

## Short Communication

# Antithrombotic Therapy: Focus on the Elderly

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In recent years, the elderly population grows rapidly, and it's estimated that by 2050, the worldwide population older than 60 years will reach about 2 billion. Advanced age is an important risk for coronary artery disease, stroke, atrial fibrillation in the general population, with increased mortality and worse outcomes [1,2]. Besides, although antithrombotic therapy significantly reduced the risk of ischemic events, age-dependent increased bleeding risk cannot be ignored. As a result, how to balance benefits against potential harms related to antithrombotic therapy aroused much concern. Here, we briefly summarize current evidence and update on guidelines regarding antithrombotic therapy in the elderly population [3].

## Particularity of the Elderly

A series of changes occurred with the increase of age, including fat redistribution, declined gastrointestinal absorption, decreased hepatic blood flow and renal function, which lead to slower rate of drug absorption, increased bioavailability and delayed elimination. Besides, the incidence of co-morbidities is higher in the elderly, which means multiple drugs might be prescribed. As a result, adverse drug-drug interactions appeared more frequently in this particular population. Furthermore, hemodynamic changes also occurred in the elderly. For example, increased levels of fibrinogen, factors VII, factors VIII, plasminogen activator inhibitor-1 and protein C contribute to the establishment of a pro-thrombotic environment. Last but not least, chronic inflammations and endothelial dysfunctions, often observed in the elderly, play important roles in thrombosis [4-6].

According to a recent epidemiological investigation, patients older than 85 years already accounted for nearly 17 percent of the overall stroke population. In patients admitted for Acute Coronary Syndrome (ACS), over one third was older than 75 years, while two thirds who died of myocardial infarction were older than 75 years [1,7]. Although antithrombotic therapy has been proved to significantly reduce stroke risk and mortality [8], several problems still existed. For one thing, the elderly population tends to be excluded in large-scale Randomized Controlled Trials (RCTs). Due to the lack of sufficient evidence, it became more difficult to balance benefits and risks in clinical practice. For another, higher incidence of complications and mortality, as well as longer hospitalization was observed in this particular group and therapeutic window of antithrombotic therapy is rather narrow [9].

## Strategies for Antithrombotic Therapy in the Elderly

The use of aspirin in CVD primary prevention remains a controversial topic. According to the recent update on 2016 U.S. Preventive Services Task Force (USPSTF) recommendation statement, low dose aspirin is recommended for primary prevention of Cardiovascular Disease (CVD) and Colorectal Cancer (CRC) in the adults aged 60-69 years [10]. However, low-dose aspirin (100mg/d) did not significantly reduce the risk of the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction among Japanese patients 60 years or older with atherosclerotic risk factors in Japanese Primary prevention Project (JPPP) [11].

In terms of secondary prevention of vascular events, a dose of 75-100mg/d aspirin was recommended to the elderly patients without increased bleeding risk, as well as no allergy/contradictions to aspirin. The potential adverse effect of long-term antiplatelet treatment is supposed to be considered cautiously. Furthermore, evidence for patients older than 75 years still lacked. In patients with higher bleeding risk than average (previous peptic ulcer/bleeding, combined anticoagulants, aged more than 65 years), H2 receptor antagonist or Proton Pump Inhibitors (PPIs) should be added to the regimen.

It must be noted that due to the insufficient evidence in Chinese population, all current regimens referred to European and US guidelines, while more suitable regimens in this population warrant further study [10,12,13].

## Antiplatelet Drugs in the Elderly

Higher incidence of antithrombotic/catheter related complications occurred in the elderly. In order to mitigate potential bleeding risk, factors including weight, renal functions, and co-morbidities should be taken into consideration.

Aspirin was widely used in the secondary prevention of vascular events, while a dose of 75-100mg/d is recommended in the elderly. Thienopyridines, including clopidogrel, ticagrelor and prasugrel, which irreversibly bind and inhibit platelet P2Y<sub>12</sub> receptors, were widely prescribed in patients undergoing Percutaneous Intervention (PCI). A 75mg/d maintenance dose of clopidogrel is recommended to the elderly ACS/PCI patients. For ACS patients with high bleeding risk, clopidogrel is preferred. Loading dose of clopidogrel is not recommended in patients older than 75 years. The novel thienopyridine, ticagrelor is favorable in ACS patients at a dose of 90mg bid. However, it might increase bleeding and potential risk of dyspnea. Prasugrel potentially increase bleeding risk in patients older than 75 years, low weight (<60kg) and with previous history of stroke/TIA. Vorapaxar and GP IIb/IIIa antagonist should be cautiously used in the elderly, especially in those with declined renal function [1,12,14].

Antiplatelet monitoring is not recommended in the guideline, partly due to poor agreement among various platelet function tests and inadequate correlation with clinical outcomes. However, in order to improve antiplatelet efficacy and safety in patients older than 75 years, it's reasonable to develop useful tests in evaluating antiplatelet responses. Our previous study in elderly CAD patients found that measuring arachidonic acid induced platelet Aggregation (Ara) possibly provide hints in predicting gastrointestinal discomfort and bleeding [15].

## Anticoagulant Therapy in the Elderly

In patients with Atrial Fibrillation (AF) and Venous Thromboembolism (VTE), anticoagulant therapy significantly reduced the risk of stroke and systemic embolism. The conventional Vitamin K Antagonist (VKA) warfarin need adjusted doses and closer monitoring of INR in the elderly. Warfarin is also recommended in patients with mechanical heart valve. However, narrow therapeutic window, food-drug interaction, as well as inter-individual variation limited its use.

In recent years, Novel Anticoagulants (NOACs) including dabigatran, rivaroxaban, apixaban were approved in the prevention of stroke in AF patients. Although the meta-analysis of six phase III clinical trials considering NOACs proved favorable efficacy and safety, the proportion of patients older than 80 years in these trials only accounts 5 percent. In RE-LY study, dabigatran 110mg bid showed similar bleeding risk when compared with INR-adjusted warfarin, while the bleeding risk related to 150mg bid dabigatran proved to be higher [16]. What's more, in a Danish AF study, increased risk of bleeding and thromboembolism were observed in patients aged more than 80 years, with liver/renal disease and previous bleeding history. A tailored dose of NOACs is recommended in patients older than 80 years and low weight (less than 60 kg) or with declined renal function [1,17]. UFH and LMWH can be used in severe renal impairment, while dose adjustment according to age is needed.

Routine monitoring of NOACs is not recommended in guidelines. As specific antidotes against NOACs are not available, several tests might help define therapeutic range of NOACs. The Activated Partial Thromboplastin Time (APTT) and Thrombin Time (TT) are used to evaluate response to dabigatran, while Prothrombin Time (PT) and anti-factor Xa chromogenic assays are recommended for rivaroxaban and apixaban [18, 19].

## Summary

To sum up, in order to minimize bleeding risk in the elderly population, benefits and harms of those antithrombotic drugs are supposed to be carefully evaluated. What's more, age, renal function, co-morbidities, life expectancy, willingness of every individual patient should also be considered. Guidelines/expert consensus might give constructive recommendations, however, it's of great importance to initiate and optimize individual treatment. Large-scale randomized controlled trials are still needed, especially in Chinese elderly patients.

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