 GISSI-2 RISC	CAPRIE, CURE, PCI-CURE, CREDO	TRITON-TIMI 38 TRILOGY ACS	PLATO	CHAMPION-PCI CHAMPION-PLATFORM CHAMPION-PHOENIX	CAPTURE, EPIC, EPILOG, EPISTENT, GUSTO4-ACS, ADMIRAL, ACE	IMPACT-II, PURSUIT, ESPIRIT	PRISM, RESTORE, TARGET, TACTICS
Contraindications and adverse effects								
Contraindications	Active bleeding	Active bleeding	Prior stroke or TIA Severe hepatic disease Active bleeding	Prior intracranial hemorrage; Severe hepatic disease Active bleeding	Active bleeding	Active bleeding Pre-existing thrombocytopenia Prior stroke (in the last 2 years for abciximab and in the last 30 days for eptifibatide and tirofiban) Concomitent thrombolysis in STEMI		
Adverse effects	Gastrointestinal bleeding	Neutropenia (0.02%–0.1%) Prurit Urticaria	Bleeding	Dyspnea Bradycardia Increase in uric acid	Bleeding	Thrombocytopenia (2%) Severe thrombocytopenia (0.5–1%)	Thrombocytopenia (0.3–0.5%)	Thrombocytopenia (0.3–0.5%)

ADP: adenozine diphosphate; COX: cyclooxygenase; GPIIb/IIIa: glycoprotein IIb/IIIa; IE: inhibitory effect; NSTEMI: non-ST-elevated myocardial infarction; PCI: percutaneous coronary interventions; STEMI: ST-elevated myocardial infarction; TIA: trainsient ischemic attack.

istered daily. At a median follow-up of 17 months, there was no significant impact of prasugrel on stroke, myocardial infarction, or death from cardiovascular causes versus clopidogrel, and similar risks of bleeding were identified.[27] In a platelet-function sub-study of the same trial, 515 patients ≥ 75 years of age (25% of the total elderly population) had serial platelet reactivity unit measurements. Cardiovascular death, myocardial infarction, stroke and bleeding were more than 2-fold higher in older subjects. The authors concluded that thrombolysis in myocardial infarction (TIMI) major bleeding and the primary end point rates were similar with reduced-dose prasugrel and clopidogrel versus 5 mg prasugrel. There was a nonsignificant treatment-by-weight interaction for platelet reactivity unit values in participants ≥ 75 years of age in the platelet-function substudy (P = 0.06), and no differences in weight were identified in all participants ≥ 75 years of age with versus without TIMI major/minor bleeding in both treatment groups.[28] We are waiting for the results of the ELDERLY-ACS2 trial, which will compare prasugrel 5 mg with clopidogrel 75 mg in the elderly.[29]

There is no benefit to administer prasugrel before PCI in a NSTEMI setting, as concluded by the ACCOAST investigators. Prasugrel (30 mg loading, pre-treatment group) or placebo (control group) was administered to 4033 patients undergoing angiography within 2–48 h after randomization. An additional 30 mg of prasugrel was administered to the pre-treatment group (at the time of PCI) and 60 mg of prasugrel was administered to the control group if PCI was indicated. The rate of death from cardiovascular causes, myocardial infarction, stroke, and urgent revascularization was not reduced with prasugrel pre-treatment; however, it did increase the rate of TIMI major bleeding at 7 and 30 days.[30]

Ticagrelor is a potent reversible inhibitor of the P2Y12, which also reaches its loading dose effect in only 30 min. It is eliminated through hepatic and biliary excretion. CYP3A inhibitors increase its plasma levels, whereas ticagrelor increases the plasma levels of drugs metabolized by CYP3A. Its main adverse effects include dyspnea without bronchospasm, ventricular pauses, and an increase in uric acid. It has not been investigated in patients undergoing thrombolysis. It is contraindicated in individuals with prior intracranial hemorrhage and moderate to severe hepatic disease. It has been validated in the PLATO trial for the prevention of cardiovascular events, in which ticagrelor (180 mg loading and 90 mg twice daily maintenance) was compared to clopidogrel (300 to 600 mg loading and 75 mg daily maintenance) in 18,624 ACS patients. The percentage of myocardial infarction, stroke, or death from vascular causes was significantly reduced with ticagrelor, with no increase in the rate of overall major bleeding; however, there was an increase in the rate of non-procedure-related bleeding.[31]

A substudy of PLATO compared ticagrelor *vs.* clopidogrel in patients ≥ 75 years old *vs.* < 75 years old and concluded that the clinical benefit of ticagrelor over clopidogrel was not significantly different between patients aged ≥ 75 years (n = 2878) and patients aged < 75 years (n = 15,744) with respect to the composite of cardiovascular death, myocardial infarction, or stroke (P = 0.56), myocardial infarction (P = 0.33), cardiovascular death (P = 0.47), definite stent thrombosis (P = 0.81), or all-cause mortality (P = 0.76); the major bleeding percentage did not increase with ticagrelor *vs.* clopidogrel (HR: 1.02; 95% CI: 0.82– 1.27) in patients aged ≥ 75 years or patients aged < 75 years (HR: 1.04; 95% CI: 0.94–1.15).[32] As in the prasugrel-ACCOAST study, ticagrelor administration in the ambulance *vs.* in-hospital (in the catheterization laboratory) for STEMI patients did not improve pre-PCI coronary reperfusion in patients with acute STEMI.[33]

Cangrelor, an intravenous P2Y12 receptor antagonist with a rapid onset and maximal platelet inhibition, which is quickly reversible, is currently approved for reducing thrombotic events in patients undergoing PCI who have not been pre-treated with a P2Y12-receptor inhibitor and are not receiving a glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor. It has been tested in several settings in the CHAMPION-PCI trial (*vs.* clopidogrel 600 mg at the beginning of PCI), the CHAMPION-PLATFORM trial (*vs.* clopidogrel 600 mg at the end of PCI), and the CHAMPION-PHOENIX trial (*vs.* clopidogrel 300 or 600 mg at the beginning or end of PCI), thus proving its superiority in periprocedural thrombotic complications at the cost of increased moderate bleeding rates. The superior results were also consistent for patients > 75 years old and patients with diabetes mellitus.[34]

Vorapaxar, an oral competitive protease-activated receptor-1 antagonist that inhibits thrombin-induced platelet aggregation, was investigated in the TRACER trial. It is contraindicated in patients at high risk of bleeding or a history of cerebrovascular disease. Although it is approved for secondary prevention, it results in only a modest benefit. The increase in major bleeding with vorapaxar in older patients makes it a drug to avoid in this segment of the population (26% of patients < 75 years old *vs.* 62% of patients ≥ 75 years).[35]

GPIIb/IIIa-inhibitors block platelet aggregation by inhibiting fibrinogen from binding to a conformationally activated form of the GPIIb/IIIa receptor on two adjacent platelets. Although in the old days we used to administer these drugs before PCI as a second anti-aggregant, in patients

treated with prasugrel or ticagrelor, a GPIIb/IIIa-inhibitor presently has narrow indications, such as bailout situations or a large thrombus burden.[36–39] Doses must be adapted to renal function, and, in the elderly, the drug must be terminated as soon as possible. Trial results are controversial regarding the outcome of elderly patients treated with these molecules.[40–44] Their use should be restricted to the previously described indications, with additional caution in older patients.

3 Anticoagulant treatment (overview of anticoagulant drugs in Table 2)

Unfractionated heparin (UFH), a sulfated mucopolysaccharide that is derived from porcine stomach and bovine lung, is a factor IIa and Xa inhibitor and has been in clinical use for more than 50 years. Approximately 33% of an administered dose of heparin binds to antithrombin, and this fraction is responsible for most of its anticoagulant effect. It reduces the risk of recurrent ischemic events in patients with ACS at the cost of increased bleeding.

Low-weight molecular heparins inhibit factor Xa and have a more predictable dose-effect relationship than UFH. Enoxaparin is the most widely used molecule, and it causes heparin-induced-thrombocytopenia less frequently. Enoxaparin overdosing is almost nonexistent after an intravenous (*i.v.*) bolus [as in PCI; however, it may appear after one or two days of subsequent subcutaneous (*s.c.*) treatment if renal function is altered]. Careful adaptation is required, particularly in the elderly. In a primary PCI setting, several studies and meta-analyses indicate that enoxaparin (0.5 mg/kg *i.v.* followed by *s.c.* treatment) was superior to UFH in primary PCI.[45,46] The ASSENT-3 PLUS trial randomized 1639 STEMI patients to an *i.v.* bolus of 30 mg enoxaparin followed by 1 mg/kg *s.c.* twice daily for seven days max *vs.* a weight-adjusted UFH for 48 h, plus tenecteplase treatment. This regimen increased intracranial hemorrhage rates in the elderly > 75 years old.[47] In a subsequent study, once the enoxaparin dosage was adapted for the elderly subjects (no bolus followed by 0.75 mg/kg *s.c.* twice daily), the net clinical benefit endpoint observed (death, non-fatal re-infarction or non-fatal major bleeding) was 27.3% in UFH patients and 25.8% in enoxaparin patients ≥75 years old [relative risk (RR): 0.94, 95% CI: 0.83–1.07, $P = 0.38$; $P_{interaction} = 0.28$]. Favoring enoxaparin, the absolute risk difference was 1.5% in patients ≥ 75 years old and 1.7% in patients < 75 years old.[48]

Fondaparinux, a synthetic pentasaccharide that prevents thrombin generation by binding non-covalently and reversibly to antithrombin with high affinity, is administered once daily, requires no monitoring or dose adjustment, does not induce heparin-induced thrombocytopenia, and has 100% bioavailability. In the OASIS-5 study, fondaparinux reduced major bleeding by 50% compared with enoxaparin with similar efficacy. Furthermore, in patients receiving a GPIIb/IIIa-inhibitor or thienopyridines, fondaparinux reduced major bleeding and improved the net clinical outcome compared with enoxaparin.[49] In the OASIS-6/STEMI trial, fondaparinux *vs.* control in patients ≥ 69 years old resulted in reduced death or myocardial infarction rates (17.2% *vs.* 19.8%, respectively; HR: 0.87, 95% CI: 0.75–1.01, P for heterogeneity = 0.87), and it reduced severe hemorrhage rates (2.1% *vs.* 2.4%, respectively; HR: 0.86, 95% CI: 0.56–1.33, P for heterogeneity = 0.86).[50]

Bivalirudin, a synthetic 20-amino-acid polypeptide modeled after hirudin, inhibits the thrombin-induced conversion of fibrinogen to fibrin, has renal clearance, and does not bind to plasma proteins; therefore, it has a more predictable effect than UFH does.[51] The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, a prospective, open-label, randomized, multicenter trial, compared several treatment strategies in moderate- or high-risk ACS individuals undergoing an early invasive strategy: heparin plus a GPIIb/IIIa-inhibitor *vs.* bivalirudin plus a GPIIb/IIIa-inhibitor *vs.* bivalirudin alone. As published in the original study, bivalirudin plus a GPIIb/IIIa-inhibitor, compared with heparin plus a GPIIb/IIIa-inhibitor, was associated with noninferior 30-day rates of the composite ischemia end point (7.7% and 7.3%, respectively), major bleeding (5.3% and 5.7%, respectively), and the net clinical outcome end point (11.8% and 11.7%, respectively); bivalirudin alone, compared with heparin plus a glycoprotein IIb/IIIa inhibitor, was associated with a noninferior rate of the composite ischemia end point (7.8% and 7.3%, respectively; $P = 0.32$, RR: 1.08, 95% CI: 0.93–1.24) and significantly reduced rates of major bleeding (3.0% *vs.* 5.7%, respectively; $P < 0.001$, RR: 0.53; 95% CI: 0.43–0.65) and the net clinical outcome end point (10.1% *vs.* 11.7%, respectively; $P = 0.02$, RR: 0.86, 95% CI: 0.77–0.97).[52] A pre-specified analysis of 30-day and one-year outcomes in four age groups [for the overall group and those undergoing PCI showed that for the 2441 patients (17.7%) that were > 75 years old] indicated similar ischemic outcomes in the bivalirudin-alone treatment strategy and significantly lower rates of bleeding compared with patients treated with heparin and a GPIIb/IIIa-inhibitor (overall and in the PCI subset).[53] However, in another important study, the HEAT-PPCI/STEMI, adults scheduled for angiography in the context of a primary PCI were randomized 1: 1 [by age (< 75 years *vs.* ≥ 75 years) and the presence of cardiogenic shock]

Table 2. Anticoagulant treatment in acute coronary syndromes.

Class	UFH	LWMH	LWMH	Direct thrombin inhibitor
Drug	Heparin	Enoxaparin	Fondaparinux	Bivalirudin
Indications	Invasive or conservatory strategy for STEMI/NSTEMI	Invasive or conservatory strategy for STEMI/NSTEMI	Invasive or conservatory strategy for NSTEMI Conservatory strategy for STEMI	Invasive strategy for STEMI/NSTEMI
Pretreatment (before cath lab)	In STEMI: yes In NSTEMI: yes	In STEMI: yes In NSTEMI: yes	In STEMI (if conservative strategy): yes In NSTEMI: yes	In STEMI: no In NSTEMI: no To be started before angiography.
Mechanism	Reversible, indirect, non-selective factor IIa and Xa-inhibitor	Reversible, indirect, semi-selective factor Xa- inhibitor Less protein bound versus UFH	Indirect, selective factor Xa-inhibitor No platelet bound	Reversible, direct IIa- inhibitor No protein bound (more predictable effect than UFH)
Pharmacokinetics				
Excretion	Mainly hepatic	Renal	Renal	Renal
Loading dose effect	Instant (*i.v.*)	3 min (*i.v.*) 3–5 h (*s.c.*)	3–5 h (*s.c.*)	Instant
Duration of loading dose	1-2 h	2 h (*i.v.*)	NA	1 h
Stop before major surgery	4 h	12 h	24 h	1–2 h
Plasma half life	1 h (*i.v.*) load of 100 U/kg)	4 h	17 h	25 min
Dosage				
Dosage in PCI strategy (crossing over to another anticoagulant during PCI is strongly discouraged)	During the PCI: - if previously anticoagulated : adapt according to ACT in the range of 250–350 s (or 200–250 s if GPIIb/IIIa-inhibitor used) - if not previously anticoagulated, load (*i.v.*) of 70–100 IU/kg (max. 5000 IU) or 50–70 IU/kg (if GPIIb/IIIa- inhibitor used), adapt according to ACT in the range of 250–350 s (or 200–250 s if GPIIb/IIIa- inhibitor used) After PCI, adapt UFH dose according to the activated partial thromboplastin time (aPTT); therapeutic window is 50–75 s, corresponding to 1.5–2.5 times the upper limit of normal).	Load: 0.5 mg/kg (*i.v.*) Maintenance: 1 mg/kg (*s.c.*) twice a day If last dose of enoxaparin was administered < 8 h before PCI, no bolus required during PCI; If last dose of enoxaparin was administered > 8 h before PCI, a additional 0.3 mg/kg (*i.v.*) bolus is recommended.	STEMI: no NSTEMI: 2.5 mg daily with additional bolus of UFH	Load: 0.1 mg/kg (*i.v.*) Maintenance: 0.25 mg/kg per hour Undergoing PCI: Load: 0.5 mg/kg (*i.v.*) Maintenance: 1.75 mg/kg per hour, stopped at the end of the procedure

Table 2. Contin.

Class	UFH	LWMH	LWMH	DIRECT THROMBIN INHIBITOR
Dosage in conservative strategy	Same as above	< 75 yrs Load 30 mg (*i.v.*) bolus followed 15 min later by Maintenance: 1 mg/kg (*s.c.*) twice daily until hospital discharge for a maximum of 8 days. The first two doses should not exceed 100 mg. > 75 yrs Load: no Maintenance: first (*s.c.*) dose of 0.75 mg/kg with a maximum of 75 mg for the first two (*s.c.*) doses	STEMI: 2.5 mg load followed by 2.5 mg daily NSTEMI: 2.5 mg daily	Not recommended
Dosage in thrombolysis	Same as above	< 75 yrs Load 30 mg (*i.v.*) bolus followed 15 min later by Maintenance: 1 mg/kg (*s.c.*) twice daily until hospital discharge for a maximum of 8 days. The first two doses should not exceed 100 mg. > 75 yrs Load: no Maintenance: first (*s.c.*) dose of 0.75 mg/kg with a maximum of 75 mg for the first two (*s.c.*) doses.	Not recommended	Not recommended
Dosage in renal failure	Same as above	eGFR 15-29 mL/1.73 m^2 per minute: 1 mg/kg once a day (*s.c.*) eGFR < 15 mL/1.73 m^2 per minute: not recommended	eGFR < 20 mL/1.73 m^2 per minute: not recommended	eGFR 30-60 mL/1.73 m^2 per minute: 1.4 mg/kg per hour eGFR < 29 mL/1.73 m^2 per minute: not recommended
Dosage in elderly (> 75 yrs)	Same as above	Load: no Maintenance: first (*s.c.*) dose of 0.75 mg/kg with a maximum of 75 mg for the first two (*s.c.*) doses. Remember to adapt the dosage to the patient's weight	2.5 mg daily. Preffered anticoagulant.	To be avoided until further results. Remember to adapt the dosage to the patient's weight.
Trials	PRISM PLUS EPIC EPILOG CAPTURE SCATI TAMI HART	SYNERGY ASSENT 3PLUS TRACT-TIMI 25	OASIS-5 OASIS-6	ACUITY ISAR-REACT 4 HEAT-PPCI HORIZONS-AMI
Contraindications and adverse effects				
Contraindications	HIT Active bleeding	HIT Active bleeding	Active bleeding	Active bleeding
Adverse effects	Thrombocytopenia (< 5%) Osteoporosis, cumulative dose Skin necrosis Alopecia Hypoaldosteronism	Thrombocytopenia (< 1%)	None major	Catheter thrombus formation during PCI

ACT: activated clotted time; aPTT - activated prothrombin time; eGFR: glomerular filtration rate; GPIIb/IIIa: glycoprotein IIb/IIIa-inhibitor; HIT: heparin-induced thrombocytopenia; LWMH: low weight molecular heparin; NSTEMI: non-ST-elevated myocardial infarction; PCI: percutaneous coronary interventions; STEMI: ST-elevated myocardial infarction; UFH: unfractioned heparin.

to bivalirudin [bolus 0.75 mg/kg; infusion 1.75 mg/kg per hour, 751 (83%) of 905 patients] or heparin [70 U/kg, 740 (82%) of 907 patients], with a follow-up after 28 days. The primary efficacy outcome (a composite of unplanned target lesion revascularization, re-infarction, cerebrovascular accident and all-cause mortality) occurred in 8.7% *vs.* 5.7% in the bivalirudin *vs.* heparin group, respectively (RR: 1.52, 95% CI: 1.09–2.13, $P = 0.01$). The primary safety outcome was constituted by the incidence of major bleeding (type 3–5 as per the BARC definitions) and occurred in 3.5% *vs.* 3.1% of patients in the bivalirudin *vs.* heparin group, respectively (0.4%; RR: 1.15, 95% CI: 0.70–1.89, $P = 0.59$). The authors concluded that the incidence of major adverse ischemic events was reduced by heparin, with no increase in bleeding complications. For elderly patients, our population of interest in this document, heparin treatment was superior to bivalirudin (RR: 1.09, 95% CI: 0.68–1.77, $P = 0.11$).[54] In our opinion, until further results are collected, bivalirudin should be avoided in elderly patients.

The role of the novel oral anticoagulants in ACS and other settings has been evaluated in other publications and is not of interest to the present discussion, in which we discuss acute medical treatment in ACS.[55,56]

Therefore, fondaparinux has the most favorable efficacy–safety profile, regardless of age. Unless angiography must be urgently performed, it is recommended, regardless of the management strategy. If fondaparinux is contraindicated as a result of severe renal failure (eGFR < 20 mL/min per 1.73 m^2), UFH should be used with a strict dose adjustment and strict activated prothrombin time monitoring.

4 Risk evaluation in the elderly

Assessment of a patient's risk only on clinical experience *vs.* the use of scores has poor outcomes.[57] The value of risk scores as prognostic assessment tools is undisputed; however, the impact of risk score implementation on patient outcomes has not been adequately investigated. In most current practice, PCI indication is based primarily on local practice and angiographic findings rather than the patient's risk status.[58]

4.1. Ischemic risk

The main two risk scores used in ACS are the GRACE risk score (http://www.gracescore.org/WebSite/default.aspx?ReturnUrl=%2f) and the TIMI risk score (http://www.timi.org/index.php?page=calculators). The 2015 NSTEMI guidelines recommend the use of the GRACE score because of: (1) the superiority of the GRACE and PURSUIT scores *vs.* the TIMI score in predicting in-hospital (C-statistics 0.81 *vs.* 0.80 *vs.* 0.68, respectively, $P < 0.001$) and 1-year mortality (C-statistics 0.79 *vs.* 0.77 *vs.* 0.69, respectively, $P < 0.0001$) and (2) the superiority of the GRACE score *vs.* the TIMI score in predicting in-hospital mortality (C-statistics 0.85 *vs.* 0.54, respectively, $P = 0.01$) and 6-month mortality (C-statistics 0.79 *vs.* 0.56, respectively, $P = 0.01$).[55,59,60]

The GRACE 2.0 risk calculator (http://www.gracescore.org/WebSite/default.aspx?ReturnUrl=%2f) provides a direct estimation of mortality while in-hospital and at six months, one year and three years. ST deviation, elevated cardiac biomarkers, age, cardiac arrest at admission, systolic blood pressure, serum creatinine, heart rate, and Killip class at presentation are the variables used in the GRACE 2.0 risk score. An in-hospital GRACE score > 140 indicates that patients should undergo a coronary angiography within 24 h; for a GRACE score between 110 and 139, invasive management should be performed within 72 h. Thus, the GRACE score is primarily used at initial presentation to identify patients most likely to benefit from an invasive strategy. For the high-risk patients with a GRACE score > 140 (one-third of patients), an early invasive strategy lowered the risk of death, myocardial infarction or stroke (13.9% *vs.* 21.0%, respectively; HR: 0.65, 95% CI: 0.48–0.89, $P = 0.006$), whereas the difference was not significant for patients with a GRACE risk score ≤ 140 (7.6% *vs.* 6.7%, respectively; HR: 1.12, 95% CI: 0.81–1.56, $P = 0.48$; $P = 0.01$ for heterogeneity).[61]

GRACE in the elderly. In the GRACE2 study, 24% ($n = 7611$) of patients were > 75 years old.[62] The major bleeding rates were 2%–3% among patients < 65 years old, and for > 6% of patients ≥ 85 years old, the hospital mortality rates, adjusted for baseline risk differences, increased with age (OR: 15.7 in patients ≥ 85 years old *vs.* < 45 years old).[63] In the elderly population, one study aimed to assess the in-hospital and 6-month clinical outcomes of invasive *vs.* conservative strategies in 118 STEMI patients (81 conservative and 37 invasive patients) and 40 NSTEMI patients (25 conservative and 15 invasive patients). The GRACE score demonstrated excellent discrimination for in-hospital mortality.[64] Another validation of the score in the elderly was performed by Vassalli, *et al.*,[65] who evaluated several scores (the GRACE score, the EuroSCORE, the AMIS score, and the SYNTAX score) in 114 patients ≥ 75 years presenting with ACS and treated with PCI within 24 h of hospital admission. The 30-day mortality rate was the primary endpoint. A composite of major adverse cardiovascular events at 30 days and 1-year served as the secondary endpoint. Thirty-day mortality was higher in the upper tertile compared with the aggregate lower/mid tertiles in all scores, including the GRACE score [40% *vs.* 4%, respec-

tively; OR = 17, 95% CI: 4–64, $P < 0.001$, area under the curve (AUC) = 0.80], thus accurately predicting mortality.[65] However, concerns have been raised regarding the overestimation of the mortality risk at 6 months in > 75-year-old patients with ACS using the GRACE score in an observational, multicenter and prospective registry: in 156 patients with a GRACE score > 140, mortality at six months was 3.2%; among dead patients, the mean GRACE index was 147, whereas the mean GRACE index among surviving patients was 163, perhaps overestimating the mortality risk in ACS.[66]

In 2017, the GRACE score should be used to estimate ischemic risk and mortality in the elderly. However, further refinement of the score is needed in this population and may require the inclusion of a frailty assessment as well as additional biomarkers and risk factors to be more precise.

4.2 Bleeding risk

The bleeding risk score is a highly reliable and useful predictor of in-hospital mortality. Current guidelines recommend the use of the CRUSADE and the ACUITY bleeding scores in ACS.[67] The CRUSADE score (http://www.crusadebleedingscore.org) is favored when quantifying bleeding risk in the current NSTEMI guidelines.[68] As published by Subherwal, *et al.*,[69] the CRUSADE bleeding score ranges from 1 to 100 and was created by the assignment of weighted integers that corresponded to the coefficient of each variable. The rate of major bleeding increased by bleeding risk score quintiles: 3.1% for individuals at very low risk (score ≤ 20); 5.5% for individuals at low risk (score 21–30); 8.6% for individuals at moderate risk (score 31–40); 11.9% for individuals at high risk (score 41–50); and 19.5% for individuals at very high risk (score > 50, $P_{trend} < 0.001$).

CRUSADE in the elderly. In one study, 2036 ACS patients (of which 369 were ≥ 75 years old) had their baseline characteristics, laboratory findings, and hemodynamic data collected; the calculation of several bleeding scores for each patient was performed (CRUSADE, Mehran, and ACTION). Elderly patients had a higher incidence of major bleeding events (CRUSADE: 5.1% *vs*. 3.8%, respectively, $P = 0.250$) and an increased bleeding risk (CRUSADE: 42 *vs*. 22, respectively; Mehran: 25 *vs*. 15, respectively; ACTION: 36 *vs*. 28, respectively, $P < 0.001$). The authors concluded that the predictive ability of these three scores was lower in the elderly (AUC, CRUSADE: 0.63 in older patients, 0.81 in young patients, $P = 0.027$; Mehran: 0.67 in older patients, 0.73 in younger patients, $P = 0.340$; ACTION: 0.58 in older patients, 0.75 in younger patients, $P = 0.041$).[70] The finding that the CRUSADE score cannot correctly predict hemorrhagic events in the elderly has also been confirmed by Faustino, *et al.*[71] The HAS-BLED bleeding score also has moderate accuracy when predicting bleeding events in the ACS population.[72] Moreover, it is also of crucial importance that the predictive value of these bleeding risk scores is not determined in patients on oral anticoagulants or patients treated medically and may vary by reducing the UFH or GPIIb/IIIa-inhibitor dose, using the newer anti-aggregant or bivalirudin or radial access. There are no studies on the impact of patient outcomes.

To summarize, for ischemic risk evaluation, the GRACE score is accurate, even in the elderly, and evaluates the risk of death/myocardial infarction in-hospital and at six months, one year and three years; age is one parameter taken into account. For bleeding risk evaluation, the CRUSADE score (which does not take age into account) evaluates in-hospital major bleeds only in NSTEMI patients. These scores cannot be compared head-to-head because they measure different things at different time intervals. They are only useful to (1) decide the timing of PCI in patients at moderate to high ischemic risk (ischemic score) or (2) decide which is the safest medical treatment (conservative strategy or PCI strategy) in patients at a high risk of bleeding.

4.3 Frailty assessment

A frailty assessment has been documented in the Survey of Health, Aging and Retirement in Europe (SHARE) trial, providing a score that evaluates this geriatric syndrome. Frailty impacts mortality, morbidity, disability, hospitalizations, falls and excess healthcare costs from consultations. The overall frailty rate in the general population of > 65 years old is 10.7% (95% CI: 10.5%–10.9%).[73] It poses an enormous challenge for families and other structures of social care and social support. According to this score, frailty is directly correlated with fatigue, low appetite, weakness, slowness and low physical activity. Patients in this trial were divided into three categories: non-frail, pre-frail and frail. Frail females had a SHARE score of < 6, which corresponded to an age-adjusted OR of 6.9 (4.9–9.7) (unadjusted mortality rate of 9.2%). Frail men had a SHARE score < 7, which corresponded to an age-adjusted OR of 10.0 (7.4–13.4) (unadjusted mortality rate of 22.6%).[74] The SHARE-FI75+ frailty score, derived from the initial SHARE score, should be considered a frailty assessment tool rather than a frailty screening tool; it is available at https://sites.google.com/a/tcd.ie/share-frailty-instrument-calculators/translated-calculators.

In one observational study that enrolled patients aged ≥ 75 years old who were hospitalized for myocardial infarction, frailty (assessed by the SHARE score) was an independent predictor of major adverse cardiac events (OR: 7.13;

95% CI: 1.43–35.42). Frail patients composed more than one-third of subjects, had a higher risk profile according to the GRACE/TIMI and CRUSADE scores at admission, had higher rates of comorbidities, were more often women, and were older.[75] The same author demonstrated in another study that frailty in patients > 75 years old admitted for ACS predicted major bleeding at the 30-day follow-up, despite a decreased catheterization rate (69.4% *vs.* 94.1%, respectively, $P < 0.001$) and less frequent use of a P2Y12-inhibitor (66.2% *vs.* 83.6%, respectively, $P = 0.007$) versus the non-frail; major bleeding (decrease of ≥ 3 g/dL of hemoglobin or requiring a transfusion) was associated with increased all-cause mortality at 30 days (18.2% *vs.* 2.5%, $P < 0.001$, for frail *vs*. non-frail, respectively).[76] In the TRILOGY-ACS trial, frailty was independently associated with a composite of cardiovascular death, myocardial infarction, or stroke over a period of 30 months (HR: 1.52, 95% CI: 1.18–1.98, $P = 0.002$, for frail *vs*. not-frail). The authors concluded that frailty contributes to risk prediction and adds to the GRACE score.[77] The need to integrate this parameter into cardiac risk scores is essential in the elderly population.

5 Conclusions

The treatment of ACS in the elderly continues to be controversial, as most ischemic risk factors are also risk factors for bleeding.[78–80] The previously discussed scores should roughly guide our approach and course of action. However, they provide separate tools for the timing of PCI (GRACE score: timing of PCI and management of low ischemic versus moderate to high ischemic risk) and the management of antithrombotic drugs (CRUSADE score: low bleeding *vs.* high bleeding risk). They measure different things (in-hospital, 6 months, 1 year and 3 years death/myocardial infarction rate versus in-hospital bleeding risk at 15 days). In 2017, there are no comprehensive scores that provide a head-to-head evaluation of the ischemic versus bleeding risk, which would provide the tools required to opt for a medical treatment (aggressive or light) or an interventional treatment (example: elderly individual with severe comorbidities but survival > 1 year with a GRACE score of 155, a frailty SHARE score of 7 and a high CRUSADE score… what decision should be made? PCI? medical treatment?).

The recommendations are simple and logical. There is a need for scores in ACS that integrate both ischemic and bleeding scores and should measure similar outcomes: death rate *vs*. death rate and ischemic events versus bleeding events and at the same time intervals (for example, 30 days, 6 months, 1 year, or 3 years). Regarding the elderly, these scores must integrate essential additional parameters for this subgroup, such as frailty, functional capacity, cognitive function and comorbidity, which are not included in the current risk scores and will certainly influence decision-making in clinical practice. Adherence to guidelines regarding reperfusion therapies and heart failure treatment is crucial, particularly in the elderly.[81,82]

Regarding the evaluation of ischemic risk, the evaluation of bleeding risk and overall frailty assessment, we recommend the use of the following in the elderly: (1) for timing of PCI and the evaluation of ischemic risk: good correlation of the GRACE risk score in the elderly (http://www.gracescore.org/WebSite/default.aspx?ReturnUrl=%2f); (2) for PCI: favor invasive *vs.* conservatory strategy (IIaA recommendation), favor radial access *vs.* femoral access; calculate drug dosage according to weight; (3) for evaluation of bleeding risk: low to moderate correlation of the CRUSADE and HAS-BLED bleeding scores in the elderly, use with caution until further score refinements for this age group can be made (http://www.crusadebleedingscore.org); and (4) for frailty assessment: use the SHARE-FI75+ frailty score (https://sites.google.com/a/tcd.ie/share-frailty-instrument-calculators/translated-calculators); favor medical treatment for patients with a high bleeding risk and patients who are frail.[55,83]

Regarding the tailoring of treatment for elderly patients at a low to moderate risk of bleeding (CRUSADE score < 41), we recommend the following: (1) for antiplatelet treatment, the use of lowest-dose aspirin (150–300 mg *p.o.* or 75–150 mg *i.v.* for loading and 75 mg/day maintenance) in association with a P2Y12-inhibitor, such as prasugrel (30 mg load and 5 mg maintenance) or ticagrelor (180 mg load and 90 mg twice daily maintenance) is indicated; pre-treatment with a P2Y12-inhibitor before PCI is controversial in the case of clopidogrel and ticagrelor, and pre-treatment with prasugrel is contraindicated; a GPIIb/IIIa-inhibitor (if there are bail-out/thrombotic complications, calculate drug dosage according to weight and terminate as soon as possible); add a proton pump inhibitor; and avoid the use of non-steroid anti-inflammatory drugs.[55] We are awaiting the results of the ELDERLY-ACS2 trial, which will compare prasugrel 5 mg *vs.* clopidogrel 75 mg in the elderly.[29]

(2) For anticoagulant treatment: the use of fondaparinux 2.5 mg/day (with additional UFH during PCI) is superior to enoxaparin; however, enoxaparin at a low dose may be considered equally (no bolus followed by 0.75 mg/kg *s.c.* twice daily); avoidance of bivalirudin as a result of discordant data until further clarifications; calculate drug dosage according to weight; anticoagulation may be stopped immediately after PCI (if there is a good angiographic result, no thrombus or thrombus-related complications during PCI) as soon

as clinically indicated (symptom-free patient, no arrhythmias, acceptable ejection fraction) or maintained until discharge.

(3) For patients currently on oral anticoagulants: if currently on a vitamin K antagonist, do not administer UFH if INR (international normalized ratio) > 2.5; perform PCI without interruption of the vitamin K antagonist or novel oral anticoagulants; aspirin may be added at its lowest dose; however, pre-treatment with a P2Y12-inhibitor before PCI must be avoided.[55]

Regarding the tailoring of treatment for elderly patients at a high and very high risk of bleeding (CRUSADE score > 41), we recommend the following: (1) for antiplatelet treatment, the use of lowest-dose clopidogrel (300 mg load/75 mg daily), lowest-dose aspirin (150–300 mg oral or 75–150 mg *i.v.* for loading and 75 mg/day maintenance); pre-treatment with a P2Y12-inhibitor before PCI is not recommended (particularly with prasugrel); avoidance of a GPIIb/IIIa-inhibitor (even if there are bailout/thrombotic complications, calculate the drug dosage according to weight and terminate as soon as possible); add a proton pump inhibitor; and avoid the use of non-steroid anti-inflammatory drugs. (2) For anticoagulant treatment: the use of fondaparinux 2.5 mg/day (with additional UFH during PCI) and the avoidance of bivalirudin as a result of discordant data until further clarifications; calculate the drug dosage according to weight; terminate anticoagulation immediately after PCI (if there is a good angiographic result, no thrombus or thrombus-related complications during PCI) or as soon as clinically indicated (symptom-free patient, no arrhythmias, and acceptable ejection fraction).[55] (3) For patients currently on oral anticoagulants: if currently on a vitamin K antagonist, do not administer UFH if INR > 2; perform PCI without interruption of the vitamin K antagonist or novel oral anticoagulant; aspirin may be added at its lowest dose; however, pre-treatment with a P2Y12-inhibitor before PCI must be avoided.[55]

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