EDITORIAL COMMENT

Dual Antiplatelet and Oral Anticoagulant Therapy

Increasing Use and Precautions for a Hazardous Combination*

Elaine M. Hylek, MD, MPH,† David E. Solarz, MD‡

Boston, Massachusetts

The prevalence of atrial fibrillation (AF) in the U.S. is projected to reach nearly 8 million individuals by 2020 (1). Stroke prevention in AF is the most common indication for warfarin. Approximately one-third of these individuals will also have coronary artery disease. Overall, the number of warfarin prescriptions has increased from 21 million in 1998 to nearly 31 million in 2004 (2). This surge in warfarin use has paralleled an increase in aspirin use for primary and secondary prevention of cardiovascular disease. The increased incidence of major hemorrhage, particularly among the older patient population, is at least in part attributable to the increased use of combination antithrombotic therapy (3). This risk was also recently highlighted in the Warfarin Antiplatelet Vascular Evaluation trial that randomized patients with peripheral arterial disease to antiplatelet or combination therapy (4).

In this issue of JACC: Cardiovascular Interventions, Rogacka et al. (5) report their findings from 127 consecutive patients discharged on aspirin, a thienopyridine (clopidogrel or ticlopidine), and warfarin after coronary stent implantation. Atrial fibrillation was the indication for warfarin in 59% of patients. The mean exposure to combination therapy was 5.6 ± 4.6 months. Of the 127 patients, 6 experienced a major hemorrhage, 4 of which were intracranial hemorrhages (ICH), and 3 were fatal. Most events occurred within the first month.

This study importantly adds to the growing body of evidence documenting the hemorrhagic risk of combined antiplatelet and warfarin therapy. The hazards of triple therapy after percutaneous coronary intervention were first highlighted in a retrospective analysis of 65 patients discharged after coronary stenting on aspirin, clopidogrel, and warfarin. Six patients (9.2%; 95% confidence interval [CI] 3.5 to 19.0) experienced a bleeding complication; 2 met criteria for major hemorrhage (6). Khurram et al. (7) subsequently published a retrospective study of 107 patients. Major bleeding occurred in 7 patients (6.6%); the hazard ratio of triple therapy was 5.4 compared with dual antiplatelet therapy alone. Similar findings were reported from Finland. Among 185 patients treated for a mean of 4 months, 18 (8.2%) sustained a major hemorrhage, including 3 ICH (2 related to trauma) (8).

Limitations of these studies include small sample size, retrospective design, lack of international normalized ratio (INR) data, and small number of events that prohibits meaningful assessment of risk. In the study by Rogacka et al. (5), the distribution of hemorrhage raises additional concern. Four of the 6 major bleeds were ICH. Information on blood pressure was not provided. The disproportionate number of ICH suggests incomplete ascertainment of major extracranial hemorrhage and a subsequent under-estimate of the aggregate bleeding rate. It is also important to note that although the authors attempt to assess differences in hemorrhage with different types of stents, in the absence of randomized data, this is problematic because of confounding by indication (i.e., patients at higher risk of hemorrhage might have preferentially received bare-metal stents to minimize exposure to triple therapy).

The risk of upper gastrointestinal bleeding or perforated peptic ulcer with aspirin use increases exponentially with age (9). Aspirin in combination with clopidogrel increases this risk more than 3-fold (adjusted rate ratio [RR] 3.9, 95% CI 2.8 to 5.5), and aspirin plus warfarin increases this risk more than 6-fold (adjusted RR 6.5, 95% CI 4.3 to 9.9) (10). The number needed to harm with antiplatelet therapy is 33 among high-risk female patients with a history of complicated ulcer who are ≥80 years of age and 17 for the comparable risk stratum in men. Nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with aspirin greatly magnify this risk (9).

Potential Strategies to Minimize Hemorrhagic Complications

Consistent risk factors for major hemorrhage on warfarin include older age, anticoagulation intensity, early course of therapy, prior bleed, and concomitant antiplatelet therapy (11,12). Additional risk factors for ICH include prior stroke and hypertension. The clinical challenge is how best to navigate optimal prevention of thrombosis while minimizing serious bleeding consequences. Combination antiplatelet therapy is less effective than warfarin for stroke preven-
tion in AF (13). Improved risk stratification in AF is a logical first step. Current AF guidelines recommend warfarin for CHADS2 scores of ≥2 (Congestive heart failure = 1 point; Hypertension = 1 point; Age ≥75 years = 1 point; Diabetes mellitus = 1 point; prior Stroke/transient ischemic attack = 2 points) and aspirin or warfarin for a CHADS2 score of 1 point (14). This point is emphasized by the current study in which 2 of the patients with ICH had CHADS2 scores of 0 and 1.

It is unclear to what degree hemorrhage on triple therapy is attributable to suboptimal control of warfarin. Proven strategies to minimize anticoagulant-related bleeding should be aggressively implemented, and interventions to ameliorate the hazards of antiplatlet therapy should be instituted (Table 1) (15). Prophylactic treatment with the proton-pump inhibitor (PPI) lansoprazole coupled with eradication of *H. pylori* infection was shown to significantly reduce the risk of recurrence of ulcer complications associated with aspirin (16,17). Patients were treated with 100 mg aspirin and lansoprazole 30 mg daily after confirmed *H. pylori* eradication. The risk of recurrence was 1.6% in the PPI group (95% CI 0% to 9%) and 14.8% in the placebo group (95% CI 7% to 26%); adjusted hazard ratio 9.6 (95% CI 1.2 to 76.1). The number needed to treat was only 7.6 to prevent 1 bleeding complication.

**Future Directions**

It is possible that newer anticoagulant drugs with shorter half-lives and a wider therapeutic window might be safer to use in combination with antiplatlet therapy. The balance between antithrombotic potency and safety will demand improved risk stratification particularly among individuals ≥75 years of age as highlighted by the recent trial that compared clopidogrel with prasugrel for the prevention of in-stent thrombosis (18). The mean age of trial participants was 61 years, and 13% were ≥75 years of age. Insights into the mechanisms of enhanced gastrointestinal susceptibility to antithrombotic therapy particularly in the elderly patient population warrant further study (19). Further data, preferentially from randomized trials, are needed to better assess the effects of staggered therapy, single versus dual antiplatlet therapy and warfarin, and optimal duration of antiplatlet therapy among different risk subgroups (20).

**Table 1. Potential Strategies to Minimize Major Hemorrhage Among Patients on Triple Therapy After Coronary Stent Implantation**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
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<td>1. Vigilant INR monitoring in the first 4 weeks, especially among patients newly starting warfarin or antiplatlet therapy</td>
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<td>2. Judicious use of “bridging therapy” with heparin (e.g., highest-risk mechanical prosthetic heart valve, venous thromboembolism within 3 months)</td>
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<td>3. Improved risk stratification for warfarin use in patients with AF (CHADS2 score ≥2)</td>
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<td>4. Increased awareness of the most potent risk factors for erratic INR control: decompensated heart failure, enteric feeding, erratic dietary vitamin K intake, amiodarone therapy, chemotherapy, protracted new use of high-dose acetaminophen</td>
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<td>5. Attention to blood pressure control with goal &lt;130/80 mm Hg (15)</td>
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<td>6. Prophylactic proton-pump inhibition for patients with peptic ulcer disease</td>
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<td>7. Eradication of <em>H. pylori</em> in patients with peptic ulcer disease and uninvestigated dyspepsia (17)</td>
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<td>8. Explicit warnings regarding use of over-the-counter NSAIDs and aspirin-containing compounds</td>
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<td>9. Physical therapy/safety evaluation before discharge to minimize fall risk</td>
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<td>10. There is insufficient evidence to support lower INR target intensities; patients and their caregivers need to be cognizant of the trade-offs inherent to this strategy</td>
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AF = atrial fibrillation; CHADS2 = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke/transient ischemic attack; INR = international normalized ratio; NSAIDs = nonsteroidal anti-inflammatory drugs.

References


