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
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

<table>
<thead>
<tr>
<th>Coagulation proteins</th>
<th>Factor V</th>
<th>Factor VII</th>
<th>Factor VIII</th>
<th>Factor IX</th>
<th>Factor XIII</th>
<th>High-molecular weight kininogen</th>
<th>Prekallikrein levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Anticoagulant proteins</td>
<td>Antithrombin III</td>
<td>↓d; ↑↑</td>
<td>Protein C</td>
<td>=d; ↑↑</td>
<td>Protein S</td>
<td>=d; ↑↑</td>
<td>Tissue factor pathway inhibitor</td>
</tr>
<tr>
<td>Fibrinolytic proteins</td>
<td>Plasmin</td>
<td>↓</td>
<td>Plasminogen activator inhibitor-1</td>
<td>↑</td>
<td>D-dimer</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

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).
events. This emphasizes the need for specifically designed randomized trials of aspirin for primary prevention in subgroups of patients at high risk of bleeding and thrombotic complications, such as the elderly.

Adenosine diphosphate P2Y12 receptor antagonists. Current guidelines recommend clopidogrel (a second-generation thienopyridine) as an alternative in aspirin-intolerant patients for secondary prevention of recurrent ischemic events (22). Clopidogrel has largely replaced ticlopidine (a first-generation thienopyridine), due to its more favorable safety profile (23). In patients presenting with an ACS and undergoing PCI, guidelines recommend the use of clopidogrel in addition to aspirin (19,20). No dose adjustment based on age is required for clopidogrel. Although new P2Y12-inhibiting drugs are on the horizon, clopidogrel is the most studied and utilized in clinical practice. In the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial, the combination of clopidogrel and aspirin was associated with a 20% relative reduction in the combined ischemic end point (composite of cardiovascular death, nonfatal myocardial infarction, or stroke) and a 38% relative increase of major bleeding at 1 year in the overall trial population, as compared with aspirin alone (24). Compared with younger patients, those older than 65 years of age showed similar absolute reduction (2.0% vs. 2.2%) and a smaller relative reduction (13.1% vs. 28.9%) of the combined ischemic end point with the addition of clopidogrel. Clopidogrel, however, was shown to be significantly more effective than placebo in both groups. Notably, certain high-risk features that have been associated with a greater benefit from clopidogrel, such as a high Thrombolysis In Myocardial Infarction (TIMI) risk score, prior revascularization, and need for PCI, are frequent among older patients (25,26).

In the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial, the more potent P2Y12 inhibitor prasugrel (a third-generation thienopyridine) was associated with a 19% relative risk reduction in ischemic events compared with clopidogrel in high-risk ACS patients undergoing PCI (27). Although prasugrel was associated with a 32% increased risk of major bleeding, the net clinical benefit was still in favor of prasugrel in the overall population. Post-hoc analysis identified patients at higher risk in whom prasugrel was associated with harm, such as patients with a prior transient ischemic attack or stroke, and those in whom there was no net clinical benefit as the ischemic benefit was offset by the risk of bleeding, including elderly (age ≥75 years) and low weight (≤60 kg) patients. In elderly patients, the net clinical benefit for the use of prasugrel versus clopidogrel was 0.99 (95% confidence interval [CI]: 0.81 to 1.21, p = 0.92). In this cohort, the rates of TIMI major or minor bleeding not related to coronary artery bypass grafting were 9.0% and 6.9% in the prasugrel and clopidogrel groups, respectively, whereas fatal bleeding occurred in 1.0% of patients treated with prasugrel and 0.1% of patients treated with clopidogrel. Due to these findings, the use of prasugrel in patients ≥75 years of age is generally not recommended. However, according to the U.S. Food and Drug Administration (FDA), a 10-mg maintenance dose of prasugrel may still be considered for use in patients ≥75 years of age in the absence of contraindications (prior transient ischemic attack/stroke or active bleeding) if high-risk features, such as either diabetes or
a past history of myocardial infarction, are present, where its effect appears to be greater than the risk of bleeding. The effectiveness of lower maintenance dose (5 mg) in the elderly is currently under investigation (NCT00699998).

Clinical data on ticagrelor, the first member of a new class of reversible P2Y12 receptor antagonists called CPTP (CycloPentylTriazoloPyrimidine), have been recently published (28). In the PLATO (Platelet Inhibition and Patient Outcomes) trial, ticagrelor was associated with a 16% reduction in ischemic events compared with clopidogrel in patients with ST-segment elevation ACS intended for primary PCI or with non–ST-segment elevation ACS intended for an invasive or medical approach (28). There were no differences in terms of bleeding according to different definitions among ticagrelor and clopidogrel groups, but ticagrelor was associated with a higher rate of major bleeding not related to coronary artery bypass grafting, including more cases of fatal intracranial bleeding. Compared with younger patients, the group of patients older than 65 years of age showed greater absolute (2.8% vs. 1.3%) and relative reduction (17.0% vs. 15.0%) of the ischemic end point with the use of ticagrelor, although ticagrelor was shown to be significantly more effective than clopidogrel in both groups. However, patients older than 75 years of age showed a similar absolute reduction (1.5% vs. 1.8%) and a smaller relative reduction (6% vs. 18%) than those younger. In this group, ticagrelor was not shown to be significantly more effective than clopidogrel. No evidence of increased risk of major bleeding was noted across multiple groups of patients stratified by age. Ticagrelor is still not approved for clinical use.

Based on the foregoing, clopidogrel is the current standard of choice for antiplatelet therapy in combination with aspirin in elderly patients, with no dose adjustment required based on age. Prasugrel is currently not recommended in patients >75 years of age, unless the patient has a history of diabetes or prior history of myocardial infarction in which the individual risk of bleeding is offset by the increased risk of thrombotic complications. Clinical testing with a reduced dose of prasugrel is ongoing and may lead to changes in current recommendations. No specific recommendations are yet available for ticagrelor.

**Intravenous glycoprotein (GP) IIb/IIIa inhibitors.** The ACC/AHA guidelines recommend the use of GP IIb/IIIa inhibitors on top of aspirin and heparin in patients in whom PCI is planned, without modification based on age (19). However, the bleeding risk in the elderly with these potent platelet-inhibiting agents remains a major concern. Three types of GP IIb/IIIa inhibitors are currently approved for clinical use (abciximab, eptifibatide, and tirofiban). Dosing adjustment based on creatinine clearance is recommended only for small-molecule GP IIb/IIIa inhibitors (tirofiban and eptifibatide) which are renally cleared (19).

A subanalysis of the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial showed that routine abciximab administration, although safe, was not of major benefit in elderly patients with acute myocardial infarction undergoing primary PCI (29). Similarly, data from the ISAR–REACT 2 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) trial have suggested that abciximab as adjunctive therapy in the context of PCI may be of lesser benefit in elderly patients with non–ST-segment elevation ACS (30). An age subgroup analysis from the PURSUIT (Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) trial showed that bleeding with eptifibatide was most notable (71.3% increased relative risk) in patients older than 80 years of age, a subgroup also experiencing both absolute and relative increase in the rate of death or myocardial infarction at 30 days with this strategy (31). In the ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) trial, patients older than 65 years of age demonstrated a greater absolute (7.2% vs. 1.3%) and relative (52.6% vs. 16%) benefit of eptifibatide in reducing the combined end point of death, myocardial infarction, or revascularization (32). Since this trial excluded patients with renal failure, this observation stresses the importance of patient selection in the balance of risk and benefit. Similarly, the PRISM (Platelet Receptor Inhibition in Ischemic Syndrome Management) and the PRISM-PLUS (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) trials, assessing the safety and efficacy of tirofiban, excluded patients with a creatinine level >2.5 mg/dl (33,34). In these trials, the treatment effect with tirofiban was similar between younger and older patients. A meta-analysis of 6 trials that evaluated the existence of a class effect showed that the benefit of GP IIb/IIIa administration in ACS patients declined with advancing age, with a 4% nonsignificant treatment effect observed in patients >70 years of age and 62% increased risk of major bleeding (35).

The aforementioned data, in aggregate, outline that the relative benefit and harm of GP IIb/IIIa inhibitor use varies across age strata, with elderly patients experiencing lower efficacy and disproportionate rates of bleeding compared with younger patients. These unfavorable outcomes may be improved by careful patient selection and GP IIb/IIIa inhibitor avoidance in patients who do not require PCI. Importantly, estimation of creatinine clearance and weight should be strictly recommended to avoid overdosing, particularly in the elderly. Dose adjustment is recommended for eptifibatide and tirofiban in patients with poor renal function. In elderly patients receiving GP IIb/IIIa inhibitors, the number of antithrombotic drugs used should be balanced against the individual risk of thrombotic and bleeding complications.

**Anticoagulant Therapy**

**Indirect thrombin inhibitors.** Current guidelines recommend the use of antithrombin therapy in patients with ACS.
and undergoing PCI (19,20). Age-specific dose adjustment in infusion is currently recommended for enoxaparin. The only trial comparing antithrombin therapy versus placebo and reporting age subgroup data was the FRISC II (Fragmin and Fast Revascularization during InStability in Coronary artery disease) trial, but it did not enroll patients ≥75 years of age (36). In this study, there was a greater absolute (1.9% vs. 0.8%) and relative (18.4% vs. 16%) reduction in events with dalteparin in patients ≥65 years of age than in those <65 years of age. A large observational study of heparin use in elderly patients failed to demonstrate a benefit in reducing the 30-day rates of mortality (37).

Trials that directly compared low molecular weight heparin (LMWH) and unfractionated heparin (UFH) provided heterogeneous results, possibly as a reflection of different heparins, dose regimens, populations, study designs, and concomitant therapies. In addition, in the single trials, age subgroup data on the efficacy and safety of LMWH and UFH are generally poorly reported. In the A to Z (38) trial, patients ≥65 years of age were more likely to benefit with the usage of enoxaparin than patients <65 years of age as compared with UFH. An age subgroup analysis of the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial showed similar efficacy but a consistent trend toward more bleeding and transfusion rates in older patients with non–ST-segment elevation ACS treated with enoxaparin as compared with those treated with UFH (39).

Overall, there is a considerable lack of data to draw definitive conclusions about the safety and efficacy of treatment with heparin in the elderly population. Elderly individuals are prone to bleeding complications and more likely to have less lean body mass and age-related renal impairment, conditions that are known to be associated with overdosing. Current guidelines emphasize a dose reduction for enoxaparin based on age in the setting of ST-segment elevation myocardial infarction (STEMI) and in patients with impaired renal function.

Direct thrombin inhibitors. Direct thrombin inhibitors have some advantages over the heparins, such as lack of dependence on plasma protein, which results in a more predictable response and makes them very attractive for use in the elderly. Bivalirudin has a Class Ib recommendation in the guidelines for the management of non–ST-segment elevation ACS (19), whereas PCI guidelines recommend bivalirudin as a Class IIa alternative to UFH and GP IIb/IIIa antagonists in low-risk patients undergoing elective PCI (20). Bivalirudin has also gained a Class Ib recommendation as a supportive measure for primary PCI (20). A pre-specified age subgroup analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) study conducted in non–ST-segment elevation ACS patients has recently demonstrated that although there were no significant differences in efficacy, the benefit of bivalirudin in terms of absolute reduction in bleeding events is most pronounced in patients ≥75 years of age (40). The positive impact of bivalirudin usage on clinical outcomes in nonagenarians undergoing PCI has also been reported (41). Argatroban, a direct thrombin inhibitor that has reduced clearance in elderly versus younger volunteers, has shown promising results when used for thromboprophylaxis or treatment in heparin-induced thrombocytopenia in elderly patients (42) or patients with impaired renal function (43).

In summary, direct thrombin inhibitors, in particular bivalirudin in patients with ACS/PCI have shown favorable safety profiles in randomized trials, making these drugs very attractive for use in the elderly. However, further clinical testing is needed to clarify the role of these drugs as the preferred anticoagulation strategy for older patients in clinical practice. Dose adjustment and anticoagulant status monitoring is recommended for bivalirudin in patients with poor renal function.

**Factor Xa inhibitors.** In patients older than 65 years of age enrolled in the OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial, fondaparinux demonstrated a nonsignificant benefit over enoxaparin for the combined end point of death, myocardial infarction, or refractory ischemia (44). A significantly better safety profile was seen independently from age, but the elderly showed a greater absolute (2.8% vs. 0.7%) and relative (50.9% vs. 33.3%) reduction of bleeding than younger patients. Patients with renal dysfunction also showed a marked benefit as a consequence of lower rates of bleeding (45), although fondaparinux should be avoided in patients with severe renal impairment. In summary, treatment with fondaparinux is associated with similar efficacy in reducing ischemic events but less bleeding than LMWH. This feature makes fondaparinux an appealing treatment strategy in the elderly, but more specific data on this subgroup are needed.

**Oral Anticoagulants**

Guidelines recommend oral anticoagulant therapy for pulmonary embolism, atrial fibrillation, mechanical heart valve, and valvular heart disease (46), morbidities that are commonly seen in the elderly population. However, there are concerns that elderly individuals may be subject to a greater risk of hemorrhagic complications accompanying the use of warfarin or other coumarins. The increased risk of developing atrial fibrillation as well as CAD with age further enhances these concerns. In the large REACH (REduction of Atherothrombosis for Continued Health) registry, the prevalence of atrial fibrillation in patients age ≥45 years with CAD was 12.5% and patients with both CAD and atrial fibrillation were on average 5 years older than those presenting with CAD alone (47). Schemes developed to stratify the risk of ischemic stroke in patients with atrial fibrillation, such as the CHADS2 (Cardiac Failure, Hypertension, Age, Diabetes, Stroke [Doubled]) score, may be helpful in identifying patients with CAD who benefit most from oral anticoagulation (48).
In general, treatment with vitamin K antagonists under careful monitoring is associated with a 0.3% to 0.5% increased risk of major bleeding per year compared with controls (49). These rates may be higher in routine clinical practice, taking into account that data mainly derive from younger cohorts than those observed in real life. In particular, there is a tendency towards a 2- to 3-fold increase in bleeding and intracranial hemorrhages among elderly patients (49,50). In addition, physicians are reluctant to prescribe warfarin in elderly patients deemed at high risk of falls, due to a 4-fold increased risk of traumatic intracranial hemorrhage compared with other patients (51). These issues may underline possible explanations for the substantial underutilization of vitamin K antagonists in the elderly population (52). However, even if elderly individuals have characteristics that may place them at higher risk for bleeding, they also have characteristics that make them more likely to benefit (53). Importantly, in the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) trial, a randomized comparison of warfarin versus aspirin in 973 patients with atrial fibrillation age $\geq$75 years, the yearly risk of the combined primary end point of stroke, intracranial hemorrhage, or clinically significant embolism was 1.8% in patients who received warfarin and 3.8% in those who received aspirin (relative risk: 0.48, 95% CI: 0.28 to 0.80, $p = 0.003$) (54).

The dose of oral anticoagulants required to maintain a therapeutic range expressed as the international normalized ratio (INR) for patients over 60 years of age decreases with increasing age, possibly because of a reduction in the clearance of warfarin with age (55–58). Overall, in elderly patients, the initial dose of warfarin should not exceed 5 mg, or even less in patients with a high risk of bleeding, those undernourished, those who have liver disease, and those who have undergone heart valve replacement surgery (59). Other factors that may influence the response to anticoagulation in elderly patients include the potential for a greater number of other medical conditions and/or concurrent drug use (57). Consequently, it is advisable to monitor older patients more frequently in order to maximize their time in the therapeutically relevant range (60). Sex also influences dose, with women requiring less warfarin to maintain a therapeutic INR than men at an equivalent age (55). A role for genetic testing in determining the optimal dosage of warfarin has been advocated (61). Various models for estimating the risk of major bleeding in patients on vitamin K antagonists have been developed based on identification of independent risk factors, including age (62–65). These predictive models may be an aid in clinical decision-making for long-term management of anticoagulant therapy (Table 2).

The combination of aspirin, thienopyridines derivatives, and oral anticoagulation (“triple therapy”) is often used in patients with permanent atrial fibrillation who undergo PCI, particularly when treated with a drug-eluting stent. However, prolonged treatment with a combination of warfarin, aspirin, and clopidogrel has shown to be associated with a 4- to 5-fold increased risk of bleeding and/or need for transfusion at 6 months and a 6- to 8-fold increased risk at 12 months (66,67). Although using a lower dose of aspirin (<100 mg) and maintaining an INR within the lower therapeutic range (INR: 2.0 to 2.5) can reduce the risk of bleeding, definitive conclusions cannot be made as dedicated studies in the elderly are either lacking or underpowered (20,68). Therefore, “triple therapy” should be prescribed with caution, and drug-eluting stents should be used in a more limited manner, particularly in elderly patients undergoing PCI who also require oral anticoagulation. These findings underscore the need for identifying oral anticoagulants with a more favorable safety profile than vitamin K antagonists. The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial recently compared the effects of warfarin in reducing the risk of stroke or systemic embolism with those of 2 fixed doses of dabigatran in 18,113 patients with atrial fibrillation (69).

Dabigatran is an oral, direct, competitive thrombin inhibitor that is administered twice daily and does not require regular monitoring. Both dabigatran doses (110 mg twice daily and 150 mg twice daily) were noninferior to warfarin with respect to the primary efficacy outcome. Moreover, the 150-mg dose of dabigatran was shown to be superior to warfarin with respect to the primary end point, and similar in terms of major bleeding risk, whereas the 110-mg dose was superior to warfarin with respect to the safety outcome. Overall, given the increased risk of developing atrial fibrillation with age, the safety profile of dabigatran may represent an attractive alternative to vitamin K antagonists.

In summary, vitamin K antagonists have shown a proven benefit in reducing thromboembolic complications in patients with atrial fibrillation, mechanical valves, and pulmonary embolism, but they are underutilized among elderly patients, who face the highest ischemic risk. Strategies to decrease the bleeding risk need to be aggressively implemented in the elderly. These include control of blood pressure, interventions to reduce falls, careful monitoring of INR, vigilant management of excessive anticoagulation, and use of predictive models. The benefit-risk ratio of triple antithrombotic therapy compared with the combination of aspirin and clopidogrel cannot be precisely established in the elderly due to lack of consistent information. Indeed, novel oral anticoagulants with a better safety profile than vitamin K antagonists, such as dabigatran, may represent promising agents in the aging population with atrial fibrillation.

**Fibrinolytic Therapy**

Although the best reperfusion strategy for elderly STEMI patients warrants further investigation, general agreement exists that eligible elderly STEMI patients who receive reperfusion therapy have a lower risk of death than those who receive no reperfusion (70). Bleeding complications, in particular intracranial hemorrhage, represent the major concern with fibrinolytic therapy. Importantly, several in-
<table>
<thead>
<tr>
<th>Bleeding Score Model (Ref. #)</th>
<th>Score Determinants</th>
<th>Score Calculation</th>
<th>Score Categories</th>
<th>Estimated Risk of Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient Bleeding Risk Index (62)</strong></td>
<td>Age ≥65 yrs, History of stroke, History of gastrointestinal bleeding, Recent myocardial infarction, hematocrit &lt;30%, creatinine &gt;1.5 mg/dl or diabetes mellitus</td>
<td>Score = [1 \times \text{age}_{\text{yrs}} + 1 \times \text{stroke} + 1 \times \text{GIB}] [+ 1 \times \text{other risk factors}]</td>
<td>0 risk factors = low risk, 1-2 risk factors = intermediate risk, 3-4 risk factors = high risk</td>
<td>At 3 months: Low = 2%, Intermediate = 5%, High = 23% At 12 months: Low = 3%, Intermediate = 12%, High = 48%</td>
</tr>
<tr>
<td><strong>Kuijer et al. (63)</strong></td>
<td>Age, Sex, Malignancy</td>
<td>Score = [1.6 \times \text{age} + 1.3 \times \text{female sex} + 2.2 \times \text{malignancy}]</td>
<td>0 = low risk, 1-3 = intermediate risk, &gt;3 = high risk</td>
<td>At 3 months: Low = 1%, Intermediate = 4%, High = 7%</td>
</tr>
<tr>
<td><strong>Shireman et al. (64)</strong></td>
<td>Age ≥70 yrs, Sex, Remote bleeding, Bleeding during the index hospitalization, Alcohol or drug abuse, Diabetes, Anemia, Antiplatelet therapy</td>
<td>Score = [0.49 \times \text{age}_{70} + 0.32 \times \text{female} + 0.58 \times \text{remote bleed} + 0.62 \times \text{recent bleed} + 0.71 \times \text{alcohol/drug abuse} + 0.27 \times \text{diabetes} + 0.86 \times \text{anemia} + 0.32 \times \text{antiplatelet therapy}]</td>
<td>≤1.07 = low risk, 1.07-2.18 = intermediate risk, ≥2.19 = high risk</td>
<td>At 3 months: Low = 0.9%, Intermediate = 2%, High = 5.4%</td>
</tr>
<tr>
<td><strong>HEMORR2HAGES score (65)</strong></td>
<td>Prior bleeding, Hepatic or renal disease, Alcohol abuse, Malignancy, Age &gt;75 yrs, Reduced platelet count or function, Uncontrolled hypertension, Anemia, Genetic factors, Excessive fall risk, Stroke</td>
<td>Score = [2 \times \text{prior bleeding} + 1 \times \text{hepatic/renal disease} + 1 \times \text{alcohol abuse} + 1 \times \text{malignancy} + 1 \times \text{age}_{75} + 1 \times \text{reduced platelet count/function} + 1 \times \text{hypertension} + 1 \times \text{anemia} + 1 \times \text{genetic} + 1 \times \text{fall risk} + 1 \times \text{stroke}]</td>
<td>0 = low risk, 1 = intermediate risk, 2-4 = high risk, ≥5 = very high risk</td>
<td>Bleeding requiring hospitalization per 100 patient-yrs: 0 = 1.9%, 1 = 2.5%, 2 = 5.3%, 3 = 8.4%, 4 = 10.4%, ≥5 = 12.3%</td>
</tr>
</tbody>
</table>

\(\text{age}_{\text{yrs}} = \text{age} \geq 65 \text{ years; GIB} = \text{gastrointestinal bleeding.}\)
dependent factors of intracranial hemorrhage with fibrinolytic therapy (e.g., low weight, blood pressure, prior stroke) are common among elderly individuals, prompting investigations on mechanical reperfusion in these patients (71). Subset analyses from trials that randomized patients to primary PCI or fibrinolytic therapy suggest that PCI is a preferred strategy in older patients (72–75). The TRIANA (Thrombolysis Versus Primary Angioplasty for AMI in Elderly Patient) trial (NCT00257309), a multicenter randomized trial comparing primary PCI versus a conservative strategy consisting in fibrinolysis or rescue angioplasty in patients over 75 years of age has been prematurely interrupted due to slow recruitment. Despite this sample limitation, the trial showed a dramatic decrease in recurrent ischemia by primary PCI (0.8% vs. 9.7%, p < 0.001) in elderly patients presenting with STEMI.

The ideal adjunctive antiplatelet and antithrombin therapy with fibrinolysis, in addition to aspirin, is also of interest in the elderly population. Adding a 75-mg maintenance dose of clopidogrel in STEMI patients was associated with a mortality benefit in a large-scale clinical trial in which elderly patients were highly represented (76). Although the utility of a 300-mg clopidogrel loading dose was also associated with improved outcomes in another large-scale clinical trial, elderly subjects (≥75 years of age) were excluded (77). The addition of GP IIb/IIIa inhibitors to fibrinolytic therapy is currently not recommended (19,20). Some studies have demonstrated that lower doses of UFH (78) or enoxaparin (79) may be helpful in ameliorating the bleeding risk associated with fibrinolytic therapy in the elderly. The attempt to achieve a good balance of safety and efficacy with reduced-dose fibrinolytic therapy and adjunctive antithrombin therapy has not been shown to be effective in elderly patients (80,81).

Conclusions

The physiological changes that accompany aging have an important impact on the effects of therapeutic agents, including antithrombotic medications. Given that atherothrombotic disease processes increase with age and that the prevalence of the elderly population is continuously growing, understanding strategies of antithrombotic management in this high-risk cohort is of key importance. This is further emphasized by the fact that antithrombotic therapy used to reduce ischemic events in the elderly is counterbalanced by their increased risk of bleeding. Numerous factors challenge the identification of the optimal antithrombotic drug regimens in the elderly. These include factors that may affect therapeutic agents in general (e.g., renal function, hepatic metabolism, body mass distribution) as well as factors more specific to thrombosis and hemostasis (e.g., platelet dysfunction, coagulation disorders). The greater risk of adverse drug–drug interactions due to polypharmacy in the elderly further enhances these concerns. The lack of dedicated studies performed in the elderly, frequently excluded from many large-scale clinical trials, often leads to either no recommendations on their most appropriate antithrombotic treatment regimen or sometimes arbitrary assumptions. The development of novel antithrombotic agents with a more favorable safety profile may have a promising role in this ever-growing population. However, more data from large-scale clinical trials and dedicated studies in the elderly assessing the safety and efficacy of antithrombotic treatment strategies are strongly warranted.


Key Words: bleeding • coagulation • elderly • platelet • thrombosis.