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SPECIAL ARTICLE

Acute, periprocedural and longterm antithrombotic therapy in older adults

2022 Update by the ESC Working Group on Thrombosis

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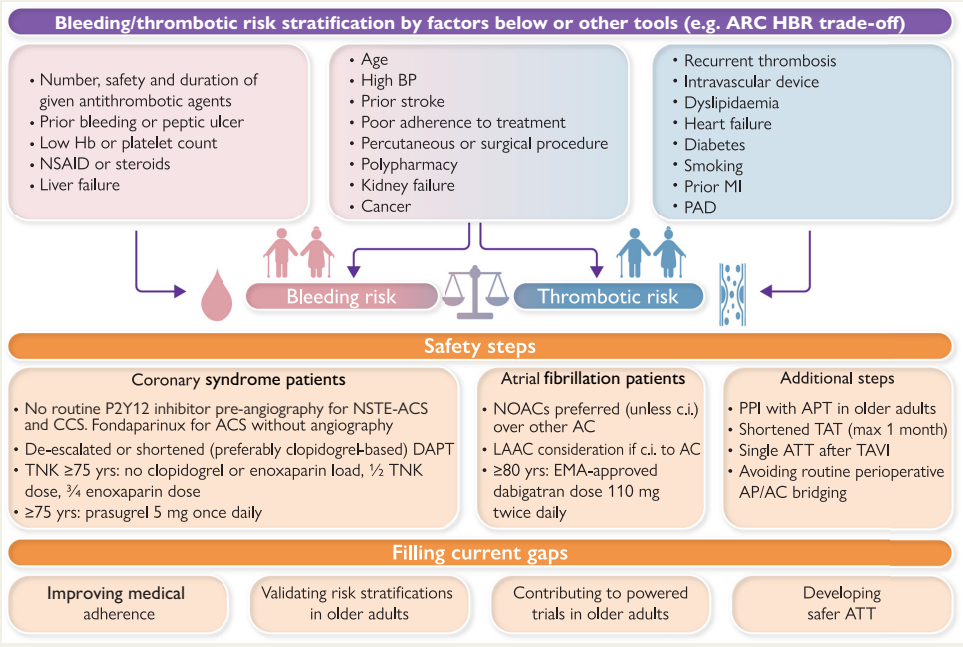
Graphical Abstract



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Antithrombotic therapy in older adults: challenges and selected consensus points. AC, anticoagulant; ACS, acute coronary syndrome; AF, atrial fibrillation; AP, antiplatelet; APT, antiplatelet therapy; ARC HBR, Academic Research Consortium High Bleeding Risk; ATT, antithrombotic therapy; BP, blood pressure; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; EMA, European Medicines Agency; Hb, haemoglobin; LAAC, left atrial appendage closure; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; NSTE, non-ST-elevation; NSAID, non-steroidal anti-inflammatory drugs; PAD, peripheral artery disease; PPI, proton pump inhibitor; TAT, triple antithrombotic therapy; TAVI, transcatheter aortic valve implantation; TNK, tenecteplase.

Abstract

The first international guidance on antithrombotic therapy in the elderly came from the European Society of Cardiology Working Group on Thrombosis in 2015. This same group has updated its previous report on antiplatelet and anticoagulant drugs for older patients with acute or chronic coronary syndromes, atrial fibrillation, or undergoing surgery or procedures typical of the elderly (transcatheter aortic valve implantation and left atrial appendage closure). The aim is to provide a succinct but comprehensive tool for readers to understand the bases of antithrombotic therapy in older patients, despite the complexities of comorbidities, comedications and uncertain ischaemic- vs. bleeding-risk balance. Fourteen updated consensus statements integrate recent trial data and other evidence, with a focus on high bleeding risk. Guideline recommendations, when present, are highlighted, as well as gaps in evidence. Key consensus points include efforts to improve medical adherence through deprescribing and polypill use; adoption of universal risk definitions for bleeding, myocardial infarction, stroke and cause-specific death; multiple bleeding-avoidance strategies, ranging from gastroprotection with aspirin use to selection of antithrombotic-drug composition, dosing and duration tailored to multiple variables (setting, history, overall risk, age, weight, renal function, comedications, procedures) that need special consideration when managing older adults.

Keywords Elderly • Antiplatelet • Anticoagulant • Coronary syndromes • Atrial fibrillation • Surgery • TAVI • LAAC

Introduction

Declining birth rates and prevention or postponement of major causes of death are causing older segments of the population to grow faster than any other.[1–3] In 2020, ~100 million Europeans were ≥65 years and 25 million >80, with the latter estimated to reach 75 million in 2100.[1] Atherothrombotic cardiovascular diseases (CVDs) remain the leading cause of death among adults worldwide,[4] and multimorbidity (defined as ≥2 chronic diseases) affects 55%–98% of people >65 years.[3] Regardless of sex, the incidence of CVD and bleeding increase continuously beyond 50–55 years.[5–8] Degenerative valvular heart disease[9] and conditions requiring percutaneous interventions or surgery also prevail in older adults.[10] Given the temporal trends in age-related morbidities and new evidence from antithrombotic trials, the European Society of Cardiology (ESC) Working Group on Thrombosis has updated its 2015 scientific document on antithrombotic therapy in the elderly.[11] Paired authors searched major literature databases on CVD, atrial fibrillation (AF), and interventions up to April 2022; venous thromboembolism, non-cardioembolic stroke, and peripheral artery disease (PAD) were deliberately omitted. While age ≥75 years is widely accepted to define 'elderly', a rigid inferior cut-off was intentionally avoided given: (i) different thresholds across studies; (ii) generally healthier contemporary older adults compared to past age-matched individuals; (iii) linear rather than stepwise increases in bleeding and thrombotic risks.[5,6,12] The key consensus points of this age-focused document are provided in *Table 1*.

Improving antithrombotic-drug adherence in older adults

Adherence is considered the extent to which patients take medications as prescribed,[13] including duration (persistence).[14] Measures include pill count, pharmacy records, electronic monitoring, and proportion of days covered.[13] Antithrombotic-drug adherence is crucial for optimal efficacy and safety[13] and a cut-off >80% of days covered (generally used to define good adherence) may be too low a threshold in relation to preventable cardiovascular outcomes.[13–16] In older adults with CVD, poor cognition/health literacy, low socioeconomic status, race/ethnicity, as well as side-effects, costs, complexity, and duration of treatment are associated with reduced adherence.[13,15,17] On the other hand, among elderly patients with AF-related stroke, caregiver administration, functional dependency, and previous antithrombotic therapy are associated with increased adherence to oral anticoagulation (OAC).[16] Deprescribing, defined as the supervised reduction of inappropriate polypharmacy, and use of polypills may increase adherence by ~30%[18–22] and lead to improved efficacy, as suggested by an individual-patient-data meta-analysis of randomized controlled trials (RCTs).[23] The latter (mean ± standard deviation age 63 ± 7 years) showed that a fixed-dose combination polypill containing at least two blood pressure lowering agents plus a statin (with or without aspirin) reduced adverse cardiovascular events over a median follow-up of 5 years compared to usual care [hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.53–0.73, $P < 0.0001$] without significantly increasing major bleeding.[23] The benefits were consistent across age (<60, 60–66, and >66 years).[23]

Bleeding in older adults: risk assessment, prevention, and general management

Tools to estimate the benefits and risks of antithrombotic therapies and to avoid undertreatment driven by perceived bleeding risk alone[11] include the CHA_2DS_2-VASc, HAS-BLED, BleeMACS, ABC, DAPT, and PRECISE-DAPT thrombotic and/or bleeding risk scores.[7,24–27] All incorporate age and require some calculation or specific biomarker measure. For patients undergoing percutaneous coronary intervention (PCI), the Academic Research Consortium (ARC) has quantified high bleeding risk (HBR) as a 1-year major bleeding rate ≥4%; it has also defined HBR qualitatively by the presence of one major or two minor simple routine features (*Table 2*).[28,29] While age ≥75 represents a minor bleeding risk feature, studies have reported major bleeding events ≥4% at 1 year in this age group,[29] likely owing to concomitant renal impairment, anaemia

or non-steroidal anti-inflammatory drug (NSAID) use that enhance bleeding risk further (*Table 2*).[28] The guideline-recommended PRECISE-DAPT score, estimating major and minor bleeding events in patients undergoing PCI and integrating age as a continuous variable, prompts short rather than prolonged dual antiplatelet therapy (DAPT) for scores ≥25.[30–32] Unlike PRECISE-DAPT, the ARC-HBR score includes surgery, cancer, and liver and brain diseases.[28] Lack of head-to-head validation of PRECISE-DAPT and ARC-HBR scores in older adults prevents the recommendation of one over the other.[33] Since age is one of many criteria (several of which affected by age), both scores likely trend towards a ceiling effect ≥75 years.[34] Of note, few bleeding scores to date have been developed specifically in the elderly.[35] For AF patients, HAS-BLED remains the guideline-recommended bleeding risk score.[24]

Although antithrombotic therapy in elderly CVD patients (including those at HBR) yields net clinical benefit given the increased thrombotic risk with age,[11,24,36–39] systematic HBR assessment is recommended by multiple ESC guidelines to drive safer strategies.[24,30–32,40,41] Indeed, recent studies indicate that older age may predict bleeding more than thrombotic events and that the trade-off of bleeding vs. thrombotic events can be estimated through a balanced integration of different risk predictors (*Graphical Abstract*).[26,42,43] Common preventive measures against intra- and extracranial bleeding include optimal blood pressure control, gastroprotection with proton pump inhibitors (PPIs), appropriate criteria for revascularisation,[31,44] avoidance of routine $P2Y_{12}$ inhibitor before coronary angiography for chronic or non-ST-elevation acute coronary syndrome (NSTE-ACS) patients,[31,44] use of radial arterial access,[32,45] stent selection,[31,44] modulation of DAPT composition/duration,[31,44] and tailoring drug regimens to age, body weight,[36] renal function, prior stroke, and bleeding risk category, according to European Medicines Agency (EMA) recommendations (*Table 3*). A PPI along with antithrombotic therapy is indicated for concomitant steroid or NSAID administration, for combined antiplatelet and OAC therapy, for DAPT,[30] and for gastrointestinal bleeding risk factors (e.g. prior peptic ulcer, prior gastrointestinal bleed, advanced age) (see below).[30,31,46,47] With clopidogrel, guidelines favour pantoprazole or rabeprazole PPIs over omeprazole or esomeprazole, as the latter may have clinically relevant interactions.[30] When bleeding occurs, reducing drug number or adjusting the dose (when appropriate), along with other secondary prevention measures (i.e. gastroprotection, *Helicobacter pylori* eradication) usually enables continuation or resumption of antithrombotic therapy after bleeding.[45]

Oral antithrombotic-drug strategies in older adults

Primary and secondary cardiovascular disease prevention

Antiplatelet monotherapy

For secondary CVD prevention, the benefit vs. risk profile of longterm low-dose aspirin vs. no antiplatelet agent is favourable in older as in younger age.[48,49] Gastrointestinal mucosal injury affects >90% of patients on aspirin or clopidogrel monotherapy.[50] In patients ≥75 years, the longterm risk of disabling or fatal bleeding with antiplatelet agents is higher than in younger age,[8] half of the major bleeds are upper gastrointestinal, and the estimated numbers needed to treat for routine PPI use to prevent a major upper gastrointestinal bleed are particularly low (from 338 < 65 years to 25 > 85 years).[8] We therefore support PPI comedication with antiplatelet therapy in elderly patients. Contemporary secondary prevention trials—accepting their limitations—indicate that major bleeding rates with low-dose aspirin monotherapy are generally similar to those with ticagrelor (including in the elderly),[51–53] and higher compared to unguided clopidogrel monotherapy (see section 'Safer antiplatelet regimens').[54]

For primary CVD prevention, among adults ≥70 years without evidence of atherosclerotic CVD and with an estimated risk of major adverse cardiovascular events <1% per year, current data indicate an unfavourable benefit–risk balance of longterm low-dose aspirin that does not justify its initiation on a routine basis.[55–58] Elderly subjects at higher CVD risk and without HBR may benefit from aspirin in primary prevention, as suggested by a recent individual-patient-data meta-analysis.[23]

Dual antiplatelet therapy in older adults with acute coronary syndrome and/or undergoing percutaneous coronary intervention

Regardless of age, current guidelines recommend a $P2Y_{12}$ inhibitor in combination with aspirin (i.e. DAPT) after ACS and/or coronary stenting, for variable durations according to patient bleeding and ischaemic risks.[30–32,40,41] The choice of $P2Y_{12}$ inhibitor is driven by efficacy, safety, and tolerability data, by clinical presentation (discussed below), and by management strategy, particularly in comorbid, comedicated elderly patients. Dyspnoea is a common side-effect of ticagrelor that may lead to treatment discontinuation,[59] whereas wide interindividual variability in platelet inhibition has been shown for clopidogrel.[60] Pharmacokinetic and pharmacodynamic data indicate that older age affects the metabolism and maximum antiplatelet effect of prasugrel and ticagrelor to a lesser extent than of clopidogrel, although with undetermined clinical implications.[61–64] For chronic coronary syndromes (CCSs), in older as in younger patients undergoing PCI, clopidogrel remains the current ESC guideline-recommended $P2Y_{12}$ inhibitor of choice.[30,32]

On the background of aspirin, compared to clopidogrel 75 mg daily, superior efficacy was shown in RCTs for prasugrel 10 mg daily in PCI-treated ACS patients over a median of 14.5 months and for ticagrelor 90 mg twice daily in ACS patients with or without PCI over a median of 9 months, although the bleeding risk was enhanced.[65,66] A subgroup analysis of 2878 ACS patients ≥75 years indicated that ticagrelor 90 mg twice daily can favourably be used vs. clopidogrel in this group as in younger patients.[67] On the other hand, among 1002 randomized patients all ≥70 years with NSTE-ACS, clopidogrel compared to ticagrelor led to less bleeding without increasing the composite of all-cause death, MI, stroke, or bleeding over 12 months.[68] SWEDEHEART registry data of 14 005 ACS patients ≥80 years suggest that ticagrelor use may be associated with 17% and 48% higher relative risks of death and bleeding, and with 20% and 22% relative risk reductions of MI and stroke, respectively, compared to clopidogrel-treated patients.[69] The EMA and ESC guidelines[31] recommend prasugrel dose reduction from 10 to 5 mg daily for patients ≥75 years, based on pharmacokinetic and clinical data.[70–72] At these doses, prasugrel showed comparable efficacy and safety to clopidogrel in randomized ACS patients ≥75 years managed either invasively ($n = 1443$)[70] or medically ($n = 2083$),[71] and superior efficacy compared to ticagrelor in a recent ACS trial of 4018 patients. In the latter, however, only 982 patients were ≥75 years.[73] A recent meta-analysis of 12 randomized trials excluding open-label ones [mean 66 (range 62–80) years] found that ticagrelor and prasugrel, compared to clopidogrel, were associated with increased major bleeding risk, and that ticagrelor but not prasugrel was associated with decreased mortality.[74] *Figure 1* summarizes antithrombotic treatment decisions in patients ≥75 undergoing PCI, according to HBR, indication for OAC, and clinical setting.

Current ESC guidelines recommend up to 12-month aspirin plus a $P2Y_{12}$ inhibitor-based DAPT after ACS, with or without PCI, extendable beyond 12 months for selected post-MI patients at high ischaemic

Table 1 Key consensus points on antithrombotic therapy in older adults

Clinical scenario and strategy	Key point
Medical adherence in older adults with CVD or AF	We encourage pharmacological and nonpharmacological strategies to improve medical adherence in older adults, such as deprescribing, polypill use, reminder tools, and educational interventions.
Bleeding and thrombotic risk assessment in older adults with CVD or AF	We propose a systematic estimate of bleeding vs. thrombotic risk trade-off in older adults through the integration of different risk predictors. Among CVD patients, current evidence suggests that older age predicts bleeding more than thrombotic events.
Aspirin in older adults for primary and secondary CVD prevention	Longterm low-dose aspirin, especially with PPI comedication, has favourable benefit/risk effects in older adults with overt CVD and SR. Among adults ≥70 years without overt CVD and with an estimated risk of major CVD events <1% per year, current data do not support the initiation of low-dose aspirin.
$P2Y_{12}$ inhibitors in older ACS and/or PCI patients	Efficacy-to-safety balance should drive $P2Y_{12}$-inhibitor choice. For PCI-treated ACS patients ≥75 years, the EMA-approved prasugrel dose is 5 mg daily. Clopidogrel-based DAPT is recommended by guidelines for PCI-treated CCS patients, regardless of age and bleeding risk, and for HBR patients after ACS. Clopidogrel or ticagrelor or aspirin monotherapy after at least 1-month DAPT are emerging strategies after ACS or PCI. We generally discourage DAPT beyond 12 months for age ≥75.
Oral anticoagulation for older adults with AF	Advanced age should not be a reason for underuse of VKA or NOACs. In the absence of severe CKD, mechanical valves or mitral stenosis, VKA is generally second choice to NOACs. Dabigatran is preferable to VKA (unless contraindicated). For age ≥80, the EMA-approved dose is 110 mg twice daily. FXa inhibitors have favourable efficacy/safety effects in elderly AF patients and are preferable to VKA (unless contraindicated).
Antiplatelet strategies to reduce bleeding risk in older ACS and/or PCI patients	Reasonable options to reduce bleeding risk in older ACS and/or PCI patients include refraining from routine $P2Y_{12}$-inhibitor administration before angiography in NSTE-ACS and CCS patients, de-escalating from ticagrelor or prasugrel to clopidogrel or lower dose prasugrel, or monotherapy with aspirin, clopidogrel or ticagrelor after 1–3 months of DAPT.
Dual pathway inhibition for secondary CVD prevention in older patients	For older patients with CCS and/or PAD who are at high risk of ischaemic events but not at HBR, DPI with rivaroxaban 2.5 mg twice daily plus aspirin is reasonable. Current data support DPI in elderly patients with PAD undergoing peripheral artery revascularization.
Antithrombotic therapy for older AF patients with ACS or undergoing PCI	For older AF patients with ACS and/or undergoing PCI, DAT (NOAC + clopidogrel) is advisable after a short period of TAT (1–2 weeks). TAT can be prolonged to 1 month if high-ischaemic risk and/or anatomical/procedural characteristics outweigh the bleeding risk. For older AF patients with CCS, (N)OAC monotherapy is advisable.
Periprocedural cangrelor and GPIs for older, high-ischaemic risk patients	For older $P2Y_{12}$ inhibitor-naïve patients undergoing PCI, intravenous cangrelor is a reasonable option. Intravenous GPI is generally limited to emergency bailout or preoperative bridging in high-ischaemic risk patients.
Heparins, fondaparinux and bivalirudin for older ACS patients	For elderly STEMI or NSTE-ACS patients, UFH or enoxaparin is generally administered when immediate PCI is planned. For conservatively-managed older NSTE-ACS patients, fondaparinux is preferable in the absence of severe kidney disease. Routine preference of bivalirudin over UFH in the elderly is not advised.
Fibrinolysis for older STEMI patients	For older STEMI patients unable to undergo primary PCI within 120 min from diagnosis, fibrinolysis is advised after careful consideration of contraindications and adjusting the doses of tenecteplase and adjunctive therapy for age ≥75.
Antithrombotic therapy for TAVI patients	Single antiplatelet therapy is preferable to DAPT, and OAC monotherapy preferable to combined OAC and clopidogrel (for those requiring longterm OAC). Based on guidelines and trials, NOACs may be preferred over VKA, although individual factors (e.g. GI bleeding risk) should guide OAC choice. OACs are contraindicated in patients undergoing TAVI who do not have a clear indication for OAC.
Antithrombotic therapy for AF patients at very HBR undergoing percutaneous LAAC	For AF patients at very HBR undergoing percutaneous LAAC, short-term (e.g. 45 days) OAC or 1–6-month DAPT (aspirin plus clopidogrel) followed by single antiplatelet or no antithrombotic therapy are reasonable options.
Perioperative antithrombotic therapy	Perioperative antithrombotic therapy is generally similar in younger and older patients undergoing cardiac and noncardiac surgery.

ACS, acute coronary syndrome; AF, atrial fibrillation; CCS, chronic coronary syndrome; CKD, chronic kidney disease; CVD, atherothrombotic cardiovascular disease; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; DPI, dual pathway inhibition; EMA, European Medicines Agency; F, factor; GI, gastrointestinal; GPI, glycoprotein IIb/IIIa inhibitor; HBR, high bleeding risk; LAAC, left atrial appendage closure; NOAC, non-vitamin K antagonist oral anticoagulant; NSTE, non-ST-elevation; OAC, oral anticoagulant; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; SR, sinus rhythm; STEMI, ST-elevation myocardial infarction; TAT, triple antithrombotic therapy; TAVI, transcatheter aortic valve implantation; UFH, unfractionated heparin; VKA, vitamin K antagonist.

Table 2 Academic Research Consortium high bleeding risk defined by at least 1 major or 2 minor features

1 MAJOR	OR	2 MINOR FEATURES
Anticipated longterm oral anticoagulation[a]		Age ≥75 years
Estimated GFR <30 mL/min		Estimated GFR 30–59 mL/min
Haemoglobin <11 g/dL		Haemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleed requiring hospitalization or transfusion within 6 months or recurrent bleed		Spontaneous bleed requiring hospitalization or transfusion within 12 months not meeting major feature
Platelet count $<100 \times 10^9$ per litre		Chronic use of NSAIDs or steroids
Bleeding diathesis or cirrhosis with portal hypertension		Any ischaemic stroke not meeting major feature
Active malignancy[b] (excluding non-melanoma skin cancer) within 12 months		
Previous spontaneous ICH (at any time)		
Previous traumatic ICH within the past 12 months		
Presence of a bAVM		
Moderate or severe ischaemic stroke[c] within 6 months		
Non-deferrable major surgery on DAPT		
Recent major surgery or trauma within 30 days		

ARC, Academic Research Consortium; bAVM, brain arterio-venous malformation; DAPT, dual antiplatelet therapy; GFR, glomerular filtration rate; ICH, intracranial haemorrhage; NSAID, non-steroidal anti-inflammatory drug.
[a]This excludes dual pathway inhibition doses.
[b]Active malignancy defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).
[c]National Institutes of Health Stroke Scale score ≥5. Modified from [28].

and low bleeding risk.[30,77–80] In the elderly, however, subgroup analyses of RCTs show attenuated net benefit of DAPT beyond 12 months (combining low-dose aspirin with either ticagrelor 60 mg twice daily, clopidogrel 75 mg daily, or prasugrel 5 mg daily).[11,77–80] Our consensus is that extended DAPT in older patients should be carefully evaluated, after taking into account bleeding and ischaemic risk factors, or be avoided, particularly in patients with prior non-cardioembolic transient ischaemic attack or stroke;[81] rather, reducing DAPT duration should be considered in line with recent trial data (see below).[31,75]

Antithrombotic therapies for stroke prevention in atrial fibrillation

Stroke prevention by vitamin K antagonists

The BAFTA trial randomized 973 patients ≥75 years (mean 82 ± 4) with AF and no mechanical heart valve or severe mitral stenosis to vitamin K antagonist (VKA) or low-dose aspirin for an average of 2.7 years.[82] The relative risk of stroke/systemic embolism strongly favoured OAC over aspirin (0.48, 95% CI 0.28–0.80, $P = 0.003$), without significantly different rates of intracranial haemorrhage (ICH, 8 vs. 6).[82] Given limited randomized data on VKAs in older adults, what follows includes observational studies. In an AF cohort ≥90 years, warfarin was associated with apparent net clinical benefit compared to antiplatelet or no antithrombotic therapy, but higher risk of ICH compared to non-VKA oral anticoagulants (NOACs).[83] In a meta-analysis of 26 randomized and observational studies of AF patients ≥65 years, warfarin appeared superior to aspirin or no antithrombotic therapy for stroke prevention, with a nonsignificant increase in risk of major bleeding.[84] In meta-analyses of randomized or adjusted observational studies of AF patients ≥75 years, warfarin appeared less effective than NOACs in preventing thromboembolism, with higher rates of ICH, higher or comparable major bleeding, and lower or comparable gastrointestinal bleeding.[85–87] Multiple drug–drug and drug–food interactions need to be considered when using warfarin or other VKAs in comorbid, comedicated elderly patients.[88]

The direct thrombin inhibitor dabigatran

The RE-LY trial randomized 18 113 AF patients to warfarin or dabigatran (110 or 150 mg twice daily); 40% ($n = 7245$) were >74 years.[89,90] Regardless of age, the incidence of stroke/systemic embolism was similar with dabigatran 110 mg and significantly lower with dabigatran 150 mg compared to warfarin; ICH rates were lower with both dabigatran doses, whereas gastrointestinal bleeds were more common with dabigatran 150 mg.[89,90] Dabigatran 110 or 150 mg twice daily compared to warfarin resulted in significantly lower overall incidences of major extracranial bleeds <75 years, but in a similar risk with 110 mg and a trend toward higher risk with 150 mg ≥75 years.[90] Age is an independent predictor of increased dabigatran plasma concentrations.[91] The EMA states that 110 mg twice daily should be considered for AF patients of 75–79 years and is required for those ≥80.[92] Dabigatran is contraindicated with creatinine clearance (CrCl) <30 mL/min and with concomitant dronedarone, cyclosporine, and certain antimycotic or antiretroviral drugs.[92,93] The dabigatran-specific intravenous antidote, idarucizumab, is effective and well tolerated regardless of age.[94,95]

Table 3 European Medicines Agency-approved antithrombotic regimens for older adults

Drug and dose	Indication	Age, weight or renal adjusted dosing	EMA-approved considerations
Oral antiplatelet drugs			
Aspirin 75–100 mg od (150–300 mg load)	Acute and chronic coronary syndromes	None	
Clopidogrel 75 mg od (600 mg load)	Acute and chronic coronary syndromes	No loading dose with fibrinolysis for age ≥75	
Ticagrelor 90 mg bid (180 mg load)	ACS	None	Avoid with prior ICH
Ticagrelor 60 mg bid	Post-MI	None	Avoid with prior ICH
Prasugrel 10 mg od (60 mg load)	PCI in ACS	5 mg od for age ≥75 or weight <60 kg	Avoid with prior stroke (including ICH) or TIA
IV antiplatelet drugs			
Cangrelor 30 μg/kg bolus + immediate 4 μg/kg/min infusion for ≥2 h. Oral $P2Y_{12}$ inhibitor load during (for ticagrelor or prasugrel) or at end (for clopidogrel) of infusion	$P2Y_{12}$-inhibitor-naïve patients with ACS undergoing PCI	None	No overall differences in safety or efficacy <75 vs. ≥75 years
Eptifibatide 180 μg/kg bolus + 2 μg/kg/min infusion	No-reflow or thrombotic complication during PCI. Preoperative bridge in high-ischaemic risk patients	Avoid if CrCl <30 mL/min. 50% infusion dose if CrCl 30–49 mL/min	Avoid with prior ICH, ischaemic stroke within 30 days, fibrinolysis, or <100 000 platelets/mm[a]
Tirofiban 25 μg/kg bolus + 0.15 μg/kg/min infusion	No-reflow or thrombotic complication during PCI. Preoperative bridge in high-ischaemic risk patients	50% dose if CrCl <30 mL/min	Avoid with prior ICH, ischaemic stroke within 30 days, fibrinolysis, or <100.000 platelets/mm[a]
Oral anticoagulants			
Apixaban 5 mg bid	AF	Avoid if CrCl <15 mL/min. 2.5 mg bid if ≥2 of: • age ≥80 • weight ≤60 kg • serum Cr ≥1.5 mg/dL or CrCl 15–29 mL/min as single criterion	Monitor renal function
Dabigatran 150 or 110 mg bid	AF	Avoid if CrCl <30 mL/min. 110 mg bid for age ≥80. Consider 110 mg bid for age 75–79	Monitor renal function
Edoxaban 60 mg od	AF	Avoid if CrCl <15 mL/min. 30 mg od if CrCl 15–50 mL/min, weight <60 kg or concomitant cyclosporine, dronedarone, erythromycin or ketoconazole	Monitor renal function
Rivaroxaban 20 mg od	AF	Avoid if CrCl <15 mL/min. 15 mg od if CrCl 15–49 mL/min	Monitor renal function
Rivaroxaban 2.5 mg bid with aspirin 100 mg od	CAD and/or PAD patients[b]	Avoid if CrCl <15 mL/min	Evaluate ischaemic vs. bleeding risks carefully
Vitamin K antagonists	AF, mechanical heart valve	With age, lower doses required to reach target INR	More frequent INR monitoring with age
Parenteral anticoagulants			
UFH IV dose adjusted to aPTT	ACS, PCI	None	Can be used with CrCl <15 mL/min

Continued

Table 3 *Continued*

Drug and dose	Indication	Age, weight or renal adjusted dosing	EMA-approved considerations
LMWH dose and route vary by compound and indication	ACS, PCI	Avoid enoxaparin if CrCl <15 mL/min. Half-dose enoxaparin for CrCl 15–30 mL/min. For age ≥75, no initial IV 30 mg enoxaparin bolus. For age ≥75, consider enoxaparin 0.75 instead of 1 mg/kg bid therapeutic SC dose	
Fondaparinux 2.5 mg SC od	ACS	Avoid if CrCl <20 mL/min	Generally limited to conservatively managed NSTE-ACS patients without severe kidney disease
Bivalirudin 0.75 mg/kg IV bolus (further 0.3 mg/kg bolus if ACT after 5 min <225 s) + 1.75-mg/kg/h infusion for up to 4 h	PCI in ACS	Avoid if CrCl <30 mL/min. Reduce infusion to 1.4 mg/kg/h if CrCl 30–59 mL/min	Avoid with active bleeding, malignant hypertension, subacute bacterial endocarditis
Fibrinolytic agents			
Tenecteplase single IV bolus of 30, 35, 40, 45, or 50 mg (for weight <60, 60–70, 70–80, 80–90, or >90 kg, respectively)	STEMI if primary PCI unavailable <120 min of diagnosis	Half-dose tenecteplase if age ≥75	Avoid with prior ICH or ischaemic stroke/TIA within 6 months[a]

ACS, acute coronary syndrome; ACT, activated clotting time; AF, atrial fibrillation; bid, twice daily; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; EMA, European Medicines Agency; ICH, intracranial haemorrhage; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NSTE, non-ST-elevation; od, once daily; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SC, subcutaneous; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack; UFH, unfractionated heparin.
[a]Further contraindications: recent trauma or surgery, active bleed, bleeding diathesis, acute pericarditis, suspected aortic dissection, intracranial/intraspinal neoplasm, arterio-venous malformation or aneurysm, severe uncontrolled hypertension, INR ≥2, severe liver disease, hypersensitivity.
[b]Reimbursement criteria vary by national health system.

Direct factor (F) Xa inhibitors: rivaroxaban, apixaban, and edoxaban

In the ROCKET AF,[96] ARISTOTLE[97], and ENGAGE AF-TIMI 48 trials,[98] 20 136 AF patients ≥75 years were randomized to rivaroxaban 20 mg daily, apixaban 5 mg twice daily, or edoxaban 60 or 30 mg daily vs. warfarin (44%, 31%, and 40% of the overall populations).[96–99] Subgroup analyses indicated superiority or noninferiority of each FXa inhibitor vs. warfarin for stroke prevention regardless of age.[99–102] Rates of ICH were significantly lower with all FXa inhibitors vs. warfarin.[96–98] An increased rate of gastrointestinal bleeding vs. warfarin was seen with rivaroxaban and higher-dose edoxaban, but not with apixaban or the lower (unlicensed) edoxaban dose.[96–98]

Among 984 Japanese AF patients ≥80 years (mean 87 ± 4) who were not candidates for standard-dose anticoagulation (on the basis of bleeding history, comedications, kidney disease, or very low body weight), edoxaban 15 mg once daily (currently not licensed) was superior to placebo over a median of 1.3 years in preventing stroke/systemic embolism (absolute annual reduction 4.4%, $P < 0.001$) without significantly increasing major bleeding (absolute annual increase 1.5%, $P = 0.09$).[103] Whether these findings are generalizable to other ethnicities is unknown.

Compared to warfarin, less bleeding in older vs. younger patients has been reported with apixaban and edoxaban.[99,100,104] In the absence of randomized head-to-head comparisons, however, whether one NOAC is safer than another is uncertain. The EMA contraindicates FXa inhibitors with CrCl <15 mL/min and with some antimycotic and antiretroviral drugs.[93] The apixaban dose should be halved when CrCl is 15–29 mL/min (irrespective of age) and (for those with CrCl ≥30 mL/min) in the presence of ≥2 factors among age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL;[93] edoxaban and rivaroxaban doses need no adjustment for age, but do for CrCl ≤50 or ≤49 mL/min, respectively.[93] The intravenous antidote against FXa inhibitors, andexanet alfa, was well tolerated and effective regardless of age.[105] Intravenous ciraparantag also provides rapid, safe, and sustained reversal of FXa inhibition in 50- to 75-year-old adults.[106]

Emerging antithrombotic strategies

Safer antiplatelet regimens

Most elderly patients are at HBR (see above). To limit DAPT-related bleeding, ESC guidelines recommend refraining from routine $P2Y_{12}$-inhibitor administration before coronary angiography for NSTE-ACS patients (in case diagnoses requiring coronary or aortic surgery are made),[31] shortening DAPT duration to 6, 3, or even 1 month followed by antiplatelet monotherapy, and de-escalating $P2Y_{12}$ inhibitors among ACS patients.[30,40,51,68,75,76,107–115] For HBR patients, ESC guidelines specifically indicate that DAPT can be shortened to 1 month after elective PCI and to 3 months (or even 1 month in very HBR) after ACS, followed by aspirin or clopidogrel monotherapy.[30,31,40,41] Ticagrelor monotherapy is allowed after 3–6 months DAPT depending on bleeding and ischaemic risk balance.[31,76,116] The above ESC recommendations are driven by recent RCTs generally reporting noninferior or superior safety and similar efficacy after 1–3 months of DAPT, followed by ticagrelor, clopidogrel,

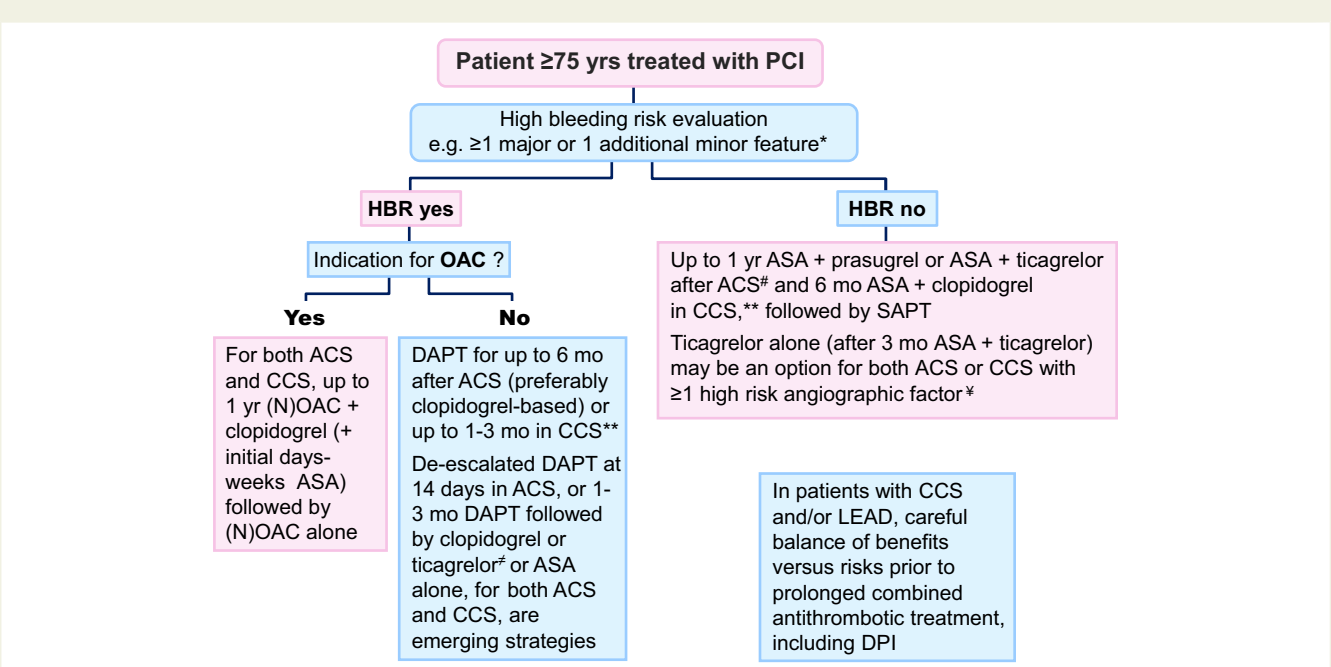

Figure 1 Antithrombotic therapy in older adults undergoing percutaneous coronary intervention, according to bleeding risk, indication for oral anticoagulation, and clinical setting. *High bleeding risk according to *Table 2*. #For contraindications and dosing see *Table 3*. ≠MASTER DAPT trial results.[75] ¥At least one high-risk angiographic factor: multivessel coronary disease, total stent >30 mm, thrombotic lesion, bifurcation requiring at least two stents, left main stem (≥50%) or proximal left anterior descending artery (≥70%) lesion, calcified target lesion(s) requiring atherectomy.[76] **In older as in younger chronic coronary syndrome patients undergoing percutaneous coronary intervention, clopidogrel + aspirin is the treatment of choice. ACS, acute coronary syndrome; ASA, aspirin; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; DPI, dual pathway inhibition; HBR, high bleeding risk; LEAD, lower extremity artery disease; mo, month; (*N*)OAC, (non-vitamin K antagonist) oral anticoagulant; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

or aspirin monotherapy, compared to longer DAPT regimens among ACS or CCS patients (*Table 4*).[51,76,107,111–113,117] The very recent STOPDAPT-2 ACS trial of 4136 East Asian ACS patients, mostly not at HBR (mean 67 ± 12 years) and receiving drug-eluting stents, has challenged previous results, since noninferiority for the 1 year combined safety and ischaemic outcome of 1-month DAPT followed by clopidogrel monotherapy vs. 12-month DAPT was not met (*Table 4*).[114] In contrast, the very recent MASTER DAPT trial of 4579 patients with ACS or CCS (mean 76 ± 9 years) all at HBR (with age ≥75 as a HBR criterion), receiving a thin-strut drug-eluting stent and 1-month DAPT, showed that aspirin or $P2Y_{12}$-inhibitor monotherapy compared to DAPT prolongation for 3 months or longer was noninferior for combined adverse events and major cardiocerebral events at 11 months, with less major or clinically relevant nonmajor bleeding.[75] The results of both very recent trials were consistent across age strata (*Table 4*). Of note, most of the above RCTs included mixed populations (ACS and CCS), were underpowered for efficacy, and had open-label assessor-masked designs.

Among ACS patients, trials of de-escalation from ticagrelor or prasugrel to clopidogrel or low-dose prasugrel have shown noninferior or superior safety compared to no de-escalation (generally regardless of age), although underpowered for efficacy (*Table 4*).[68,108–110,115,119,120] Although recent evidence indicates improved outcomes with guided compared to non-guided choices,[31,120,121] platelet function or genetic testing to guide $P2Y_{12}$-inhibitor escalation/de-escalation has not yet become routine practice.

The HOST-EXAM trial randomized 5438 East Asian CCS patients (mean 63 ± 11 years), who had uneventfully completed 6–18 months of DAPT after PCI, to clopidogrel 75 mg daily or aspirin 100 mg daily for 2 years.[54] Clopidogrel showed superior combined efficacy and safety unrelated to age (≥ or <65 years), with no significant difference in all-cause mortality [51 deaths (1.9%) with clopidogrel vs. 36 (1.3%) with aspirin (HR 1.43, 95% CI 0.93–2.19, $P = 0.101$)] and similar trends for both cardiac and noncardiac deaths.[54] Whether these findings are generalizable to other geographical settings is pending.

For elderly patients, we support avoiding routine $P2Y_{12}$-inhibitor administration before coronary angiography in the setting of NSTE-ACS and CCS. For HBR patients post-ACS or PCI, we generally support clopidogrel-based DAPT or, alternatively, antiplatelet monotherapy with either clopidogrel, ticagrelor or aspirin, after at least 1 month of DAPT (*Table 1*, *Figure 1*).

Dual pathway inhibition

Dual pathway inhibition (DPI) refers to concomitant inhibition of platelets and coagulation. The three-armed COMPASS trial randomized 18 278 patients with CCS and/or PAD (mean 68 ± 8 years) to either DPI with aspirin 100 mg daily plus rivaroxaban 2.5 mg twice daily, rivaroxaban 5 mg twice daily alone, or aspirin alone; DPI compared to aspirin alone reduced the composite of cardiovascular death, MI or stroke over a mean follow-up of 23 months, while increasing modified International Society on Thrombosis and Haemostasis-defined major bleeding, but not ICH or fatal bleeding. There was no significant interaction between age and treatment effects, although the benefit-to-risk ratio of DPI was numerically less favourable among the 21% ≥75 years compared to the younger strata,[122] suggesting the need for carefully individualized decisions (*Table 1*, *Figure 1*). Of note, patients <65 years required additional

Table 4 Recent trials of abbreviated or de-escalated dual antiplatelet therapy after percutaneous coronary intervention, with analyses by age

Trial name (design)	No. of pts	Pt type	% ACS	Mean age (% older)	Experimental arm (Exp.)	Control arm (Ctrl)	Follow-up	Safety events Exp. vs. Ctrl	Ischaemic events Exp. vs. Ctrl	Combined adverse events Exp. vs. Ctrl	Analyses by age
Abbreviated DAPT followed by P2Y12 inhibitor or aspirin monotherapy											
GLOBAL LEADERS[51,107] (open)	15 968	PCI	47	65 y (16% >75)	1 mo Tic + Asa → 23 mo Tic 90 bid	12 mo DAPT →12 mo Asa	24 mo	BARC bleed 3 or 5: 2.0% vs. 2.1% (RR 0.97, 95% CI 0.78–1.20; $P=0.77$)	Death, new Q-wave MI: 3.8% vs. 4.4% (RR 0.87, 95% CI 0.75–1.01; $P=0.073$)	Death, stroke, MI, BARC bleed 3 or 5: 7.72% vs. 8.17% (RR 0.95, 95% CI 0.85–1.06; $P=0.34$)	Int-P between age ≤ or >75 and treatment strategy = 0.06 for safety and 0.23 for ischaemic events[51,107]
TWILIGHT[76] (double-blind)	7119	PCI	71	65 y (52% ≥65)	12 mo Tic 90 bid + placebo (after 3 mo uneventful Tic-based DAPT)	12 mo Tic + Asa (after 3 mo uneventful Tic-based DAPT)	12 mo	BARC bleed 2, 3 or 5: 4.0% vs. 7.1% (HR 0.56, 95% CI 0.45–0.68; $P<0.001$)	Death, MI, stroke: 3.9% vs. 3.9% (HR 0.99, 95% CI 0.78–1.25; P for NI < 0.001)		No significant interaction between age < or ≥65 (or ARC HBR status) and treatment strategy for safety and ischaemic events[76,116]
SMART-CHOICE[111] (open)	2993	PCI	58	65 y (51% ≥65)	3 mo DAPT → 9 mo Clo	12 mo DAPT	12 mo	BARC bleed 2–5: 2.0% vs. 3.4% (HR 0.58; 95% CI, 0.36–0.92; $P=0.02$)	MACCE: 2.9% vs. 2.5% (difference 0.4%, 1-sided 95% CI −∞ to 1.3; P for NI = 0.007)	MACCE plus BARC bleed 2–5: 4.5% vs. 5.6% (HR 0.81, 95% CI 0.58–1.12; $P=0.2$)	Int-P between age < or ≥65 and treatment strategy = 0.10 for safety and = 0.90 for ischaemic events[111]
STOPDAPT-2[112] (open)	3045	PCI	38	69 y (32% ≥75)	1 mo DAPT → 11 mo Clo	12 mo DAPT	12 mo	BARC bleed 3 or 5: 0.54% vs. 1.81% (HR 0.30, 95% CI 0.13–0.65; $P=0.003$)	CV death, MI, definite ST, ischaemic or haemorrhagic stroke: 1.96% vs. 2.51% (HR 0.79, 95% CI 0.49–1.29; $P=0.34$)	CV death, MI, definite ST, ischaemic or haemorrhagic stroke, TIMI major or minor bleed: 2.4% vs. 3.7% (HR 0.64; 95% CI 0.42–0.98; $P=0.04$)	Int-P between age < or ≥75 and treatment strategy = 0.20 for combined adverse events[112]
TICO (open)[113]	3056	PCI	100	61 y (39% ≥65)	3 mo Tic + Asa → 9 mo Tic 90 bid	12 mo Tic + Asa	12 mo	TIMI major bleed: 1.7% vs. 3.0% (HR 0.56, 95% CI 0.34–0.91; $P=0.02$)	MACCE: 2.3% vs. 3.4% (HR 0.69, 95% CI −0.45 to 1.06; $P=0.09$)	Death, MI, stroke, definite or probable ST, TV revasc, TIMI major bleed: 3.9% vs. 5.9% (HR 0.66, 95% CI 0.48–0.92; $P=0.01$)	Int-P between age ≥64 and benefit of Exp. vs. Ctrl = 0.036 for combined adverse events[118]
MASTER DAPT[75] (open)	4579	HBR PCI (33% AF)	37	76 y (69% ≥75)	11 mo P2Y12i or Asa after 1 mo uneventful DAPT	≥2 mo DAPT after 1 mo uneventful DAPT	11 mo	BARC 2, 3, 5: 6.5% vs. 9.4% ($P<0.001$)	Death, stroke, MI: 6.1% vs. 5.9% (P for NI = 0.001)	Death, stroke, MI, BARC bleed 3 or 5: 7.5% vs. 7.7% (P for NI < 0.001)	No significant interaction between age < or ≥75 and treatment strategy for safety, ischaemic or combined adverse events[75]
STOPDAPT-2 ACS[114] (open)	4136	PCI	100	67 y	1 mo DAPT → 11 mo Clo	12 mo DAPT	12 mo	Any TIMI bleed: 0.54% vs. 1.17% ($P<0.05$)	CV death, MI, definite ST, stroke: 2.76% vs. 1.86% ($P>0.05$)	CV death, MI, definite ST, stroke, TIMI bleed: 3.2% vs. 2.8% (P for NI = 0.06)	Int-P between age ≤ or >75 and treatment strategy = 0.47 for safety, 0.75 for ischaemic, and 0.46 for combined adverse events[114]
De-escalation from newer $P2Y_{12}$ inhibitor to clopidogrel or low-dose prasugrel											
TROPICAL-ACS[108] (open)	2610	PCI	100	59 y (14% >78)	PFT-Clo + Asa or Pra + Asa at 2 weeks → 12 mo	12 mo Pra + Asa	12 mo	BARC bleed ≥2: 5% vs. 6% (HR 0.82,	CV death, MI, stroke: 3% vs. 3% (HR 0.77, 95% CI	CV death, MI, stroke, BARC bleed ≥2: 7% vs. 9% (HR	Int-P between age as continuous variable and

Continued

Table 4 *Continued*

Trial name (design)	No. of pts	Pt type	% ACS	Mean age (% older)	Experimental arm (Exp.)	Control arm (Ctrl)	Follow-up	Safety events Exp. vs. Ctrl	Ischaemic events Exp. vs. Ctrl	Combined adverse events Exp. vs. Ctrl	Analyses by age
								95% CI 0.59–1.13; $P = 0.23$)	0.48–1.21; P for NI = 0.0115)	0.81, 95% CI 0.62–1.06; P for NI = 0.0004; $P = 0.12$)	treatment strategy = 0.027 (safety and ischaemic combined endpoint benefit of Exp. vs. Ctrl ≤70 y)[119]
POPular-Genetics[120] (open)	2488	PCI	100	62 y (15% >75)	Clo in CYP 2C19*2 or *3 non carriers + Asa → 12 mo	12 mo Tic (91%)/ Pra + Asa	12 mo	PLATO major or minor bleed: 9.8% vs. 12.5% (HR 0.78, 95% CI 0.61–0.99; $P = 0.04$)	CV death, MI, definite ST, stroke: 2.7% vs. 3.3% (HR 0.83, 95% CI 0.53–1.31)	Any death, MI, definite ST, stroke, PLATO major bleed: 5.1% vs. 5.9% (P for NI < 0.001)	Int-P between age < or ≥75 and treatment strategy = 0.88 for safety and 0.72 for combined adverse events[120]
POPular-AGE[68] (open)	1002	PCI	100	77 y (100% ≥70, 35% ≥80)	Clo + Asa at 26 days → 12 mo	12 mo Tic (95%)/ Pra + Asa	12 mo	PLATO major or minor bleed: 17.6% vs. 23.1% (HR 0.74, 95% CI 0.56–0.97; $P = 0.03$)	Death, MI, stroke: 12.8% vs. 12.5% (HR 1.02, 95% CI 0.72–1.45; $P = 0.91$)	Death, MI, stroke, PLATO major or minor bleed: 27.3% vs. 30.7%; P for NI = 0.06)	All patients ≥70 y
TOPIC[109] (open)	646	PCI	100	60 y	1 mo Tic (44%)/Pra + Asa →11 mo Clo + Asa	12 mo Tic (41%)/ Pra + Asa	12 mo	BARC bleed ≥2: 4.0% vs. 14.9% (HR 0.30, 95% CI 0.18–0.50; $P <$ 0.01)	Any ischaemic event: 9.3% vs. 11.5% (HR 0.80, 95% CI 0.50–1.29; $P = 0.36$)	CV death, urgent revasc, stroke, BARC bleed ≥2: 13.4% vs. 26.3% (HR 0.48, 95% CI 0.34–0.68; $P < 0.01$)	Not available
HOST-REDUCE-POLYTECH-ACS[110] (open)	2338	PCI	100	59 y (0.1% ≥75)	1 mo Pra 10 + Asa → 11 mo Pra 5 + Asa	12 mo Pra 10 + Asa	12 mo	BARC bleed ≥ 2: 2.9% vs. 5.9% (HR 0.48, 95% CI 0.32–0.73; $P =$ 0.0007)	CV death, MI, ST, ischaemic stroke: 1.4% vs. 1.8% (HR 0.76, 95% CI 0.40–1.45; $P = 0.40$)	Death, MI, ST, ischaemia-driven revasc, stroke, BARC bleed ≥2: 7.2% vs. 10.1% (HR 0.70, 95% CI 0.52–0.92; $P <$ 0.012)	Int-P between age < or ≥65 and treatment strategy = 0.68 for combined adverse events[110]
TALOS-AMI[115] (open)	2697	PCI	100	60 y (27% ≥75)	1 mo Tic + Asa → 11 mo Clo + Asa	12 mo Tic + Asa	12 mo	BARC ≥ 2: 3.0% vs. 5.6% (HR 0.52, 95% CI 0.35–0.77; $P = 0.0012$)	CV death, MI, stroke: 2.1% vs. 3.1% ($P = 0.15$)	CV death, MI, stroke, BARC bleed ≥2: 4.6% vs. 8.2% (P for NI < 0.001, $P = 0.0001$)	Int-P between age < or ≥75 and treatment strategy = 0.98 for combined adverse events[115]

ACS, acute coronary syndrome; ARC, Academic Research Consortium; Asa, aspirin once daily; BARC, Bleeding Academic Research Consortium; bid, twice daily; CI, confidence interval; Clo, clopidogrel once daily; Ctr, control; CV, cardiovascular; DAPT, dual antiplatelet therapy; Exp., experimental; HBR, high bleeding risk; HR, hazard ratio; i, inhibitor; int-P, P for interaction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; mo, month; NI, noninferiority; PCI, percutaneous coronary intervention; PFT, platelet function testing; PLATO, Study of Platelet Inhibition and Patient Outcomes; Pra, prasugrel; Pt, patient; revasc, revascularisation; RR, rate ratio; ST, stent thrombosis; Tic, ticagrelor; TIMI, Thrombolysis in Myocardial Infarction; TV, target vessel; vs., versus; y, years; 5, 5 mg; 10, 10 mg; 60, 60 mg; 90, 90 mg.

ischaemic risk factors for enrolment.[122] Models estimating individual lifetime benefit and bleeding risk may help select older patients for adjunctive low-dose rivaroxaban.[123,124] In the VOYAGER-PAD trial of 6564 patients with recent lower extremity revascularization [median (interquartile range) 67(61–73) years], a rivaroxaban 2.5 mg twice daily plus aspirin strategy vs. aspirin alone reduced the rate of major cardiovascular events and limb ischaemia over a median of 2.3 years, without significantly increasing TIMI major bleeding.[125] The 20% of patients ≥75 years showed a particularly favourable benefit-to-risk ratio.[125]

Managing atrial fibrillation patients with concomitant coronary artery disease

Meta-analyses of six randomized trials of AF patients with concomitant ACS or undergoing PCI (mean age 70) indicate that triple antithrombotic therapy (TAT with either VKA or NOAC plus aspirin and clopidogrel) causes increased major or clinically relevant bleeding compared to double antithrombotic therapy (DAT with OAC and clopidogrel), but reduces stent thrombosis and MI events.[39,126,127] Each trial was individually underpowered for ischaemic events or for robust information on the use of ticagrelor or prasugrel. For these patients, ESC guidelines recommend an initial 1-week course of TAT, whereas meta-analyses support TAT duration up to 1 month.[24,39,128–130] Early DAT may be preferred in patients not undergoing PCI, given the lack of stent thrombosis risk.[24,31,39,128,131,132] Non-vitamin K antagonist oral anticoagulants are preferable to VKAs given their superior safety profile.[24,31,39,131–133]

Among 2236 Japanese AF patients with CCS and prior PCI (mean 74 ± 8 years), rivaroxaban monotherapy showed lower rates of ischaemic events, major bleeds, haemorrhagic strokes, and all-cause death vs. rivaroxaban plus an antiplatelet agent at a 23 month follow-up, regardless of age < or ≥75.[134] Among 696 AF patients with CCS (out of 2000 planned, mean 75 ± 8 years), OAC monotherapy (VKA or NOAC) vs. OAC plus an antiplatelet agent showed similar rates of combined ischaemic and major bleeding events after 2.5 years, although the primary noninferiority endpoint for ischaemic events was not met.[135]

For elderly AF-ACS/AF-PCI patients, in line with current guidelines[31,32] and with the MASTER DAPT trial of HBR patients (36% taking OAC; mean 73 ± 9 years),[75] our consensus supports DAT with a NOAC (at the recommended dose for stroke prevention) and an antiplatelet agent (preferably clopidogrel) after a short period of TAT (1–2 weeks from the acute event). Triple antithrombotic therapy can be prolonged if high-ischaemic risk or other anatomical/procedural characteristics outweigh the bleeding risk, followed by DAT up to 1 year and (N)OAC monotherapy thereafter (*Table 1*, *Figure 1*).

Parenteral antithrombotic drugs in older adults

Cangrelor and glycoprotein IIb/IIIa inhibitors

Intravenous cangrelor, a rapid, reversible, direct $P2Y_{12}$ inhibitor, has been compared to oral clopidogrel, started either before or at PCI.[136–138] In both younger and older (≥75) patients, the largest trial[138] showed significantly reduced rates of ischaemic events at 48 h with cangrelor vs. a 600 or 300 mg loading dose of clopidogrel, without increasing severe bleeding.[139] Transfer of trial data to contemporary practice, however, may be limited by: (i) 25% of patients assigned to clopidogrel receiving a 300 mg loading dose; (ii) 37% of patients receiving clopidogrel during or after, rather than before, PCI, and (iii) unreported intervals between receipt of study drug and PCI for the 63% of patients receiving clopidogrel before the procedure.[138]

Most trials evaluating the intravenous glycoprotein IIb/IIIa inhibitors (GPIs) abciximab, eptifibatide and tirofiban in ACS or PCI patients preceded the era of early DAPT and newer $P2Y_{12}$-inhibitor loading.[140,141] Today, given unproven benefits on ischaemic events when added to DAPT, and a clear increase in bleeding, ESC guidelines recommend intravenous GPIs only for no-reflow or 'bailout' thrombotic complications during PCI, or as a bridge before surgery in patients at very high-ischaemic risk.[30,31,40,41,140] In patients ≥70 years, particularly those at HBR, the net benefit is even more uncertain, supporting restricted use.

Heparins, the pentasaccharide fondaparinux, and bivalirudin

In the young as in the elderly, parenteral unfractionated heparin (UFH) or the low-molecular-weight heparin (LMWH) enoxaparin is recommended by ESC guidelines for patients undergoing PCI in the setting of ST-elevation MI (STEMI), NSTE-ACS, or CCS.[31,32,41,142,143] In NSTE-ACS patients (mean 67 ± 11 years), fondaparinux halved major bleeds and reduced 6-month mortality compared to enoxaparin, with similar ischaemic event rates.[144,145] The findings were consistent for ≥65 and <65 years.[144] Additional UFH (60–85 U/kg), however, needs to be given to invasively managed NSTE-ACS patients on fondaparinux to prevent catheter thrombus formation.[146] As per EMA, enoxaparin's therapeutic dose should be halved when CrCl is <30 mL/min and is contraindicated when <15 mL/min,[147] whereas fondaparinux is contraindicated with CrCl <20 mL/min.[148] Reduced bleeding rates with peri-PCI intravenous bivalirudin vs. UFH or LMWH with or without GPIs have not been borne out in meta-analyses comparing bivalirudin to UFH alone.[149] Moreover, stent thrombosis rates are increased with bivalirudin vs. UFH, with or without GPIs.[149] In the subgroup of 1592 MI patients ≥75 years enrolled in the VALIDATE-SWEDEHEART trial, however, no difference in 180-day ischaemic and bleeding outcomes were reported for bivalirudin vs. heparin monotherapy.[150] Prolonged high-dose infusion of bivalirudin (1.75 mg/kg/h for 3–4 h) may attenuate the stent thrombosis risk.[151] Bivalirudin and fondaparinux may be used in the setting of heparin-induced thrombocytopenia.[140]

Fibrinolysis

Irrespective of age, intravenous fibrinolysis vs. placebo improves survival when administered to STEMI patients within 12 h of symptom onset, despite an early hazard of ICH.[152] If delay to treatment is similar, primary PCI, however, is a better reperfusion strategy than fibrinolysis in terms of early and longterm survival,[153] a superiority that has been confirmed in older patients.[154] Intravenous fibrinolysis followed by rescue PCI as needed is still an alternative to primary PCI if the latter is unavailable within 120 min from STEMI diagnosis.[41,155] Advanced age, lower body weight, female sex, previous cerebrovascular disease, and hypertension on admission are significant predictors of ICH during fibrinolysis.[156] For patients ≥75 years receiving tenecteplase, ESC guidelines recommend halving the dose of the fibrinolytic agent, avoiding the loading dose of clopidogrel and enoxaparin, and reducing the enoxaparin maintenance dose by 25% to reduce the excess risk of ICH.[41,155,157]

Periprocedural antithrombotic regimens in older adults

Invasive vs. conservative management of older non-ST-elevation acute coronary syndrome patients

For biomarker-positive NSTE-ACS patients, an invasive strategy is superior to a conservative one to prevent ischaemic events, with the greatest benefit in high-risk groups, including those ≥70 and ≥80 years.[158–160] Regardless of the acute setting, age ≥80 tends to favour coronary revascularization by PCI over bypass surgery.[40,161–163] The role of conservative vs. invasive management in elderly NSTE-ACS patients is being further investigated in the SENIOR-RITA trial (ClinicalTrials.gov NCT03052036). For periprocedural antithrombotic regimens, see above.

Medical management of NSTE-ACS is not uncommon among the elderly (67% >80 years vs. 33% <70 years in the GRACE registry)[164] owing to unsuitable coronary anatomy, contraindications to angiography/PCI or, less often, lack of obstructive coronary stenoses.[71,128] DAPT as per current ESC guidelines is warranted in medically managed older NSTE-ACS patients in association with short-term parenteral anticoagulation (fondaparinux or enoxaparin).[31,71] However, the relative net benefit of different types and durations of antithrombotic regimens in the elderly in this setting is still undefined.[165]

Transcatheter aortic valve implantation

For patients ≥75 years with severe aortic stenosis, transcatheter aortic valve implantation (TAVI) is a lifesaving procedure, preferable to surgery when performed transfemorally.[166,167] Patients undergoing TAVI are on average aged ≥80;[168–172] 40–50% have concomitant AF, chronic kidney disease[168,169] or CCS.[170] Bleeding complications are common (up to three times more frequent than ischaemic stroke) and impact survival.[173] To predict bleeding events at 30 days, a risk score and web calculator (comprising low haemoglobin, small femoral artery diameter, low CrCl, DAPT, OAC, and—optionally—low serum iron) has been developed using artificial intelligence and validated in over 10 000 TAVI patients.[35]

Defining optimal antithrombotic therapy for TAVI has been challenging, with early recommendations based on small randomized studies[174,175] or experience from PCI. Intraprocedural anticoagulation with UFH, achieving an activated clotting time (ACT) of 200–300 s, is commonly used in trials, registries and routine practice. Whether ACT-guided antagonization with protamine sulfate improves safety is pending.[176] After the procedure, guidelines[166,167] recommend either (i) antiplatelet monotherapy (usually aspirin)[173,177] lifelong or (ii) OAC lifelong (for patients with other indications for anticoagulation).[178] Aspirin vs. aspirin plus clopidogrel resulted in fewer major bleeds, fewer combined bleeding and ischaemic events, and noninferiority for ischaemic events in the POPular-TAVI trial cohort A (665 patients, mean 80 years).[177] In patients with a clear indication for OAC, OAC monotherapy caused fewer total bleeds than OAC plus clopidogrel, without a significant increase in ischaemic events (313 patients, cohort B, mean 81 years).[178]

Registry data of NOACs vs. VKA in TAVI patients who need OAC have yielded contrasting findings in terms of survival, safety, and ischaemic events.[179–181] Four randomized trials have since tested NOACs vs. usual care in TAVI patients.[172,182–184] The GALILEO trial of 1644 sinus rhythm TAVI patients (mean 81 years) was interrupted after 17 months for higher risks of death, thromboembolism and bleeding in the rivaroxaban 10 mg daily plus aspirin arm vs. clopidogrel plus aspirin arm.[182] The ENVISAGE-AF trial of 1426 AF TAVI patients (mean 82 years) demonstrated noninferior net clinical benefit but increased gastrointestinal bleeds with edoxaban 60/30 mg daily vs. VKA at a median of 1.5 years.[183] The ATLANTIS trial of 1500 TAVI patients (mean 82 years) with or without a clear indication for OAC demonstrated similar 1-year major bleeding rates with apixaban 5 mg twice daily vs. usual care, regardless of OAC indication.[184,185] Apixaban vs. antiplatelet therapy markedly reduced valve thrombosis at 3–6 months, but with a signal for increased noncardiovascular death.[184,185] The recent ADAPT-TAVR trial randomized 229 patients without a clear indication for OAC (mean 80 years) to edoxaban 60/30 mg daily or DAPT.[172] At 6 months, subclinical valve thromboses were numerically lower, but the number of patients with new brain lesions numerically higher in the NOAC group.[172] In line with guideline indications, the above data suggest that a NOAC may be considered over VKA but not over antiplatelet therapy post-TAVI.[166,182–184] Because superiority over VKA therapy of apixaban[184] or edoxaban[183] was not shown, with increased major (gastrointestinal) bleeds for the latter,[183] careful evaluation when choosing OAC type after TAVI is encouraged. Non-vitamin K antagonist oral anticoagulants are favoured by guidelines over VKAs for long-term stroke prevention in older AF patients, except in those with clinically significant mitral stenosis or mechanical heart valves.[166,183,184]

Left atrial appendage closure (LAAC)

The main indication for left atrial appendage closure (LAAC) is stroke prevention in AF HBR patients in whom lifelong OAC is contraindicated.[186,187] Preliminary data indicate that percutaneous LAAC in the elderly is effective and reasonably safe.[187–190] However, individualized weighing of potential benefits against risks (stroke, bleeding, procedure-/device-related adverse events) is advised. A review of 10 154 patients undergoing catheter-based LAAC with imaging during follow-up (mean 73 ± 9 years) reported device-related thrombosis in 3.8% (≤90 days in 42%, at 90–365 days in 57%, and >1 year in 1%).[191] While further trials are ongoing (NCT03463317 Closure-AF and NCT03642509 Occlusion-AF), a recent meta-analysis of 1516 randomized patients followed for 3 years (mean 73 ± 8 years) supports percutaneous LAAC vs. OAC (warfarin or apixaban) in terms of safety (significantly fewer ICH and nonprocedural major bleeds) and a favourable signal on cardiovascular mortality.[192] Procedural complications, however, were not accounted for in the safety profile.[192] Conceptual support for LAAC comes from the recent LAAOS III trial that randomized 4770 anticoagulated AF patients with CHA_2DS_2-VASc ≥2 undergoing cardiac surgery (mean 71 ± 8 years) to either surgical LAAC or none: at 3.8 years, ischaemic stroke/systemic embolism occurred in 4.8% vs. 7.0% ($P = 0.001$, number needed to treat = 37), without significant differences in rates of bleeding, heart failure or death. The effect was greatest among those ≥72 years.[193]

Periprocedural anticoagulation during percutaneous LAAC is mandatory. After the procedure, antithrombotic therapy usually includes short-term anticoagulation (e.g. 45 days) when the Watchman device is used, or DAPT with aspirin and clopidogrel over 1–6 months (until complete endothelialization of the thrombogenic foreign surface), followed by single antiplatelet or no antithrombotic therapy.[194]

Cardiac and noncardiac surgery

Surgery is common in the elderly.[10] Perioperative aspirin vs. no aspirin in noncardiac surgery (NCS) results in similar mortality, reduced risk of

venous thromboembolism, but increased major bleeding in patients with coronary artery disease, PAD, prior stroke, or multiple CVD risk factors, including older age.[195–200] In one RCT, the subgroup with prior PCI (mean 68 years) benefited from perioperative aspirin.[201] In patients at HBR or refusing blood transfusions, ESC guidelines recommend preoperative discontinuation of aspirin or clopidogrel for 5 days, of ticagrelor for 3–5 days, and of prasugrel for 7 days.[30,199,200] In patients on DAPT following recent PCI, postponement of NCS is advised.[30,199,200] When NCS is undeferrable, temporary discontinuation of oral $P2Y_{12}$ inhibition, with or without bridging with a rapid, reversible intravenous GPI (tirofiban, eptifibatide) or cangrelor (*Table 3*) is reasonable, depending on the patient- and surgery-related bleeding and ischaemic risk.[30,138,139,199]

For patients on warfarin, ESC guidelines recommend preoperative reduction of the international normalized ratio (INR) <1.5.[199,202] If the thromboembolic risk is very high (e.g. AF with CHA_2DS_2-VASc ≥4, mechanical heart valve, recent mitral valve repair, previous venous thromboembolism, or thrombophilia), it is reasonable to stop warfarin 3–5 days preoperatively, with daily INR monitoring and bridging with therapeutic LMWH doses, adapted to renal function (*Table 3*).[36,199,202] Measuring anti-FXa activity with a target of 0.5–1.0 U/mL at peak, or diluted thrombin time or ecarin clotting time to assess residual anti-Xa or anti-IIa levels, is advisable when managing mechanical heart valves or severe obesity.[36,199,202] In patients taking NOACs, LMWH bridging is not advocated given NOACs' reversible pharmacodynamics and short half-life.[93,203] For moderate or HBR surgery, discontinuation of dabigatran is advised 24–48 or 48–96 h before, respectively, and of FXa inhibitors 24 or 48 h before, depending on renal function.[93,203] For low bleeding risk surgery (e.g. cataract or minor skin or dental surgery), no OAC interruption is needed according to ESC guidelines, with INR levels in patients on warfarin maintained in the lower therapeutic range.[200] The above applies to all age strata.[30,199,200,203]

Future challenges and needs

Efforts to improve drug adherence and to ascertain the effectiveness of deprescribing in older adults are encouraged. Application of new and existing scores weighing bleeding vs. thrombotic risks to old and very old cohorts, with the help of artificial intelligence and in silico modelling, is encouraged.[204] As risks increase continuously with age, quantitative rather than qualitative scores are likely preferable.[34] By the same token, to determine critical age ranges in clinical trials, analyses by continuous rather than arbitrary cut-off values are encouraged. Randomized controlled trials powered to assess the efficacy and safety of single or combined antithrombotic regimens in old and very old adults with acute or chronic CVD and/or AF are needed. Novel antithrombotic therapies with potentially favourable safety profiles (e.g. FXI/XIa inhibitors) should be tested particularly in the elderly.

Conclusions

Net benefits of antithrombotic therapies and interventions remain largely favourable in elderly patients with CVD or AF, achieving greater absolute effects compared to younger patients.[11,37–39,48,49,82,99,100,104,125,139,166,167] Choosing optimal regimens for older adults, although challenging, is possible on the basis of individual characteristics (*Tables 2 and 3*) and the multiple treatment options summarized in this document (*Table 1*). We encourage deprescribing, polypill use, systematic bleeding risk assessment and bleeding-avoidance measures (e.g. PPI, abbreviated or de-escalated DAPT), particularly among HBR patients (*Graphical Abstract*, *Tables 1–4*, *Figure 1*). While robust evidence to refine antithrombotic therapy in older adults is increasing, powered dedicated studies are still needed.

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Data availability

No original data were generated or analysed for this manuscript.

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