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STATE-OF-THE-ART PAPERS

Antithrombotic Therapy in the Elderly

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Antithrombotic therapy represents the mainstay of treatment for prevention of recurrent ischemic events in patients with atherothrombotic disease processes. Although the benefits of antithrombotic pharmacotherapy in the elderly are well established, the elderly are generally more vulnerable to the adverse effects of antithrombotic drugs. Such higher vulnerability may be related to distinct pharmacokinetic and pharmacodynamic responses in the late age of life, during which drug–drug interactions due to polypharmacy further enhance the risk of adverse effects associated with the use of antithrombotic agents. Given that the prevalence of atherothrombotic disease, as well as diseases with thromboembolic potential, increases exponentially with age and that the elderly population is in continuous growth, understanding strategies of antithrombotic management in these patients is of key importance. The present paper provides an overview of the current available evidence on the use of antithrombotic therapy in elderly patients with the primary focus on treatment of coronary artery disease. (J Am Coll Cardiol 2010;56:1683–92) © 2010 by the American College of Cardiology Foundation

Aging is a major cardiovascular risk factor, and coronary artery disease (CAD) is the most common cause of death in the elderly (1). Importantly, due to increasing longevity and declining fertility, the geriatric population is rapidly expanding in industrialized countries. In 2020, the proportion of the population age 80 years and above is expected to range between 3.7% and 7.5% (2). Antithrombotic therapy represents a mainstay of treatment in patients with CAD. Although the benefits of pharmacotherapy in elderly patients with CAD are well established, the elderly are generally more vulnerable to the adverse effects of antithrombotic drugs. This may be further exacerbated by the concomitant presence of other disease processes at high risk for thromboembolic potential, such as atrial fibrillation, which also require dedicated antithrombotic drug regimens. Physicians are challenged with peculiar pharmacokinetic and pharmacodynamic mechanisms of altered drug response in the late age of life, which are aggravated by other issues, including multimorbidity and polypharmacy. Therefore, understanding whether a drug should or should not be prescribed as well as individualizing dosage regimens is pivotal to balance the safety and efficacy profiles of antithrombotic drugs when used either solely or in combination. The present paper provides an overview of the currently available evidence on the use of antithrombotic therapy in elderly patients, with the primary focus on treatment of CAD manifestations.

Biological and Pharmacological Considerations in the Elderly

Age-dependent alterations of hemostasis in the elderly are summarized in Table 1. Overall, the elderly experience a shift of the hemostatic balance towards increased clotting and decreased fibrinolysis (3). Aging may also lead to changes intrinsic to the platelet that are associated with increased platelet reactivity. Increased platelet activity has been correlated with a higher content of platelet phospholipids, suggesting an age-related increase in platelet transmembrane signaling or second messenger accumulation (4). Although hemostatic factors vary significantly with age, additional factors such as blood stasis and vessel wall degeneration with endothelial dysfunction play a key role and contribute to increased platelet activation and arterial thrombosis in the elderly (5–7).

Several pharmacological aspects need to be considered in managing antithrombotic therapies in elderly people. These include age-related changes in absorption, distribution, metabolism, and clearance of antithrombotic drugs (Fig. 1). Since polypharmacy is common in elderly patients, this exposes them to a greater risk of adverse drug–drug interactions. In addition to pharmacokinetics, age-related changes in pharmacodynamics may also occur, leading to a reduction of homeostatic mechanisms (3,8). This implies that drug reactions may be stronger or drug effects may be

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Abbreviations and Acronyms

ACS = acute coronary syndrome
CAD = coronary artery disease
GP = glycoprotein
INR = international normalized ratio
LMWH = low molecular weight heparin
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction
UFH = unfractionated heparin

less attenuated. Overall, these pharmacokinetic and pharmacodynamic considerations may, therefore, impact the safety and efficacy of antithrombotic treatment in the elderly, as described in the following text.

Antithrombotic Therapy in the Elderly: General Considerations

Currently, there is no general consensus about the definition of *elderly*, and therefore, to generalize findings from different clinical trials is often problematic. In addition, older patients are frequently excluded from cardiovascular clinical trials. Since current treatment guidelines have been developed on the basis of observations from predominantly younger populations and mainly provide general considerations that are applicable to older patients, the management and outcomes of this subgroup is often uncertain. Adding to the paucity of evidence-based data, safety concerns and economic disparities also often result in a substantial underuse of antithrombotic therapies in older patients (9,10). Further, excess dosing of antithrombotic drugs occurs more frequently in vulnerable populations, including the elderly (11).

Antiplatelet Therapy

Aspirin. Although a clear excess of adverse events has been shown with aspirin even at a lower dosage in studies involving elderly patients (12,13), very few primary or secondary prevention trials have specifically addressed the aspirin benefit-risk ratio in the elderly population, and available data in old patients are frequently derived from large clinical trials in which data are stratified by age. The magnitude of the absolute benefits and risks of primary prevention with aspirin therapy in specific groups, such as the elderly, is not fully known. In fact, although patients with high baseline thrombotic risk are more likely to benefit from aspirin, bleeding complications including stroke and gastrointestinal bleeding are more common in the elderly and might counteract the small benefit in those at lower risk. Therefore, whether aspirin should be prescribed in primary prevention remains controversial, and a risk-based approach to aspirin prescription has been recommended by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines and the U.S. Preventive Services Task Force (14,15).

In a meta-analysis from the Antiplatelet Trialists' Collaboration, which pooled data from 195 trials involving more than 135,000 patients, aspirin use for secondary prevention was associated with a 22% reduction in the risk of the combined end point of vascular death, myocardial infarction, and stroke (16). This relative risk reduction was shown to be similar among age groups (19.4% vs. 23.1% in patients older and younger than 65 years of age, respectively), resulting in a greater absolute benefit of aspirin among the elderly (4.5% vs. 3.3%), who have a higher than average risk of vascular events. Overall, the odds of major extracranial bleeding with aspirin was 1.6, but this safety issue was far offset by the reduction observed in the ischemic end point across all the categories of high risk. Data support that low-dose aspirin is as effective as higher doses in preventing ischemic events but is also associated with a lower rate of major bleeding and an improved net efficacy to safety balance (17). The ACC/AHA guidelines, which are applicable to elderly patients, recommend the use of aspirin, in the absence of contraindications, in patients with chronic stable angina (18), acute coronary syndrome (ACS), or undergoing percutaneous coronary intervention (PCI) (19,20). However, the rate of use of aspirin still tends to be lower in older people with established atherosclerotic disease (21).

Overall, data support the use of aspirin for the secondary prevention of vascular events in elderly patients. Although current guidelines do not recommend dosage modifications based on age, a 75- to 150-mg dose of aspirin has shown to be as effective as higher dosages with a lower risk of gastrointestinal toxicity and bleeding, outlining the potential for a relevant role of this dosing reduction in elderly patients, particularly when requiring combination therapy with clopidogrel. Evidence supporting aspirin prescription for primary prevention in elderly is less conclusive, as the possibility of a smaller benefit than that observed in secondary prevention might not counterbalance the risk of bleeding

Table 1 Age-Dependent Alterations of Hemostasis in the Elderly

Coagulation proteins	
Fibrinogen	↑
Factor V	↑
Factor VII	↑
Factor VIII	↑
Factor IX	↑
Factor XIII	↑
High-molecular weight kininogen	↑
Prekallikrein levels	↑
Anticoagulant proteins	
Antithrombin III	↓♂; ↑♀
Protein C	=♂; ↑♀
Protein S	=♂; ↑♀
Tissue factor pathway inhibitor	↓♂; ↑♀
Fibrinolytic proteins	
Plasmin	↓
Plasminogen activator inhibitor-1	↑
D-dimer	↑

Arrows ↑ and ↓ indicate an increase and reduction, respectively, of age-related variations in the serum levels of the proteins involved in hemostasis; equal sign (=) indicates no change. Sex-related differences are also shown. Adapted, with permission, from Franchini (3).