



# Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis

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## Introduction

Contemporary medicine is shifting towards person rather than disease-oriented care.<sup>1</sup> With increasing life expectancy and the ageing of baby boomers, the proportion over 60 years is growing faster than the overall population, with worldwide estimates reaching 2 billion by 2050 (<http://www.un.org/esa/population/publications/worldageing19502050>).<sup>2</sup> In parallel, acute coronary syndromes (ACS) and atrial fibrillation (AF)—the most frequent indications for dual platelet inhibition or anticoagulation—occur mostly in older patients.<sup>2–6</sup> There is general agreement that people  $\geq 75$  years can be defined ‘elderly’; however, cutoffs as low as 65 years have been applied to important clinical datasets and risk scores.<sup>3,7–10</sup> Moreover, ageing is a continuous process and life-span expansion is deflating (<http://www.nber.org/papers/w18407>). For these reasons, a threshold to define ‘elderly’ has been intentionally avoided in this document. Of note, over one third of patients admitted with acute myocardial infarction (MI) and two thirds dying from MI are over 75 years, but  $< 7\%$  of patients in ACS trials are reported  $\geq 75$  years.<sup>11</sup> Older patients have multi-organ changes, increased

risk of both bleeding and ischaemic events,<sup>3,5,12</sup> frequent comorbidities/comedication, and reduced adherence to prescriptions. Given the challenges of antithrombotic treatment in the elderly, the European Society of Cardiology (ESC) Working Group on Thrombosis gathered a task group to address the topic.

## Integrating age into ischaemic and bleeding risks

Antiplatelet, anticoagulant, and fibrinolytic drugs can prevent, postpone, or attenuate the severity of thrombotic events—namely stroke, transient ischaemic attack (TIA), MI, systemic embolism (SE), deep vein thrombosis (DVT), or pulmonary embolism (PE)—and retard cardiovascular and all-cause death, but at the cost of increased bleeding. The critical conundrum is whether, in the older patient, the benefits outweigh the bleeding risks, given that bleeding associates with earlier mortality<sup>13,14</sup> and that predictors of ischaemic vs. bleeding events often co-exist, as illustrated by the progressively increasing hazards of both outcomes with

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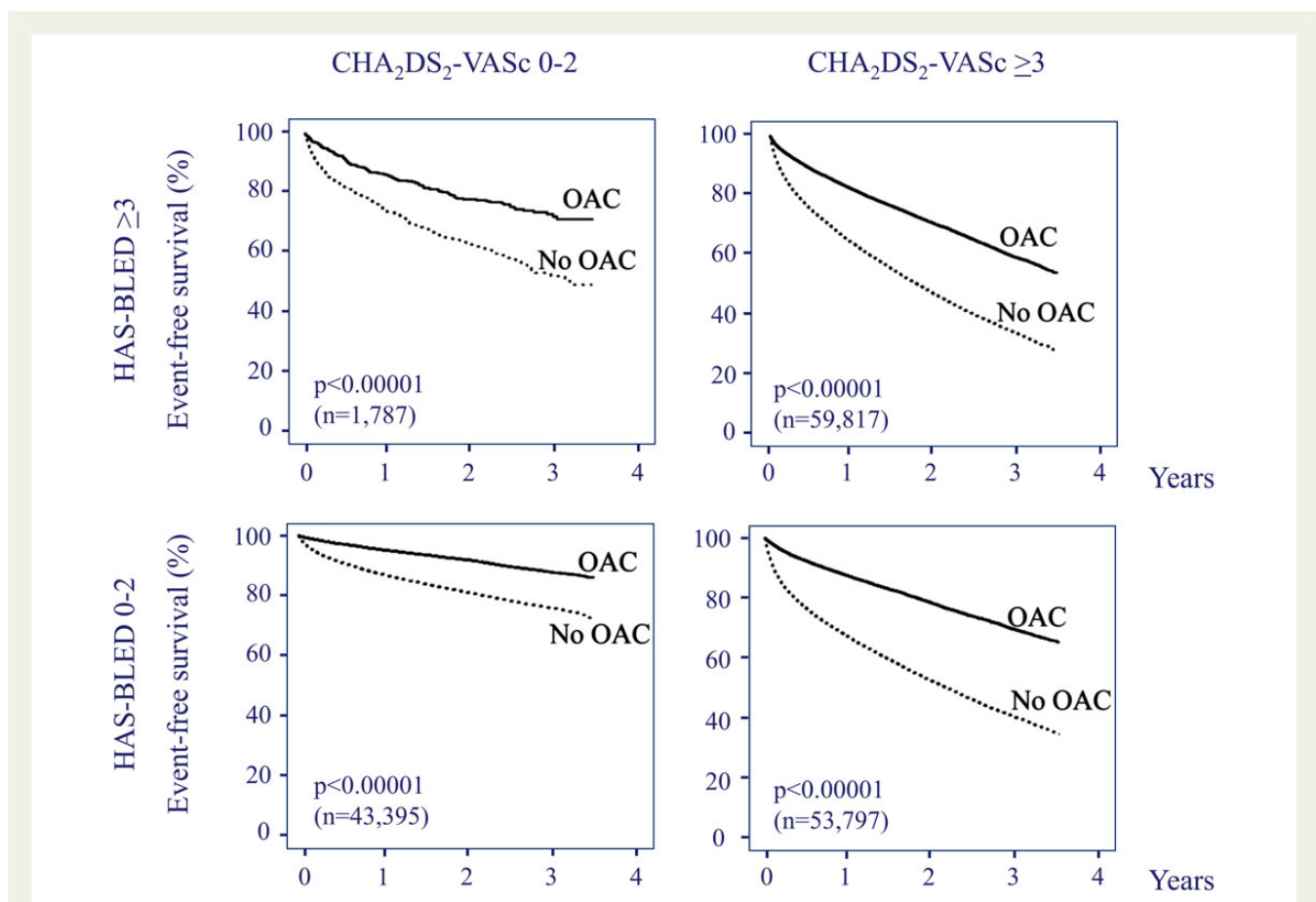
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most traditional cardiovascular risk factors, including age.<sup>3</sup> Measures of 'frailty' are not necessarily the solution, as these, like age, correlate with both ischaemic and bleeding events.<sup>15</sup> Scores partly overcome this limitation by providing more robust measures of risks and potential benefits compared with single measures like age alone.<sup>15,16</sup> Examples are HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history/predisposition, labile international normalised ratio (INR), elderly  $\geq 65$ , and drugs/alcohol abuse] and CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive heart failure, hypertension, age  $\geq 65$ , diabetes, prior stroke/TIA, vascular disease, and female sex category) for estimating, respectively, bleeding and thromboembolic hazards with anticoagulants.<sup>17</sup> Figure 1 shows how the benefit associated with anticoagulants—expressed as freedom from death, ischaemic stroke, and intracranial haemorrhage (ICH)—runs parallel with increasing embolic risk, even in those at higher bleeding risk (HAS-BLED  $\geq 3$ , of which age  $\geq 65$  is a key determinant).<sup>17</sup> The use of such integrated estimates of benefits and risks may avoid under-treatment based on perceived bleeding risk alone.

## Organ function and age

Changes in haemostatic factor levels or activity may contribute to the risk of cardiovascular disease (CVD) with age (Table 1),<sup>18</sup> while age-related amyloid angiopathy may enhance the risk of bleeding.<sup>19</sup> Experimental manipulation of vascular age can delay atherosclerosis, emphasising the relation between ageing and vascular pathology.<sup>20</sup> In the elderly, increasing levels of fibrinogen, factor (F)VII, FVIII, plasminogen activator inhibitor-1, and thrombin-activatable fibrinolysis inhibitor in both genders—and decreased plasminogen in women—create a prothrombotic environment with reduced fibrinolytic efficiency.<sup>21–23</sup> Increased concentrations of antithrombotic proteins, such as plasma protein C, antithrombin, and tissue factor pathway inhibitor, are possibly limited to older women.<sup>21,24,25</sup> Endothelial dysfunction, inflammation, and an imbalance between oxidative stress and antioxidant defence may play key roles in age-related atherothrombosis.<sup>26–30</sup> Blood rheology is also impaired with age, mainly via enhanced plasma viscosity and erythrocyte rigidity.<sup>31</sup>



**Figure 1** Relative benefits of oral anticoagulants vs. no oral anticoagulant (antiplatelet therapies or no antithrombotic therapy) as a function of the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores. The clinical benefit of OAC vs. no OAC—expressed as freedom from death, ischaemic stroke, and intracranial haemorrhage—is reflected by the separation of the curves, not only for patients at higher thromboembolic risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc  $\geq 3$ ) but also for patients at higher bleeding risk (HAS-BLED  $\geq 3$ ). Age  $\geq 65$  is a key determinant of both embolic and bleeding risk scores. Modified from Friberg et al.<sup>17</sup>

In older people, antithrombotic therapy is complicated by physiological organ changes (Table 2).<sup>4,32,33</sup> Decreased hepatic blood flow and changes in hepatic size and architecture<sup>34</sup> slow down the activity of cytochrome P450(CYP) 1, 2C4 and 2D6, while CYP3A4 and phase II enzymes are less affected.<sup>34,35</sup> Kidney function and blood flow are reduced, nephron histology is altered,<sup>36,37</sup> and body water and lean mass decline with age<sup>32,38,39</sup> (Table 2). Chronically reduced

renal function and intercurrent illnesses (e.g. pneumonia or heart failure) may cause an acute decline of creatinine clearance (CrCl) with impact on antithrombotic drugs primarily cleared by the kidney [e.g. low-molecular-weight heparins (LMWHs), fondaparinux, bivalirudin, dabigatran, eptifibatide, and tirofiban]. Renal function in the elderly should be estimated by equations that include age and weight, rather than by serum creatinine alone, which overestimates renal function in this population.<sup>40,41</sup> Overall, the above changes enhance interindividual variability of response, increase drug toxicity, and potentially attenuate net therapeutic benefits, especially for drugs with a narrow therapeutic index<sup>33,42</sup> such as warfarin (Figure 2).<sup>43,44</sup>

**Table 1 Association between older age and haemostatic factor plasma levels**

Haemostatic factor	Effect of age
<b>Procoagulant factors</b>	
Fibrinogen	↑
Factor VII	↑
Factor VIII	↑
<b>Fibrinolytic system</b>	
Plasminogen activator inhibitor-1	↑
Thrombin-activatable fibrinolysis inhibitor	↑
Plasminogen	↓ (in women)
<b>Antithrombotic factors</b>	
Protein C	↑ (in women)
Antithrombin	↑ (in women)
Tissue factor pathway inhibitor	↑ (in women)

## Oral antiplatelet drugs

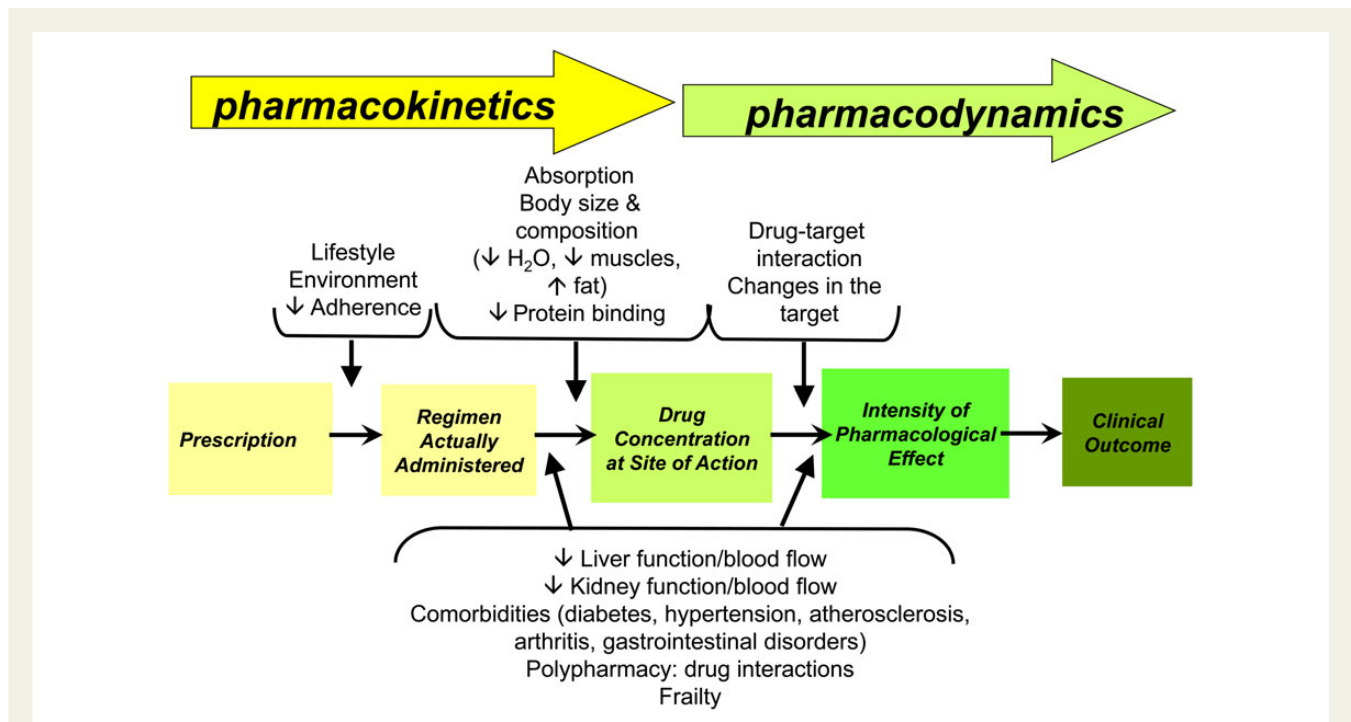
### Aspirin

Aspirin is an irreversible platelet cyclooxygenase-1 inhibitor. The most comprehensive information on age-related benefits and risks of low-dose aspirin (defined as 75–100-mg once daily—o.d.) is a meta-analysis of individual data from six primary prevention randomised trials on 95 000 individuals at low-average risk (660 000 person-years) and 16 secondary prevention randomised trials on 17 000 individuals at high average risk (43 000 person-years) that compared long-term aspirin vs. control.<sup>3</sup> Subjects >70 years, however, were underrepresented (for instance, 1480 of 22 071 or ~7% in the Physicians' Health Study)<sup>46</sup> despite being the dominant demographic group at elevated CVD risk.<sup>3</sup> In primary prevention, aspirin yielded similar proportional reductions of serious vascular events in

**Table 2 Age-related organ changes affecting drug pharmacokinetics**

Physiological change	Pharmacological consequence
<b>Gastrointestinal tract</b>	
Slight increase in gastric pH	Slightly decreased absorption (rarely clinically significant)
Delayed gastric emptying	Different bioavailability/solubility of pH-sensitive drugs
Reduced splanchnic blood flow	
Decreased absorption surface	
Decreased mobility	
<b>Body composition and drug distribution</b>	
Increased body fat and/or decreased lean (muscle) body mass	Increased Vd and increased half-life of lipophilic drugs
10–15% decrease in total water	Decreased Vd and increased plasma concentration of hydrophilic drugs
~10% decrease in serum albumin	Increased free fraction in plasma of highly protein-bound acidic drugs
Stable or increased $\alpha$ 1-acid glycoprotein	Variable free fraction of basic drugs
<b>Liver</b>	
30–50% decrease in blood flow	First-pass metabolism less effective
20–40% decreased hepatocyte functional mass	Some phase I enzymatic families impaired
Modified architecture	Phase II enzymes usually unaffected
<b>Kidney</b>	
Decreased renal blood flow	Impaired elimination
Decreased glomerular filtration rate	
Changes in tissue histology	

Vd, volume of distribution.



**Figure 2** Pharmacokinetic and pharmacodynamic variables influencing the efficacy and safety of drugs in elderly subjects. Age-related changes in many organs and systems can result in different-from-expected clinical outcomes in response to several drugs. Modified from Rocca and Patrono.<sup>45</sup>

subjects <65 years (13% reduction) and ≥65 years (12% reduction); the effect was most marked on nonfatal MI.<sup>3</sup> Because of the higher control rate of vascular events in the older vs. younger population (1.53 vs. 0.40% per year), the absolute benefit of antiplatelet prophylaxis was about three-fold larger in the older population (16 vs. 5 major vascular events prevented per 10 000 subjects treated with aspirin for 1 year).<sup>3</sup> The recent Japanese Primary Prevention Project (JPPP) of 14 464 individuals aged 60–85 years, with hypertension, dyslipidaemia or diabetes, randomised to aspirin 100-mg o.d. or no aspirin,<sup>47</sup> was discontinued after a median of 5.0 years for likely futility; cardiovascular death, MI, and stroke occurred in 2.77% [95% confidence interval (CI) 2.40–3.20] with aspirin vs. 2.96% (95% CI 2.58–3.40) without aspirin [hazard ratio (HR) 0.94, 95% CI 0.77–1.15;  $P = 0.54$ ]. Aspirin roughly halved the incidence of MI and TIA, but almost doubled that of major extracranial haemorrhages.<sup>47</sup> Of note, JPPP individuals had a three-fold higher stroke: MI ratio than the 95 000 subjects randomised in previous primary prevention trials, largely explaining the difference between the two analyses. The ongoing Aspirin in Reducing Events in the Elderly trial in a predominantly Western population will provide further information on the benefit–risk balance of low-dose aspirin in men and women >70 years without overt CVD.<sup>48,49</sup>

For secondary prevention, the proportional reduction in vascular events by aspirin is similar to that for primary prevention, but the absolute benefit is an order of magnitude greater in both younger and older patients (see Supplementary material online, Figure S1). Besides age being an independent risk factor for major coronary events (rate ratio per decade 1.84, 95% CI 1.74–1.95) and ischaemic

stroke (rate ratio 2.46, 95% CI 2.27–2.65), age is also a risk factor for haemorrhagic stroke (rate ratio 1.59, 95% CI 1.33–1.90) and major extracranial bleeding (rate ratio 2.15, 95% CI 1.93–2.39).<sup>3</sup> Consequently, the absolute bleeding hazard of low-dose aspirin is two- to three-fold larger in older than younger people in both genders (see Supplementary material online, Figure S1). Moreover, the risk of upper gastrointestinal bleeding increases sharply ≥70 years,<sup>50</sup> especially with a history of gastrointestinal disturbances (see Supplementary material online, Figure S2) or concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs)<sup>51</sup> related to prevalent osteoarthritic conditions.

We recommend long-term low-dose aspirin in elderly patients with overt atherothrombotic disease, unless contraindicated because of allergy, active bleeding or prior ICH. For primary prevention, the benefit–risk balance of treatment is uncertain<sup>52,53</sup> and is being defined by recently completed or ongoing studies (Table 3).<sup>53</sup> Some evidence suggests that low-dose aspirin may reduce the risk of colonic<sup>54</sup> and other cancer<sup>55</sup> which might tip the long-term balance in its favour.

### Thienopyridines: ticlopidine, clopidogrel, and prasugrel

Thienopyridines are prodrugs with active metabolites that irreversibly bind and inhibit platelet P2Y<sub>12</sub> receptors. Clopidogrel (75 mg o.d.) has replaced ticlopidine because of superior safety; it is an alternative to aspirin in aspirin-intolerant patients with stable coronary artery disease<sup>71</sup> and is standard care, added to aspirin, up to

**Table 3** Task group summary of recommendations on antithrombotic agents in the elderly<sup>a</sup>

Drug	Approved dose Major indications in brackets	Dose reduction in the elderly	Dose reduction according to renal function (EMA- approved unless stated otherwise)	Special considerations in the elderly or in those with prior stroke
<b>Antiplatelet drugs</b>				
Aspirin	75–100 mg o.d., maintenance (secondary prevention of vascular events)			In primary prevention: – Benefits over risks not established; – No apparent benefit in elderly Japanese (III B); <sup>47</sup> – Ongoing trials in Western populations. <sup>48,49,53</sup>
Clopidogrel	75-mg o.d., maintenance (ACS; PCI)			For age ≥ 75 years, no 300-mg loading dose with fibrinolysis for STEMI (III A). <sup>56,57</sup>
Prasugrel	10-mg o.d., maintenance (PCI in ACS)	If prasugrel is deemed necessary, 5-mg o.d. is EMA/FDA-approved for age ≥ 75 years (IIa B) <sup>58,59</sup>		Contraindicated if prior stroke/ TIA, including ICH (III B). <sup>60</sup>
Ticagrelor	90-mg b.i.d., maintenance (ACS)			Caution if COPD/asthma or advanced sinoatrial disease (IIb B). <sup>61,62</sup> Contraindicated if prior ICH (III B). <sup>61,62</sup>
Vorapaxar	2.5-mg o.d. (post-MI, PAD)			Caution in the elderly (IIb A). <sup>63,64</sup> Contraindicated if prior stroke/ TIA, including ICH (III A) <sup>63,64</sup>
GPIs	Weight-adjusted IV bolus (abciximab and eptifibatide) + infusion; doses vary by molecule (high-risk PCI)		Abciximab: caution if CrCl < 15 mL/min; avoid in haemodialysis. Eptifibatide: 50% infusion dose if CrCl 30–50 mL/min; avoid if CrCl < 30 mL/min. Tirofiban: 50% dose if CrCl < 30 mL/min	Caution if age ≥ 70 years (IIb A). <sup>w10</sup> Eptifibatide and tirofiban contraindicated if any prior ICH or if ischaemic stroke within 30 days (III A). <sup>65</sup> Abciximab contraindicated if history of any stroke in past two years (III A). <sup>65</sup> GPIs contraindicated with fibrinolysis for STEMI (III A) <sup>w21,w22</sup>
<b>Oral anticoagulants</b>				
VKA	INR-adjusted dose (AF, VTE, mechanical heart valve)	With age, lower doses required to achieve target INR		Closer monitoring in the elderly
Dabigatran <sup>b</sup>	110-mg b.i.d. (not for VTE; 110-mg not available in the USA) and 150-mg b.i.d. (nonvalvular AF, VTE)	In AF, 110-mg b.i.d. should be considered for age 75–79 years (IIa B); <sup>66</sup> 110-mg b.i.d. is EMA-approved for AF patients ≥ 80 years	Avoid if CrCl < 30 mL/min. 75-mg b.i.d. FDA-approved if CrCl 30 mL/min with concomitant dronedarone or systemic ketoconazole.	For age ≥ 75 years, rates of major extracranial bleeds with 110-mg b.i.d. not significantly lower (with 150-mg b.i.d. numerically higher) vs. warfarin <sup>66</sup>
Rivaroxaban <sup>b</sup>	20-mg o.d. (for VTE, 15-mg b.i.d. in first 21 days) (nonvalvular AF, VTE)		15-mg if CrCl 15–49 mL/min. Avoid if CrCl < 15 mL/min	No dose adjustment for age (I A) <sup>67,68,w34,w35</sup>
Apixaban <sup>b</sup>	5-mg b.i.d. (nonvalvular AF, VTE)	2.5-mg b.i.d. EMA/ FDA-approved if 2 or more of: age ≥ 80 years, body weight ≤ 60 kg, serum Cr ≥ 1.5 mg/dL (I A) <sup>8,9,w36</sup>	2.5-mg b.i.d. if 2 or more of age ≥ 80 years, body weight ≤ 60 kg, serum Cr ≥ 1.5 mg/dL. Avoid if CrCl < 15 mL/min	

Continued

**Table 3** Continued

Drug	Approved dose Major indications in brackets	Dose reduction in the elderly	Dose reduction according to renal function (EMA- approved unless stated otherwise)	Special considerations in the elderly or in those with prior stroke
Edoxaban <sup>b,c</sup>	60-mg o.d. (FDA-approved for nonvalvular AF and VTE)		30-mg o.d. if CrCl 15–50 mL/min (FDA-approved). FDA recommends avoidance if CrCl <15 or >95 mL/min	No dose adjustment for age (I A) <sup>69,w38</sup>
Parenteral anticoagulants				
UFH	Adjusted to aPTT (ACS, PCI, and VTE)			Can be used in severe renal impairment (CrCl <15 mL/min)
LMWHs	Varies by molecule and indication (ACS, PCI, VTE)		Reduce dose if CrCl <30 mL/min (e.g. enoxaparin 1-mg/kg o.d. instead of 1-mg/kg b.i.d.) <sup>70</sup>	For age ≥75 years: reduce dose from 1 to 0.75-mg/kg b.i.d.; avoid 30-mg IV bolus with fibrinolysis (I B) <sup>70</sup>
Fondaparinux	2.5-mg o.d. (ACS, VTE)		For ACS, 1.5-mg o.d. may be considered if CrCl 20–50 mL/min (this regimen has EMA-approval for VTE) ( <a href="http://www.ema.europa.eu/docs/en_GB/document_library/EPAR-Product_Information/human/000403/WC500027746.pdf">http://www.ema.europa.eu/docs/en_GB/document_library/EPAR-Product_Information/human/000403/WC500027746.pdf</a> ). Avoid if CrCl <20 mL/min	
Bivalirudin	0.75-mg/kg IV bolus + 1.75-mg/kg/h infusion for up to 4 h (PCI in ACS)		Reduce infusion rate to 1.4 mg/kg/h if CrCl 30–59 mL/min. Avoid if CrCl <30 mL/min	
Fibrinolytic agents				
Tenecteplase	Weight-based IV bolus of 6000–10 000 U (30–50-mg) (STEMI, PE)	With a pharmacoinvasive strategy <sup>d</sup> , half-dose EMA-approved for STEMI patients ≥75 years (I B) <sup>w54</sup>		Caution with full dose for age ≥75 years (IIb A). <sup>w49,w54,w56</sup> With pharmacoinvasive strategy, half-dose for STEMI patients ≥75 years (I B). <sup>w54</sup> Contraindicated if prior ICH or if ischaemic stroke/TIA in previous 6 months (III A). <sup>w49,w54,w56</sup>

aPTT, activated partial thromboplastin time; ACS, acute coronary syndrome; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; EMA, European Medicines Agency; ESC, European Society of Cardiology; FDA, Food and Drug Administration; GPls, glycoprotein IIb/IIIa inhibitors; ICH, intracranial haemorrhage; INR, international normalized ratio; LMWHs, low-molecular-weight heparins; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; PE, pulmonary embolism; STEMI, ST-elevation myocardial infarction; UFH, unfractionated heparin; VTE, venous thromboembolism; VKA, vitamin K antagonists; w, web appendix reference.

<sup>a</sup>Grades in parenthesis represent the consensus of the present task group. Grade definitions are those used in ESC guidelines.

<sup>b</sup>Recommendations for dosing may be influenced by comedication. For detailed information about drug interactions, see summaries of product characteristics/regulatory documents.

<sup>c</sup>FDA-approved; approval recommended by EMA Committee for Medicinal Products for Human Use.

<sup>d</sup>Pharmacoinvasive strategy: in patients presenting with ST-segment elevation MI within 3 h of onset of symptoms not able to undergo primary PCI within 1 h of first medical contact, a single weight-based 30–50 mg IV tenecteplase bolus followed by angiography within 6–24 h or by rescue coronary intervention.

1 year after ACS<sup>7</sup> or after elective percutaneous coronary intervention (PCI).<sup>72</sup> In the CURE trial of ACS patients, clopidogrel plus aspirin for up to 12 months reduced the composite of cardiovascular death, MI, or stroke vs. aspirin alone [relative risk (RR) 0.80, 95% CI 0.72–0.90;  $P < 0.001$ ];<sup>7</sup> this was also true for the 6208 (49%) >65 years; clopidogrel plus aspirin increased major bleeding vs. aspirin alone (RR 1.38, 95% CI 1.13–1.67;  $P = 0.001$ ), although age-related bleeding events were not reported (see Supplementary material

online, Table S1). The COMMIT trial of ST-elevation MI (STEMI) patients receiving fibrinolytic therapy and aspirin<sup>56</sup> found that clopidogrel 75-mg o.d. (without loading) given for up to 4 weeks provided net benefit compared with placebo; the 1854 patients (26%) ≥70 years showed consistent results with the overall findings. Similarly, the CLARITY-TIMI 28 trial<sup>57</sup> showed net benefit of a 300-mg clopidogrel load followed by 75-mg o.d. up to angiography or discharge, compared with placebo, when added to aspirin and fibrinolytic

therapy; patients >75 years, however, were excluded. Because it is not known whether a clopidogrel load in the elderly receiving thrombolytic therapy is safe, clopidogrel loading cannot be recommended.<sup>52</sup> Optimal duration of dual antiplatelet therapy (DAPT) with contemporary stenting is a matter of debate.<sup>73,74</sup> The recent DAPT trial randomised 9961 patients (40% ACS) to 12 months or 30 months aspirin plus a thienopyridine followed by aspirin alone; longer compared with shorter DAPT yielded significantly lower rates of ischaemic events but more bleeding complications, with a borderline ( $P = 0.05$ ) increase of all-cause mortality; among 1032  $\geq 75$  years (11.6%) the results were consistent with the overall findings.<sup>74</sup>

TRITON-TIMI 38 randomised 13 608 ACS patients naive for thienopyridines, undergoing PCI and receiving aspirin, to either prasugrel or clopidogrel for a median of 14.5 months. Prasugrel (60-mg load and 10-mg o.d. maintenance), generating a higher plasma active metabolite concentration compared with clopidogrel, significantly reduced the rate of cardiovascular death, MI, or stroke vs. clopidogrel (HR 0.81, 95% CI 0.73–0.90;  $P < 0.001$ ).<sup>60</sup> The 1769 patients  $\geq 75$  years (13%) had a 6% RR reduction with prasugrel, compared with a 25% RR reduction in those <65 years (interaction  $P$  not significant) (see Supplementary material online, Table S1). There was increased non-coronary artery bypass graft (CABG)-related TIMI major bleeding with prasugrel (HR 1.32, 95% CI 1.03–1.68;  $P = 0.03$ ), including fatal and life-threatening bleeds, especially in patients  $\geq 75$  years.<sup>60</sup> Patients with prior stroke or TIA-derived harm from prasugrel.<sup>60</sup> In a prespecified analysis, patients  $\geq 75$  years had no net benefit (death, MI, stroke, or non-CABG-related TIMI major bleeding; HR 0.99, 95% CI 0.81–1.21).<sup>60</sup> Given concerns over fatal bleeding and ICH and lack of net benefit in the elderly, the 2012 ESC STEMI guidelines state that prasugrel 60-mg load/10-mg o.d. 'is generally not recommended in patients  $\geq 75$  years'.<sup>75</sup> The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have approved a 5-mg daily dose for patients  $\geq 75$  years, largely on the basis of a TRITON-TIMI 38 pharmacokinetic substudy ( $N = 1159$ ), showing a 19% higher prasugrel active metabolite concentration in patients  $\geq 75$  years.<sup>58</sup> Among medically managed non-ST-elevation (NSTEMI)-ACS patients receiving aspirin, prasugrel 30-mg load/10-mg o.d. in patients <75 years or 30-mg load/5-mg o.d. in those  $\geq 75$  years for a maximum of 30 months did not show superior efficacy, with comparable safety, vs. clopidogrel 300-mg load/75-mg o.d.;<sup>59,76</sup> efficacy and safety with the half maintenance dose in patients  $\geq 75$  years were consistent with those seen in patients <75 years with the full dose (see Supplementary material online, Table S1). Among 4033 NSTEMI-ACS patients randomised to receive prasugrel either at initial diagnosis or after angiography (median 4.3 h later), earlier dosing led to a 1.9-fold significant increase in major bleeding without ischaemic benefits; the findings were consistent in the 715  $\geq 75$  years.<sup>77</sup>

In the elderly, we recommend clopidogrel on top of aspirin for up to 1 year after elective PCI. After ACS, clopidogrel rather than prasugrel or ticagrelor should be considered if bleeding risk is high. A loading dose of clopidogrel with fibrinolysis is not recommended for those >75 years. Following ACS, the use of prasugrel is cautioned in patients  $\geq 75$  years and is contraindicated for those with prior stroke/TIA; for NSTEMI-ACS, prasugrel should not be given before angiography, regardless of age; when prasugrel is deemed

necessary in the elderly, a 5-mg rather than 10-mg o.d. maintenance should be considered, because bleeding rates with 5-mg are similar to those seen in younger patients receiving 10-mg, without apparent loss in efficacy; the 5-mg dose however has not been investigated in the setting of coronary stenting (Table 3).

## Ticagrelor

Ticagrelor is a reversibly binding inhibitor of the platelet P2Y<sub>12</sub> receptor, recommended in preference to clopidogrel in patients with NSTEMI-ACS (regardless of management strategy) or STEMI managed with primary PCI.<sup>75,78</sup> The parent drug and its active metabolite are cleared mainly through hepatic metabolism and biliary excretion.<sup>61,79</sup> The PLATO trial randomised 18 624 ACS patients, nearly all receiving aspirin, to either ticagrelor or clopidogrel for up to 12 months; 2878 (15%) were  $\geq 75$  years.<sup>80</sup> The significant reductions in ischaemic events and total mortality found in the overall trial with ticagrelor (180-mg load and 90-mg b.i.d. maintenance) vs. clopidogrel were consistent among older and younger patients ( $P$  for interaction  $\geq 0.56$ ). Given the higher risk of older patients, the absolute mortality reduction with ticagrelor vs. clopidogrel was numerically greater in those  $\geq 75$  years (9.8 vs. 12.4%; HR 0.77, 95% CI 0.60–0.98) than in those <75 years (3.6 vs. 4.8%; HR 0.80, 95% CI 0.68–0.95).<sup>80</sup> Overall, major bleeding rates (defined by PLATO criteria to include CABG-related bleeding) were not significantly greater with ticagrelor vs. clopidogrel, neither in the entire population nor in the older subgroup, although there were 11 fatal ICH with ticagrelor vs. 1 with clopidogrel ( $P = 0.02$ ); the increase in non-CABG-related major bleeding with ticagrelor vs. clopidogrel (HR 1.25, 95% CI 1.03–1.53;  $P = 0.03$ ) was not significantly affected by age (see Supplementary material online, Table S1). The advantage of ticagrelor over clopidogrel in elderly patients is corroborated by the amplified benefits of ticagrelor in patients with renal dysfunction.<sup>81</sup> Prehospital ticagrelor has been compared with ticagrelor administered at angiography (median 31 min later) in 1862 STEMI patients; earlier dosing was not associated with significant differences in rates of persisting ST-segment elevation or TIMI 3 flow before primary PCI, or in non-CABG-related major bleeding at 48 hrs and 30 days; the findings were consistent in different age groups.<sup>82</sup> Rates of 30-day definite stent thrombosis were lower for the prehospital-treated group (0.2 vs. 1.2%,  $P = 0.02$ ; no age analysis, given small number of events).<sup>82</sup> Although ticagrelor is contraindicated in those with prior ICH, it lowered mortality compared with clopidogrel in those with prior ischaemic stroke/TIA (no age analysis, given small subgroup).<sup>83</sup> Ticagrelor significantly increases the frequency of dyspnoea and sinoatrial pauses vs. clopidogrel, without age–treatment interaction;<sup>80,84</sup> its use is cautioned in patients with sinoatrial disease who do not have a permanent pacemaker<sup>84</sup> and in those with a history of asthma and/or chronic obstructive pulmonary disease (COPD) ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_Product\\_Information/human/001241/WC500100494.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/001241/WC500100494.pdf)).

We recommend ticagrelor in elderly ACS patients in the absence of contraindications such as active bleeding or prior ICH, with caution in those presenting advanced sinoatrial disease not treated with a permanent pacemaker and in those with a history of asthma and/or COPD (Table 3).

## Other oral antiplatelet agents: dipyridamole (see Supplementary material online, Appendix), cilostazol (see Supplementary material online, Appendix), and vorapaxar

Vorapaxar, a potent selective antagonist of the platelet protease-activated receptor 1 with a 7-day half-life, was tested against placebo on top of dual or single antiplatelet therapy in 12 944 ACS patients (TRACER; 40-mg load and 2.5-mg o.d. maintenance) for a median of 16 months<sup>63</sup> and in 26 449 patients with a history of MI, ischaemic stroke, or peripheral arterial disease—PAD (TRA 2P-TIMI 50; 2.5-mg o.d.) for a median of 30 months.<sup>64</sup> Background P2Y<sub>12</sub> inhibitor was clopidogrel in the vast majority.<sup>63,64</sup> In both trials, rates of CV death, MI, and stroke were reduced by vorapaxar (HRs: 0.89, 95% CI 0.81–0.98;  $P = 0.02$  in TRACER; 0.87, 95% CI 0.80–0.94;  $P < 0.001$  in TRA-2P). However, in TRACER, the reduction in the primary outcome of CV death, MI, stroke, ischaemia-driven hospitalization, or urgent coronary revascularisation was not statistically significant. In both trials, the rates of ICH were increased 2- to 3-fold with vorapaxar ( $P < 0.001$ ). For patients  $\geq 75$  years ( $\sim 17$  and 12% of the populations, respectively), the results were consistent with the overall trial results. In TRACER, however, the proportional increase of major bleeds with vorapaxar was 26% in those  $< 75$  years (HR 1.26, 95% CI 1.05–1.51) vs. 62% in those  $\geq 75$  years (HR 1.62, 95% CI 1.22–2.16; absolute differences not provided; interaction  $P = 0.136$ ). In TRA 2P-TIMI 50, enrolment of patients with prior stroke was discontinued; the absolute increase of major bleeds with vorapaxar was 1.5%  $< 75$  years (from 2.2 to 3.7%; HR 1.65, 95% CI 1.39–1.96) and 2.9%  $\geq 75$  years (from 5.5 to 8.4%; HR 1.69, 95% CI 1.22–2.33; interaction  $P = 0.87$ ). Vorapaxar has received FDA and EMA approval for patients with previous MI or PAD and no prior stroke/TIA or ICH. We recommend great caution in the elderly owing to the 2- to 3-fold increased risk of ICH and to amplification of the age-related increased risk of major bleeding. The drug cannot be used in those with prior ischaemic stroke/TIA or ICH (Table 3).

## Intravenous antiplatelet agents: glycoprotein IIb/IIIa inhibitors and cangrelor

See Supplementary material online, Appendix, Table 3, and Table S1.

## Oral anticoagulants

### Vitamin K antagonists

Older age increases the risk of major haemorrhage with vitamin K antagonist (VKA).<sup>85</sup> Of 99 628 emergency hospitalisations for adverse drug events among older adults in the USA, warfarin was implicated in approximately one third of them.<sup>86</sup> Annual rates of major haemorrhage during warfarin therapy, derived from randomised trials in AF, range from 1.7 to 3.0% for patients  $< 75$  years and

from 4.2 to 5.2% for those  $\geq 75$  years.<sup>87</sup> The higher bleeding risk in the elderly is multifactorial and includes age- and warfarin-specific factors. Older individuals require significantly lower VKA doses to achieve the same target INR as younger individuals, partly explaining the greater early bleeding hazard.<sup>88</sup> In addition, elderly patients are slower to normalise an elevated INR, with resultant longer exposure to risk-laden levels above the target range.<sup>12</sup> Despite these caveats, in the BAFTA trial of 973 nonvalvular AF patients  $\geq 75$  years randomised to INR-adjusted warfarin or to aspirin 75-mg o.d. over 2.7 years, warfarin was markedly more effective vs. aspirin in preventing severe strokes/SE (RR 0.48, 95% CI 0.28–0.80;  $P = 0.0027$ ) with comparable bleeding hazards (1.4 vs. 1.6% yearly rates of extracranial haemorrhage and 8 vs. 6 ICH for warfarin vs. aspirin)<sup>89</sup> (see Supplementary material online, Table S2). Vitamin K antagonists are also indicated in the secondary prevention of venous thromboembolism (VTE); further details on VKA and non-VKA oral anticoagulants (NOACs) in the elderly are below. Thus, older age *per se* is not a contraindication to the use of VKA in AF or VTE, but lower doses and tighter monitoring may be required (Table 3).

### Direct thrombin inhibitors: dabigatran

#### Nonvalvular atrial fibrillation

The phase III randomised trial comparing dabigatran with warfarin in 18 113 nonvalvular AF patients found no significant age interaction for the efficacy outcome of stroke/SE; the latter outcome was significantly reduced by dabigatran 150-mg b.i.d. (but not by 110-mg b.i.d.) vs. warfarin.<sup>66</sup> In contrast, for major extracranial bleeding, there was a significant age-treatment interaction: the 20% RR reduction in major bleeding with the lower dabigatran dose (110-mg b.i.d.) compared with warfarin, apparent in the whole trial population, was not evident in those  $\geq 75$  years, while there was a numerical increase in major extracranial bleeding with dabigatran 150-mg b.i.d. compared with warfarin in the elderly<sup>66</sup> (see Supplementary material online, Table S2). The risk of ICH was consistently reduced by dabigatran vs. warfarin, irrespective of age and dose.<sup>66</sup> Gastrointestinal bleeds instead were more common with dabigatran 150-mg b.i.d. compared with warfarin. Given that elderly patients often have impaired renal function, particular attention in elderly patients is required, considering dabigatran's  $\sim 80\%$  renal clearance.<sup>90</sup> Still, the efficacy of both doses of dabigatran was consistent with the overall trial irrespective of kidney function.<sup>91</sup> The drug is contraindicated when CrCl is  $< 30$  mL/min. The FDA suggests a 75-mg b.i.d. dosing if CrCl is 30 mL/min and dronedarone or systemic ketoconazole are being taken. The EMA but not the FDA recommends dabigatran 110-mg b.i.d. instead of 150-mg b.i.d. for patients  $\geq 80$  years. The 110-mg formulation is not available in the USA. Advanced age alone should not exclude the use of dabigatran,<sup>92</sup> although age appeared the most important covariate of dabigatran plasma concentration, which in turn was closely related with ischaemic and bleeding risks.<sup>93</sup> The 110-mg instead of the 150-mg b.i.d. regimen should be considered for patients aged 75–79 and is recommended  $\geq 80$  years in Europe (Table 3).

#### Dabigatran for venous thromboembolism

See Supplementary material online, Appendix, and Table S3.



## Direct FXa inhibitors: rivaroxaban, apixaban, and edoxaban

### Nonvalvular atrial fibrillation

Phase III randomised trials have compared rivaroxaban, apixaban, or edoxaban with warfarin in nonvalvular AF patients followed for ~2 years. ROCKET-AF<sup>67</sup> enrolled 14 264 patients at high risk for stroke, 44% of which  $\geq 75$  years; overall, rivaroxaban 20-mg o.d. (15-mg for CrCl 15–49 mL/min) was non-inferior to warfarin for the prevention of stroke/SE, without significant difference in major bleeding rates; outcomes with 15-mg rivaroxaban were consistent with the overall trial results.<sup>68</sup> Intracranial haemorrhage and fatal bleeding occurred less—but gastrointestinal bleeding more—frequently with rivaroxaban vs. warfarin. There was no significant interaction between treatment and age for the primary outcome of stroke/SE, nor for major and non-major clinically relevant bleeding (see Supplementary material online, Table S2).<sup>94</sup>

In ARISTOTLE,<sup>9</sup> 31% of the 18 201 AF patients with at least one additional risk factor for stroke were  $\geq 75$  years; apixaban 5-mg b.i.d. [2.5-mg b.i.d. if any two of three conditions were present: age  $\geq 80$  years, body weight  $\leq 60$  kg, and serum creatinine  $\geq 1.5$  mg/dL (133  $\mu\text{mol/L}$ )] was superior in preventing stroke/SE, caused significantly fewer major, total, or ICH, and resulted in lower mortality across all age groups vs. warfarin ( $P$  for interaction  $> 0.10$  for all) (see Supplementary material online, Table S2). Results were consistent for the 13% of patients  $\geq 80$  years.<sup>95</sup> Gastrointestinal bleeds were not more common with apixaban compared with warfarin. The advantages concerning major bleeding with apixaban were amplified in patients with renal dysfunction.<sup>96</sup> Apixaban 5-mg b.i.d., or 2.5-mg b.i.d. as above, was also compared with aspirin (81–324-mg o.d.) in 5599 nonvalvular AF patients considered unsuitable for VKA.<sup>8</sup> Rates of stroke/SE were markedly reduced with apixaban vs. aspirin (HR 0.45, 95% CI 0.32–0.62;  $P < 0.001$ ), with no significant differences in major bleeding or ICH and with consistent results across age strata (see Supplementary material online, Table S2).

In ENGAGE AF-TIMI 48,<sup>69</sup> 40% of 21 105 patients at moderate-to-high thromboembolic risk were  $\geq 75$  years; both 60- and 30-mg o.d. edoxaban regimens were non-inferior to warfarin in preventing stroke/SE and caused significantly less overall major bleeding and ICH. Gastrointestinal bleeds were more common with the higher edoxaban dose vs. warfarin. The 30-mg edoxaban regimen was associated with higher rates of ischaemic stroke but lower rates of all-cause death and gastrointestinal bleeding compared with warfarin. Results were consistent in different age subgroups (see Supplementary material online, Table S2). The FDA has approved 60-mg o.d. edoxaban for stroke prevention in AF for individuals with CrCl 50–95 and 30-mg o.d. for individuals with CrCl 15–50 mL/min; based on subgroup analyses, the FDA signals reduced efficacy in patients with excellent renal function related to lower drug levels. Edoxaban has received approval recommendation from the EMA Committee for Medicinal Products for Human Use.

In elderly nonvalvular AF patients with CrCl  $> 15$  mL/min, we recommend oral FXa inhibitors in preference to warfarin, given the lower incidence of ICH, the favourable overall efficacy and safety, and the lack of routine monitoring (Table 3). Attention towards a limited number of drug–drug interactions,<sup>97</sup> possible gastrointestinal bleeds, and dose reductions in patients with

impaired kidney function are warranted, although the prevalent excretion route of these FXa blockers is liver metabolism, bile, and faeces (50–75%, depending on specific agent).

### Direct FXa inhibitors in ACS and venous thromboembolism

See Supplementary material online, Appendix, Table 3, and Table S3.

## Parenteral anticoagulants

### Unfractionated and low-molecular-weight heparins

Unfractionated heparin (UFH) is not renally cleared and is a reasonable option for CrCl  $< 30$  mL/min. However, over or underdosing, related to changes in bioavailability, inflammatory state, cardiac output, and body weight, can arise rapidly and frequently in older people. The superior bioavailability and overall efficacy of LMWHs, such as enoxaparin, have prompted preferential use of s.c. LMWHs over IV UFH. Randomised trials in the setting of DVT/PE, ACS, thrombolysis, primary or elective PCI, haemodialysis, and AF have mostly shown comparable or better efficacy of LMWH vs. UFH, with overall comparable bleeding rates.<sup>98–101</sup> Low-molecular-weight heparins are primarily eliminated through the kidneys. Age, gender, body weight, and creatinine are all taken into consideration in the Cockcroft Gault equation to calculate CrCl, which is a valuable guide to down-titrate weight-adjusted LMWHs (see ExTRACT-TIMI 25). Accumulation may occur after repeated injections but is less common during the first 24–36 h and does not exist with a single IV injection, as used in PCI.

In SYNERGY, ~25% of 9977 ACS patients randomised to enoxaparin vs. UFH were  $\geq 75$  years.<sup>102</sup> Age-related analyses suggested caution in subjects  $\geq 75$  years because of excessive severe bleeding with enoxaparin.<sup>102</sup> A pooled analysis of ASSENT-3 and -3PLUS in STEMI patients treated with tenecteplase found a significant interaction ( $P = 0.001$ ) among age, sex, and enoxaparin for ICH: in women  $> 75$  years, ICH occurred in 10/183 on enoxaparin (5.5%) vs. 1/185 (0.5%) on UFH ( $P = 0.005$ ).<sup>103</sup> ExTRACT-TIMI 25 randomised ~20 500 STEMI patients receiving fibrinolysis to UFH or enoxaparin, which was dose-adjusted for age and renal function: 30-mg IV bolus and 1-mg/kg s.c. every 12 h for age  $< 75$  years; no IV bolus and 0.75-mg/kg s.c. every 12 h for age  $\geq 75$  years; 24 h dosing interval if CrCl  $< 30$  mL/min. There was consistent benefit and no excess bleeding with enoxaparin vs. UFH among the ~2500 patients  $\geq 75$  years.<sup>70,104</sup>

Thus, UFH remains an option for parenteral anticoagulation in elderly patients with severe renal impairment. For enoxaparin, we recommend o.d. s.c. dosing when CrCl is  $< 30$  mL/min and reduction from 1 to 0.75 mg/kg without an initial bolus for age  $\geq 75$  years, especially with concomitant fibrinolysis (Table 3). A single IV injection of LMWH, as used in PCI, does not need dose adjustment.

### Fondaparinux

Fondaparinux is a synthetic, indirect FXa inhibitor, eliminated mainly by the kidney, that is contraindicated for CrCl  $< 20$  mL/min.<sup>105</sup>

OASIS-5 randomised 20 078 patients with NSTEMI-ACS to 2.5 mg s.c. fondaparinux o.d. or enoxaparin 1-mg/kg s.c. b.i.d. for 8 days maximum.<sup>13,105</sup> Death, MI, or refractory ischaemia at 9 days occurred in 5.8% for fondaparinux vs. 5.7% for enoxaparin (HR 1.01, 95% CI 0.90–1.13) fulfilling non-inferiority. Major bleeds were reduced by ~1/2 with fondaparinux: 2.2 vs. 4.1% (HR 0.52, 95% CI 0.44–0.61;  $P < 0.001$ ).<sup>13</sup> Net benefit was observed for fondaparinux in all predefined subgroups including the elderly.<sup>105</sup> In patients  $\geq 65$  years, bleeding rates fell from 8% with enoxaparin to 4.1% with fondaparinux (HR 0.49, 95% CI 0.37–0.66;  $P < 0.00001$ ) and in those  $< 65$  years from 2.5 to 1.5% (HR 0.58, 95% CI 0.34–0.99;  $P = 0.047$ ). The reduced bleeding rate was associated with lower mortality at 6 months ( $P = 0.05$ ).<sup>106</sup> Fondaparinux has received a class I recommendation in the 2011 ESC NSTEMI-ACS guidelines.<sup>78</sup> In patients referred for angiography, however, UFH or bivalirudin has to be added to prevent procedural thrombotic complications.<sup>78</sup> OASIS-6 randomised 12 092 STEMI patients to fondaparinux or usual care (placebo or UFH).<sup>107</sup> Rates of death or reinfarction at 30 days were reduced by fondaparinux from 11.2 to 9.7% (HR 0.86, 95% CI 0.77–0.96;  $P = 0.008$ ). Mortality was also significantly reduced. However, there was a benefit of UFH over fondaparinux in primary PCI. The balance of benefits and risks of fondaparinux was consistent across all age groups.<sup>108</sup> In VTE prevention, a 1.5-mg o.d. dose (instead of 2.5-mg o.d.) has been approved for patients with CrCl 20–50 mL/min ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR-Product\\_Information/human/000403/WC500027746.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR-Product_Information/human/000403/WC500027746.pdf)).

Given the lower bleeding rates and overall equal efficacy vs. the comparators, we recommend fondaparinux in NSTEMI-ACS patients and in STEMI patients not undergoing primary PCI; for non-primary PCI, adjunctive UFH/bivalirudin needs to be added; fondaparinux is contraindicated in severe renal failure (CrCl  $< 20$  mL/min); a 1.5-mg o.d. dose may be considered for patients with CrCl 20–50 mL/min (Table 3).

## Bivalirudin

See Supplementary material online, Appendix, Table 3, and Table S4.

## Fibrinolytic therapy for ST-elevation myocardial infarction and pulmonary embolism

See Supplementary material online, Appendix, and Table 3.

## How to prevent and manage bleeding in the elderly

Since the elderly *per se* are at increased bleeding risk during anti-thrombotic therapy, and bleeds are associated with increased mortality in both the short and long term, it is essential to consider preventive measures.<sup>109</sup>

## Duration and intensity of therapy

For ACS, regardless of management strategy, dual oral antiplatelet therapy is currently recommended for 1 year.<sup>75,78</sup> Bleeding is

increased by prasugrel or ticagrelor instead of clopidogrel, although ticagrelor is associated with reduced mortality vs. clopidogrel even in those  $\geq 75$  years.<sup>60,62,80</sup> In stable patients, the precise duration of DAPT is decided on the basis of stent type and individual bleeding risk.<sup>110</sup> In elderly ACS patients that require long-term anticoagulation, DAPT may be shortened by the use of bare metal instead of drug-eluting stents in case of PCI.<sup>14,111,112</sup> Prolonged triple antithrombotic therapy should be avoided; in one phase II safety trial, aspirin was omitted with significant reduction in bleeding,<sup>113</sup> although evidence for omitting aspirin rather than clopidogrel is limited; beyond the first 12 months, in patients with no recurrent ischaemic event, it is recommended to avoid antiplatelet drugs in favour of oral anticoagulation.<sup>111,112</sup>

## Surgery

Surgery should be avoided in elderly patients requiring both anti-coagulant and antiplatelet therapy, unless absolutely necessary, or at least postponed until antithrombotic therapy can be stopped or reduced, given the perisurgical bleeding hazards.<sup>114</sup>

## Access site during percutaneous coronary intervention

Arterial access bleeding is frequent and a radial rather than a femoral approach for angiography/PCI is recommended, accepting the occasional need to cross-over to the femoral access and the observation that the benefits of the radial approach seem to emerge with greater experience of centres.<sup>115–120</sup>

## Use of proton pump inhibitors

European Society of Cardiology guidelines recommend a PPI with DAPT to reduce gastrointestinal bleeding events.<sup>75,78,121</sup> It is not known whether a PPI is beneficial in elderly patients receiving a single antithrombotic drug, given lack of adequately sized randomised trials with major gastrointestinal bleeding as primary endpoint. With clopidogrel, PPIs with low CYP2C19 inhibitory capacity (e.g. pantoprazole) are preferred.<sup>121</sup>

## Other measures

These include blood pressure control, avoidance, or limited use of other drugs that enhance bleeding (e.g. NSAIDs, steroids), close monitoring of INR during VKA therapy, avoidance of heavy alcohol intake.

## Management of bleeding

As in younger patients, management includes identification and treatment of the bleeding source, haemostatic intervention (manual, endoscopic, and surgical), discontinuation of anti-thrombotic drugs (partial or complete), replacement therapy, and antidotes if available, depending on bleeding severity and risk of ischaemic recurrence.<sup>14,52,78,97</sup> Transfusions are recommended in haemodynamically unstable patients or with haematocrit  $< 25\%$  or haemoglobin  $< 7$  g/dL.<sup>14,122</sup> Knowledge of the mechanism of action, half-life and elimination route of the anticoagulant/antiplatelet agent, as well as timing of last administration and kidney function, are important for optimal management.

## When to stop, when to restart treatment

Minor or nuisance bleeding and minor interventions (cutaneous, percutaneous, dental, and endoscopy) should not trigger interruption of appropriately prescribed antithrombotic therapy.<sup>14,52</sup> Discontinuation may be required for major bleeding, after a stroke, or because of surgery in a critical/closed space (posterior eye, spinal, and intracranial) or at high haemorrhagic risk (major, reconstructive, and prostatic surgery).<sup>52</sup> Non-VKA oral anticoagulants may be resumed ~3, 6, and 12 days after a small, moderate, or large ischaemic stroke, respectively.<sup>97</sup> After ICH, resuming antithrombotic therapy should be considered with great caution, especially after lobar bleeds that have higher recurrence rates than deep cerebral bleeds;<sup>123</sup> left atrial appendage occlusion may be an alternative.<sup>97,124</sup>

## Case illustrations

Some examples of how to apply the above recommendations are given, acknowledging the numerous gaps in evidence related to the absence of randomised comparisons:

- A 78-year-old man presents with chest pain, elevated high-sensitivity troponin, and ischaemic ECG changes; history includes diabetes mellitus and chronic kidney disease with CrCl 40 mL/min/1.73 m<sup>2</sup>. Recommended treatment is aspirin 300-mg loading dose followed by 75–100-mg o.d., ticagrelor 180-mg loading dose followed by 90-mg b.i.d., and s.c. fondaparinux 2.5-mg o.d. until coronary angiography, which should be performed by the radial route if the operator has sufficient experience. If PCI is performed, no GPIIb/IIIa inhibitor is required and anticoagulant choices include UFH 70 U/kg or bivalirudin. Ticagrelor is continued for 1 year and aspirin continued long term.
- A 76-year-old woman with permanent AF, hypertension, and prior TIA on long-term warfarin undergoes PCI with drug-eluting stent to the mid left anterior descending (LAD) artery for management of stable angina. Aspirin 300-mg and clopidogrel 600-mg are given prior to PCI and pantoprazole is started. Percutaneous coronary intervention is performed via the radial route and warfarin continued with INR 2.2 at the time of PCI. Unfractionated heparin 50 U/kg is given to cover the PCI procedure. After PCI, aspirin 75-mg o.d. is continued for 4 weeks then stopped and clopidogrel 75-mg o.d. is continued for 6 months then stopped. The INR is controlled to maintain it at 2.0–2.5 for 6 months. After 6 months, warfarin only is continued long term with an INR range of 2.0–3.0. Optimal management of such a case remains to be established given the absence of randomised comparisons between, e.g. VKA vs. NOAC, additional periprocedural anticoagulation vs. none, or VKA/aspirin vs. VKA/clopidogrel after an initial phase of triple antithrombotic therapy.
- An 81-year-old man with permanent AF, hypertension, diabetes mellitus, and previous gastrointestinal bleeding is admitted with chest pain; treatment includes apixaban 2.5-mg b.i.d. and a PPI; a NSTEMI is diagnosed. Estimated CrCl is 38 mL/min. Oral aspirin 300-mg and clopidogrel 600-mg are given and apixaban continued. No parenteral anticoagulation is administered. The

condition is stable; echocardiography shows preserved LV ejection fraction; angiography reveals occluded mid right coronary artery and non-significant lesions of the circumflex and LAD arteries. A conservative strategy without PCI is chosen and aspirin discontinued. Clopidogrel 75-mg daily is maintained for 12 months, after which apixaban alone is continued. Optimal treatment of this type of patient with simultaneously high ischaemic/cardioembolic and bleeding risks is unknown; aspirin may be chosen instead of clopidogrel and antiplatelet therapy duration may be <12 months. Non-VKA oral anticoagulants are acceptable alternatives to VKA.

- A 72-year-old woman with mechanical bileaflet mitral prosthesis and permanent AF develops sudden headache and visual impairment. She is on VKA and aspirin 75-mg o.d. and reports taking NSAIDs for arthritic pain. Blood pressure is 185/100 mmHg, INR 3.8, CrCl 50 mL/min, Hb 11 g/dL. Computerized tomography shows a small-to-moderate occipital ICH, and echocardiography a well-functioning prosthesis, preserved LV function, and enlarged left atrium. Vitamin K antagonist and aspirin are discontinued; vitamin K, fresh frozen plasma, PPI, and furosemide are administered IV. Surgical drainage is not performed. Spontaneous gradual recovery, neuroimaging at 2 weeks, and discussion with the 'brain team' lead to resumption of VKA after 3 weeks. The patient is discharged with instructions to maintain the INR ~2.5, avoid NSAIDs/antiplatelets, and monitor BP. The decision on whether or not and when to restart VKA is based on limited/imprecise data with no randomised controlled trial evidence. Non-VKA oral anticoagulants are associated with fewer ICH vs. warfarin but are not recommended for patients with mechanical heart valves.

## Summary and future challenges

The number of elderly individuals exposed to one or more antithrombotic treatments is growing. Effective therapies generally provide larger absolute benefits in older than in younger patients despite a higher risk of bleeding. To avoid older people being denied antithrombotic drugs because of unjustified concerns, or conversely being inappropriately overtreated, this patient-oriented consensus document has focused on age-specific risks and benefits of antithrombotic drugs tested in phase III trials and provides recommendations summarised in *Table 3*. Elderly patients are underrepresented in trials and accurate information on the benefit–risk balance of most antithrombotic drugs is limited. There is a need to define/refine therapy for older groups to maximize benefits and minimise risks. The lack of interaction between current risk scores and the effects of various treatments means that improved methods of estimating risks and benefits of different interventions in specific groups and settings are urgently needed. Because trials to test antithrombotic regimens may be difficult in the elderly owing to inadequate sample sizes and logistical barriers (e.g. reduced cognitive function and mobility), mechanistic studies are being considered.<sup>125</sup> The limits of current evidence provide the rationale for undertaking, if not appropriately powered trials, at least mechanistic studies to guide decisions in older patients based on clinical and laboratory characteristics.<sup>45,126</sup>

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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