Antithrombotic Therapy: Focus on the Elderly

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Abstract

Advanced age brings a higher incidence of thrombosis-related diseases. Although antithrombotic therapy significantly reduces the risk of ischemic events, relatively higher bleeding rates result in increased mortality and worse prognosis in the elderly. Thus the benefits and harms of antithrombotic drugs should to be carefully evaluated. In this review, we summarize current evidence and updated guidelines regarding antithrombotic therapy in the aging population.

Keywords: elderly; antiplatelet; anticoagulant; bleeding

Introduction

In recent years the elderly population has grown rapidly. Advanced age is a crucial risk factor for coronary artery disease, stroke/thromboembolism, and atrial fibrillation (AF), with increased mortality and worse prognosis [1, 2]. Although antithrombotic therapy reduces the risk of ischemic events, age-dependent increased bleeding risk cannot be overlooked. Thus balancing the benefits against potential harms related to antithrombotic therapy in the elderly is rather challenging. Here we summarize current evidence and updated guidelines regarding antithrombotic therapy in the elderly [3] (Table 1).

Characteristics of the Elderly

A series of changes occurs with increasing age, including fat redistribution, declining gastrointestinal absorption, and decreased hepatic blood flow and renal function, which lead to a slower rate of drug absorption, increased bioavailability and delayed elimination. Besides, the incidence of comorbidities is higher in the elderly, which means multiple drugs might be prescribed. As a result, adverse drug-drug interactions appear more frequently in this particular population. Further, hemodynamic changes, such as increased levels of fibrinogen, factor VII, factor VIII, plasminogen activator inhibitor 1 and protein C, promote the establishment of a prothrombotic environment. Further, chronic inflammation and endothelial dysfunction, often observed in the elderly, play critical roles in thrombosis [4–6].

As a populous country, China is facing problems due to the rapid increase of the aging population. It is estimated that the number of elderly people will reach more than 400 million by 2050, about 30% of the total population [7]. The elderly account for a considerable proportion of patients with a high incidence of ischemic events.

Although antithrombotic therapy significantly reduces stroke risk and mortality [5], several problems still exist. Firstly, although more attention is being paid to the elderly nowadays, sufficient evidence is still lacking in China, making it difficult to balance the benefits and risks, as well as to optimize...
Table 1  Recommendations for Antithrombotic Agents.

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<tr>
<th>Drug</th>
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<td><strong>Antiplatelet agents</strong></td>
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| Aspirin      | 75–100 mg/day  
Secondary prevention of vascular events | Low dose in the primary prevention of CVD and CRC in adults aged 60–69 years | Evaluation of 10-year CVD risk and bleeding risk |
| Clopidogrel  | 75 mg/day  
Maintenance dose ACS, PCI | 300-mg loading dose is not recommended in patients older than 75 years | More frequent dyspnea and ventricular pauses  
Caution in advanced sinoatrial disease and with history of asthma or COPD; contraindicated if prior ICH |
| Ticagrelor   | 90 mg bid  
Maintenance dose ACS, PCI | EMA/FDA approved lower dose (5 mg/day) in patients aged 75 years or older | Caution with low body weight(<60 kg)  
Contraindicated in patients with prior stroke or TIA, ICH |
| Prasugrel    | 10 mg/day  
Maintenance dose ACS, PCI | 110 mg bid considered in patients aged 75–79 years  
EMA approved 110 mg bid in AF patients aged 80 years or older | Lower dose in AF patients with impaired renal function and low body weight (<60 kg)  
Avoid if CrCl<30 mL/min |
| GPIs         | High-risk PCI  
Thrombotic complications | Dose-adjusted tirofiban in patients with severe renal dysfunction (CrCl<30 mL/min) | Not recommended in patients older than 75 years  
Contraindicated in patients with ICH or ischemic stroke within 30 days, fibrinolysis for STEMI |
| **Oral anticoagulant agents** |                                  |                           |                                         |
| VKAs         | INR-adjusted dose  
AF, VTE, mechanical heart valve | Preferred in patients with severe renal dysfunction | Closer monitoring in the elderly |
| Dabigatran   | 110 mg bid/150 mg bid  
Nonvalvular AF, VTE | 110 mg bid considered in patients aged 75–79 years  
EMA approved 110 mg bid in AF patients aged 80 years or older | Lower dose in AF patients with impaired renal function and low body weight (<60 kg)  
Avoid if CrCl<30 mL/min |
| Rivaroxaban  | 20 mg/day  
Nonvalvular AF, VTE | 15 mg/day if CrCl=15–49 mL/min | Avoid if CrCl<15 mL/min  
No dose adjustment for age |
| Apixaban     | 5 mg bid  
Nonvalvular AF, VTE (United States and Europe) | FDA approved 2.5 mg/day in patients with at least two of the following: older than 80 years, body weight less than 60 kg, serum creatinine level 1.5 mg/dL or higher | Avoid if CrCl<15 mL/min  
Avoid if CrCl<15 mL/min |
| Edoxaban     | 60 mg/day  
Nonvalvular AF, VTE (United States) | 30 mg/day if CrCl=15–50 mL/min | Avoid if CrCl<15 mL/min  
No dose adjustment for age |
| **Intravenous anticoagulant** |                                  |                           |                                         |
| UFH          | Adjusted to aPTT  
ACS, PCI, VTE | Reduced dose in patients older than 75 years | Can be used in severe renal dysfunction (CrCl<15 mL/min) |
| LWMH         | ACS, PCI, VTE | For ACS 1.5 mg/day if CrCl=20–50 mL/min | Avoid if CrCl<20 mL/min |
| Fondaparinux | 2.5 mg/day  
ACS, VTE |                                      |                                         |
| Fibrinolytic agents |                                  |                           |                                         |
antithrombotic therapy in clinical practice. Besides, as increasing age, low body weight, renal insufficiency, and comorbidities are powerful predictors of bleeding complications, higher incidences of complications and death as well as longer hospitalization have been observed in this particular group [8, 9]. Further, suboptimal platelet inhibition during treatment occurs more frequently in the elderly, which has been linked to a higher risk of stroke and adverse events [10]. Anticoagulants were still underused in real-world clinical practice, although the guidelines emphasize the importance of anticoagulation in the prevention of stroke and thromboembolism. Instead, antiplatelet agents are more commonly prescribed because of factors including combined diseases, age-related cognitive decline, and fear of bleeding [11–13].

As stated in the updated US Preventive Services Task Force recommendation, low-dose aspirin is recommended for primary prevention of CVD and colorectal cancer (CRC) in the adults aged 60–69 years, with 10% or more 10-year CVD risk and without increased bleeding risk [16]. However, for primary prevention in adults aged 70 years or older, insufficient evidence for aspirin use was established. In patients with diabetes mellitus, the 2015 AHA/ADA scientific statement suggests use of low-dose aspirin (75–162 mg/day) in those at high 10-year CVD risk (≥10%). In adults at intermediate CVD risk (5–10%), use of low-dose aspirin is also reasonable [17].

According to the meta-analysis of secondary prevention trials by the Antithrombotic Trialists’ Collaboration, aspirin significantly reduces the risk of serious cardiovascular events and stroke, with a nonsignificant increase in the risk of hemorrhagic stroke. An aspirin dosage of 75–100 mg/day is recommended in elderly patients without increased bleeding risk, as well as no allergy or contradictions to aspirin use [14].

To alleviate potential bleeding risk, the age-related reduced renal function, comorbidities, and polypharmacy should be carefully considered. Furthermore, evidence for patients older than 75 years is still lacking. In patients with higher bleeding risk than average, an H2 receptor antagonist or a proton pump inhibitor should be added to the regimen. Because of insufficient evidence in the Chinese population, all current regimens refer to European and US guidelines, while more suitable regimens in this population warrant further study [1, 18].

### Antiplatelet Drugs in the Elderly

#### Aspirin

The use of aspirin in primary prevention of cardiovascular disease (CVD) remains controversial. According to a meta-analysis performed by the Antithrombotic Trialists’ Collaboration [14], aspirin treatment mainly reduces the risk of nonfatal myocardial infarction, while the risk of major gastrointestinal and extracranial bleeding increase significantly. In the Japanese Primary Prevention Project, low-dose aspirin did not reduce the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction among Japanese elderly patients with atherosclerotic risk factors [15].
**P2Y$_{12}$ Receptor Antagonist**

P2Y$_{12}$ receptor antagonists, including clopidogrel, ticagrelor, and prasugrel, which irreversibly bind and inhibit platelet P2Y$_{12}$ receptors, are broadly prescribed in patients undergoing percutaneous coronary intervention (PCI) in combination with aspirin. A 75 mg/day maintenance dosage of clopidogrel is recommended in the elderly with acute coronary syndrome (ACS) or undergoing PCI. Clopidogrel is preferred in ACS patients at high bleeding risk. A loading dose is not recommended for patients older than 75 years. However, a small proportion of patients have an inadequate response to clopidogrel, correlated with crucial gene polymorphisms involved in the process of active metabolite generation [18].

The novel thienopyridine ticagrelor is favorable in elderly ACS patients at a dosage of 90 mg twice daily in the absence of contraindications, on the basis of the expert position article of the European Society of Cardiology Working Group on Thrombosis [1]. In the PLATO (Prospective Randomized Platelet Inhibition and Patient Outcomes) trial, clinical efficacy and safety of ticagrelor and clopidogrel in elderly ACS patients were compared. No significant differences between patients aged 75 years or older and patients younger than 75 years were observed in terms of the primary composite end point as well as major bleeding. However, dyspnea and ventricular pauses occurred more frequently during ticagrelor treatment [19]. Thus ticagrelor should be prescribed with caution in patients with advanced sinoatrial disease and with a history of asthma or chronic obstructive pulmonary disease (COPD).

In TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38), decreased rates of myocardial infarction and urgent target-vessel revascularization as well as higher risk of major bleeding were observed in patients receiving prasugrel [20, 21]. In the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial, the incidence of major bleeding and ischemic events were similar between lower-dose prasugrel and clopidogrel in patients aged 75 years or older [22]. Prasugrel (10 mg/day) might potentially increase bleeding risk in low-weight patients (<60 kg) and those with a history of stroke or transient ischemic attack (TIA). As a result, a lower dose (5 mg/day) is approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for patients aged 75 years or older. Prasugrel use should be avoided in patients with prior stroke or TIA, including intracerebral hemorrhage (ICH) [1, 18].

The GENERATIONS (Pharmacodynamic and Pharmacokinetic Study in Stable Coronary Artery Disease Patients) trial demonstrated that a lower dose of prasugrel in very elderly patients resulted in a lower incidence of poor responders than with clopidogrel, without higher mild bleeding risk [23]. Currently, several ongoing trials, including the POPular AGE study [24] and the Elderly-ACS 2 study [25] will provide more evidence for use of novel thienopyridines in elderly patients.

**Other Antiplatelet Agents**

Other antiplatelet agents, including vorapaxar and glycoprotein IIb/IIIa antagonists, should be cautiously used in the elderly, especially in those with reduced renal function. Use of vorapaxar, a potent selective antagonist of platelet protease-activated receptor 1, is contraindicated in patients with prior stroke, TIA, or ICH. Glycoprotein IIb/IIIa inhibitors could be considered for thrombotic complications. However, in patients older than 75 years, they are not recommended because of the potential increase in the risk of ICH. Abciximab should be avoided in hemodialysis patients and those with a history of any stroke within the past 2 years. Dose-adjusted tirofiban could be used in patients with severe renal failure (creatinine clearance less than 30 mL/min), but is inadvisable within 30 days in patients with ICH or ischemic stroke [1, 18].

**Anticoagulant Therapy in the Elderly**

**Vitamin K Antagonists**

The incidence of AF exceeds 10% in adults aged 80 years or older. In patients with AF and venous thromboembolism (VTE), anticoagulant therapy significantly reduces the risk of thrombosis-related events. As the elderly exhibit a higher incidence of bleeding complications during treatment with
warfarin, the conventional vitamin K antagonist (VKA), closer monitoring of the international normalized ratio (INR) and timely dose adjustment are required. Further, the narrow therapeutic window, the slow onset of action, more frequent diet or drug interactions, and interindividual variation limit its use [26].

The benefits of VKA treatment would not be concealed in the elderly by the relatively higher incidence of thrombosis-related events and bleeding. In the Loire Valley AF project, VKA treatment was associated with lower mortality in both patients aged 75 years or older and patients younger than 75 years, while the risk of major bleeding did not rise [27]. Similarly, another study in Chinese AF patients older than 80 years (n = 2339) demonstrated that warfarin therapy significantly reduced the incidence of ischemic stroke and death [5]. In the BAFTA trial, a lower incidence of ischemic events and hemorrhage was observed in elderly AF patients receiving warfarin when compared with aspirin. This evidence supports the use of warfarin in AF patients older than 75 years with indications for anticoagulation. In addition, VKAs are recommended for patients with a mechanical heart valve or VTE. In patients with severe renal dysfunction or even receiving hemodialysis, VKAs are preferred [28].

### Novel Oral Anticoagulants

In recent years, novel oral anticoagulants (NOACs), including dabigatran, rivaroxaban, and apixaban, have been approved for the prevention of stroke and systemic thromboembolism (SSE) in patients with AF or VTE in the United States and Europe. However, in China, only dabigatran and rivaroxaban have been approved in AF patients, while apixaban can be prescribed for VTE prophylaxis in patients undergoing hip or knee replacement. Although the meta-analysis of six phase III clinical trials involving 27,023 VTE patients revealed that NOACs had favorable efficacy and safety when compared with VKAs, the proportion of patients older than 80 years was only for 5% [29, 30].

The direct thrombin inhibitor dabigatran is mainly excreted through the kidney, and thus should be prescribed cautiously in patients with impaired renal function. In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study, dabigatran at 150 mg or 110 mg twice daily resulted in a similar reduction in the incidence of stroke and SSE when compared with warfarin. In terms of safety, both doses of dabigatran reduced bleeding risk in patients younger than 75 years in comparison with INR-adjusted warfarin. However, in patients older than 75 years, more extracranial bleeding was observed in patients who received both doses of dabigatran [8]. In the study by Chan et al. [31] with 571 AF patients aged 80 years or older, dabigatran (110 mg twice daily) was associated with lower ischemic stroke risk and similar ICH risk. Thus the European position article recommended a lower dose (110 mg twice daily) of dabigatran be considered in patients aged 75–79 years. The EMA approved the use of 110 mg dabigatran twice daily in AF patients older than 80 years. A tailored dose of dabigatran is also recommended in AF patients with impaired renal function and low weight (less than 60 kg) [1].

Direct factor Xa inhibitors include rivaroxaban, apixaban, and edoxaban. In the ARISTOTLE (Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, apixaban treatment resulted in a lower incidence of stroke, SSE and major bleeding, when compared with warfarin. Similar reduction in the rates of stroke and systemic embolism was exhibited in patients older than 75 years [32]. In the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial, apixaban treatment significantly reduced the incidence of stroke and SSE, with similar bleeding rates in comparison with aspirin. In patients older than 75 years, the tendency to reduce the incidence of stroke and SSE remained, with slight increase of bleeding risk [33]. The guidelines recommend apixaban at 5 mg/day in the treatment of nonvalvular AF and VTE. To mitigate bleeding risk, the FDA approved a tailored dose (2.5 mg/day) in patients with at least two of the following: older than 80 years, body weight less than 60 kg, serum creatinine level 1.5 mg/dL or higher [1].

In ROCKET-AF (The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), rivaroxaban
at 20 mg/day was associated with a lower rate of stroke and SSE, as well as similar bleeding incidence. In patients older than 75 years, a tendency toward higher bleeding risk was observed in rivaroxaban group. Current guidelines do not recommend any dose adjustment for age, but it should be used with caution in patients with reduced renal function [34].

In the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) trial, both doses of edoxaban resulted in similar effects on stroke and SSE reduction in patients older than 75 years at moderate to high thromboembolic risk, while the bleeding risks remained lower [35]. The guidelines do not recommend dose adjustment by age, but a lower dose of edoxaban (30 mg/day) should be used in patients with impaired renal function (creatinine clearance 15–50 mL/min).

It must be emphasized that there is still inadequate evidence for NOAC use in patients with severe renal dysfunction because patients with creatinine clearance less than 25–30 mL/min were excluded from these large-scale trials. Thus the guidelines do not support NOAC use in patients with severe renal dysfunction. Dabigatran use should be avoided in patients with creatinine clearance less than 30 mL/min. Use of rivaroxaban, apixaban, and edoxaban should be avoided in patients with creatinine clearance less than 15 mL/min [1, 36].

**Low Molecular Weight Heparin/ Unfractionated Heparin**

Intravenous antithrombotics, including unfractionated heparin (UFH), low molecular weight heparin (LMWH), and fondaparinux, are also extensively used in ACS patients. The ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis in Myocardial Infarction 25) trial compared enoxaparin and UFH in patients with ST-segment elevation myocardial infarction (STEMI). Enoxaparin was superior in reducing the incidence of death and nonfatal myocardial infarction in patients with better renal function. However, in patients with renal dysfunction, enoxaparin treatment increased the incidence of both major and minor bleeding [37].

In the OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators) trial, fondaparinux reduced the incidence of major bleeding significantly, and resulted in lower incidence of death, myocardial infarction, and stroke 30 days after PCI [38]. UFH and LMWH are recommended in patients with severe renal impairment, while dose adjustment according to age is required.

**Thrombolytic Therapy**

The optimal reperfusion strategy for elderly patients with STEMI is still controversial. In general, reperfusion treatment, including PCI or thrombolytic therapy, is considered superior to conservative treatment.

In the TRIANA (Thrombolysis Versus Primary Angioplasty for AMI in Elderly Patient) trial [39], patients older than 75 years with STEMI were enrolled, and a dramatic decrease in the incidence of recurrent ischemia was observed in patients who received PCI in comparison with fibrinolysis. Both groups showed a similar incidence of the primary end point, death, reinfarction and major bleeding. In the study by Renilla et al. [40], which included 182 STEMI patients aged 85 years or older, similar mortality rates were observed in the thrombolysis group and the primary PCI group, both superior to the mortality rate in the non-reperfusion treatment group.

The optimal dose of fibrinolytic agents has also aroused much concern. In the study by Solhpour et al. [41], the combination of reduced-dose fibrinolytic agents and urgent PCI resulted in lower 30-day mortality and earlier infarct artery patency. In the study by Armstrong et al. [42], tenecteplase dose reduction was associated with lower incidence of reinfarction, cardiogenic shock, ICH, and 30-day all-cause death. Thus the EMA approved a half-dose of tenecteplase in STEMI patients aged 75 years or older, and it is contraindicated in patients who have experienced ICH or ischemic stroke/TIA in the previous 6 months. Adjunctive antithrombotic agents should be used with caution, and a loading dose of clopidogrel is not recommended, to reduce the risk of ICH.
Strategies to Optimize Anti-thrombotic Therapy

Older age is associated with a higher incidence of thrombosis-related events, while antithrombotic therapy in the elderly brings about more bleeding complications, both posing great threats to overall mortality. As a result, balancing the benefits and harms as well as optimizing antithrombotic therapy is of paramount importance. To minimize the incidence of bleeding complications, anticoagulant dose adjustment according to body weight and renal function is required. Besides, paying more attention to patients at high bleeding risk is necessary, including those with a history of gastrointestinal ulcer or hemorrhage, combined use of anticoagulants, long-term NSAID/corticosteroid use, long-term alcohol use, gastroesophageal reflux disease, or *Helicobacter pylori* infection and those older than 65 years. Various scoring systems, including the HAS-BLED score and the CRUSADE score, are recommended for evaluation of bleeding risk [18].

Further, optimization of the duration of dual anti-platelet therapy (DAPT) also helps reduce the risk of bleeding complications. The 2016 American College of Cardiology/American Heart Association guidelines recommended the use of the DAPT score to evaluate the optimal DAPT duration after PCI, taking into account lots of variables, including old age, cigarette use, diabetes, and previous myocardial infarction or PCI. In patients with a high DAPT score (≥2), prolonged DAPT duration might be beneficial [43].

A small proportion of patients receiving PCI were undergoing long-term anticoagulant treatment, because of various indications, including AF, mechanical heart valves, and VTE. Triple therapy (combination of anticoagulants and antiplatelet agents) might be performed, and closer monitoring is crucial in minimizing the incidence of bleeding events in the elderly. In patients receiving warfarin with aspirin or clopidogrel, it is much safer to maintain an INR within 2.0–2.5. Clopidogrel is preferred over novel thienopyridines whenever needed. Besides, lower doses of antithrombotics are advisable. Proton pump inhibitors are routinely recommended [18, 36]. The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial revealed the superiority of double therapy (clopidogrel plus warfarin) in terms of bleeding complications, while the incidence of thrombosis did not increase when compared with triple therapy [44]. Thus in elderly patients with indications for combination of anticoagulants and antiplatelet agents, double therapy is preferred, and individual risk factors should be considered.

In addition, it might be fair to evaluate antiplatelet responses in patients older than 75 years. Our previous study in elderly patients demonstrated that measurements of arachidonic acid–induced platelet aggregation possibly provide hints for predicting gastrointestinal discomfort and bleeding [45]. In study by Tang et al. [46] supported the combination of CYP2C19 genotype and ADP-induced platelet inhibition in predicting adverse cardiovascular events in Chinese patients receiving clopidogrel. Although platelet function tests are not routinely recommended in established guidelines, risk stratification via appropriate use of platelet function tests might be beneficial in optimizing antithrombotic therapy as well as reducing the incidence of adverse effects in the elderly, especially in older than than 75 years. According to the recent expert consensus on antiplatelet therapy in China, it is reasonable to use point-of-care platelet function tests or light transmission aggregometry in patients at high thrombotic risk [47].

Routine monitoring of NOACs is not recommended in the guidelines, while several tests might help define the therapeutic range of NOACs. The activated partial thromboplastin time and thrombin time are used to evaluate response to dabigatran, while the prothrombin time and anti-factor Xa chromogenic assays are recommended for rivaroxaban and apixaban [48, 49].

Summary

To sum up, to minimize bleeding risk in the elderly population, the benefits and harms of antithrombotic drugs should be carefully evaluated. Further, age, renal function, comorbidities, life expectancy, and willingness of every individual patient should also be taken into account. Guidelines and expert consensus might give constructive recommendations; however, it is of great importance to initiate
and optimize individual treatment. Large-scale randomized controlled trials are still required, especially in Chinese elderly patients.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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