In a recent study, investigators of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A) enrolled 7554 patients with atrial fibrillation (AF) at high risk of developing vascular events such as stroke, myocardial infarction, systemic embolism, and vascular death. These patients, in whom anticoagulation was contraindicated, were randomly assigned to receive either 75 mg clopidogrel or placebo in addition to 75 to 100 mg aspirin daily. After a median follow-up period of 3.6 years, a significant 11% reduction in vascular events was observed in those receiving clopidogrel as compared with placebo, contributed primarily by a reduction in the incidence of disabling strokes. These benefits, however, come at a high cost of bleeding complications; a 57% higher incidence of major and severe bleeding was observed in those receiving clopidogrel plus aspirin, affecting predominantly the gastrointestinal tract, possibly cancelling the benefit from reduction in vascular events.

Although the increase in bleeding risks may limit the acceptance of clopidogrel plus aspirin in the thromboprophylaxis of patients with AF, one should not disregard their potential benefits to carefully selected individuals who are predisposed to vascular events but with low bleeding risks. At present, the Cardiac Failure, Hypertension, Age, Diabetes, Stroke (Doubled) (CHADS2) score has been widely used to identify high-risk patients who may benefit from antithrombotic therapy; patients with 2 moderate risk factors (age >75 years, hypertension, diabetes, or heart failure) or one high risk factor (prior stroke, prosthetic heart valve, or mitral stenosis) are at risk of stroke, approximately 3% to 5% per year. This score, however, does not take into account structural cardiac features and prothrombotic features (such as elevated D-dimer and von Willebrand factors) that may confer a higher risk of vascular events to individual patients. Therefore, it makes clinical sense to incorporate these additional risk markers to improve on our ability to identify individuals who may be at risk of vascular events more accurately, possibly through the use of data obtained from ACTIVE A.

A similar effort should also be extended to help identify patients at high risk of serious bleeding complications. For instance, peptic ulcer disease was not systematically screened for in ACTIVE A. Although patients with documented peptic ulcer disease were excluded from the study, there were no active attempts to exclude the presence of peptic ulcer disease during randomization, which may be a glaring omission given their potential contribution to the excess in bleeding risks. This begs a pertinent question: are there accurate measures to screen patients who may be at higher risk of bleeding? At present, there are limited data to justify the risks of endoscopy (such as aspiration pneumonia and bowel perforation) before the initiation of antiplatelet therapy in an effort to stratify the risks of bleeding better. Further studies are needed to assess cost-effectiveness of routine endoscopy to stratify the risks of gastrointestinal bleeding and the use of morphological gastrointestinal features to predict the risk of gastrointestinal bleeding. The practice of adding proton pump inhibitors to antiplatelets, aimed at reducing the risks of gastrointestinal bleeding, has recently been challenged after in vivo observations of a significant decrease in platelet activation and aggregation effects, potentially leading to treatment failure. It is important to emphasize that the present evidence indicates that anticoagulation remains the most efficacious therapy in high-risk patients with AF. In a similar study (ACTIVE W) that compared the efficacy of anticoagulation against aspirin and clopidogrel, the trial was stopped early due to the clear superiority of anticoagulation (relative risk, 1.44; 1.18 to 1.76; P<0.001). However, the acceptance of anticoagulation in the “real world,” however, is less than...
satisfactory. In the United Kingdom, epidemiological data indicate that only 25% of eligible patients consent to the use of antiocoagulation, especially among the elderly. The reasons are numerous: antiocoagulation carries a greater risk of bleeding, regular blood-taking is needed to monitor the levels of the international normalized ratio, changes in lifestyle are necessary to take into account dietary restrictions and avoidance of alcohol-containing drinks, physical immobility from age-related health problems could lead to an increase in falls, and the lack of caregiver commitments to ensure compliance to treatment and follow-up visits. Concerns have also been raised as to whether participants in clinical trials, who are generally more closely followed up to ensure adherence to the study protocol, are representative of patients seen in “real-world” practice who may not necessarily be compliant with management protocols.

Does the combined use of antiplatelets prevent cardioembolic stroke or just atherothrombotic events? Because incident strokes were not classified in ACTIVE A, it is not possible to answer this question, although the gap in effectiveness between dual antiplatelets and antiocoagulation may be explained by this possible difference in mechanism of action. Intuitively, by targeting different pathways, the combined use of 2 antiplatelets (at least in theory) should better protect against atherothrombotic diseases such as ischemic stroke and myocardial infarction. For example, clopidogrel blocks activation of platelets by ADP by selectively and irreversibly inhibiting the binding of this agonist to its receptor on platelets, thereby affecting ADP-dependent activation of the GpIIb-IIIa complex, the major receptor for fibrinogen present on the platelet surface.8 Aspirin, on the other hand, alters platelet function by inhibiting the cyclooxygenase-1 enzymatic activities. In cardiac patients, findings from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Clopidogrel for the Reduction of Events During Observation (CREDO) studies lend credence to this hypothesis, in which the addition of clopidogrel to aspirin significantly reduced the incidence of vascular events.6,7 In patients with stroke, however, the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) (which randomized patients after cerebral ischemia to receive aspirin plus dipyridamole versus aspirin) was the only recent study to confirm the benefits of using combined antiplatelet agents against recurrent vascular events after stroke.8 Three other contemporaneous major studies that evaluated the use of combined antiplatelet agents, Management of Atherothrombosis with Clopidogrel in High-Risk patients (MATCH) (which randomized patients at high risks of atherothrombotic events to either clopidogrel plus aspirin versus clopidogrel),9 Prevention Regimen For Effectively Avoiding Second Strokes (PROFESS) (which included patients after ischemic stroke randomized to extended-release dipyridamole plus aspirin versus clopidogrel),10 and Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) (which randomized patients at high risk of vascular events to either clopidogrel plus aspirin versus aspirin)11 did not demonstrate significant reduction in vascular events of combined antiplatelets over a single agent. To date, ACTIVE A is the largest study to include patients with AF under a common protocol and showed that, in carefully selected patients at high risk of vascular events, there may be a possible benefit for the use of combination antiplatelet therapy (aspirin plus clopidogrel) in the secondary prevention of stroke. It remains possible that other dual antiplatelet regimes might also be effective (for example, dipyridamole plus aspirin) with less bleeding risk.

Several challenges exist in our effort to optimize treatment in high-risk patients with AF. First, at the primary prevention level, further measures are needed to improve the treatment of predisposing factors that contribute to AF such as hypertension, valvular heart disease, arteriosclerotic heart disease, hyperthyroidism, diabetes mellitus, and heart failure. Second, at the secondary prevention level, further efforts should be placed to better manage AF, in particular, to assess the roles of ventricular heart rate control and restoration of sinus rhythm through the use of newer medications and techniques such as catheter ablation. Third, the clinical role of indices or the prothrombotic and hypercoagulable state of AF (as measured by p-dimer, von Willebrand factor, and P-selectin) warrants further evaluation to assess their abilities to identify patients at higher risk of stroke and assist decision-making on the choice of antithrombotics.12 Fourth, promising new antiplatelet agents should be assessed. In patients with acute coronary syndrome, the Triton trial showed that prasugrel, which has a mechanism similar to that of clopidogrel but with superior pharmacokinetics, was more effective than clopidogrel in reducing ischemic events, although it was associated with an increased risk of bleeding,13 hence limiting its use. Other newer antiplatelets include ticagrelor, a nonthienopyridine that binds reversibly to the platelet P2Y12 receptor; cangrelor, an intravenously administered analog of ticagrelor;14 and terutroban, a specific TP receptor antagonist, which may hopefully strike an optimal balance between the arrest of thrombotic events and serious bleeding.

Disclosures

None.

References


Key Words: ACTIVE A ■ aspirin ■ atrial fibrillation ■ clopidogrel
Optimizing Antiplatelet Therapy in High-Risk Patients With Atrial Fibrillation: Insights From Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE A)

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