Optimizing Benefit of Antithrombotic and Anticoagulant Agents

In this *Heartbeat*, we present data about a couple of ways to maximize benefits of antithrombotic and anticoagulant treatment while minimizing downside risk.

**Aspirin Benefit and Risk**

Low-dose aspirin is recommended for secondary prevention after a myocardial infarction (MI), cerebral vascular accident (CVA) or a transient ischemic attack (TIA) per guidelines. Aspirin (ASA) is taken by 40% to 60% of people over 75. The studies demonstrating the safety of ASA were performed in trials with younger participants. The authors of a new study published in *Lancet* state, “Although the risks of major bleeding in patients aged younger than 75 years were similar to the risks in previous trials of ASA and other antiplatelet drugs, the risks at older ages were higher and more sustained than at younger ages, and the functional outcome was much worse, with a substantial risk of disabling or fatal upper gastrointestinal (GI) bleeding.”

The researchers followed over 3,000 patients for up to 10 years after their first ischemic cardiovascular event; secondary prevention was mostly aspirin-based antiplatelet therapy. The annual risk for all bleeding events was about 3.4%, and for major bleeds, about 1.5%. The risk for major bleeds increased sharply starting at age 70, reaching 4.1% at age 85 and above.

As physicians, we obsess about benefit versus risk when we treat high-risk atrial fibrillation (AF) patients with anticoagulants, but we’re not as vigilant when addressing antithrombotic treatment. We’ve always known that bleeding risk increases with age. This study points out that bleeding complications are a major issue in elderly patients with ischemic vascular disease on antiplatelet therapy and how to ameliorate it.

The authors point out that proton pump inhibitors (PPIs) have been found to reduce upper-GI bleeding in antiplatelet users by 75%. On that basis, they estimate that 80 patients under age 65 would need to be treated to prevent one major upper-GI bleed; among those aged 75 to 84, just 23 would need to be treated.

While there is some evidence that long-term PPI use might have some small risks, this study shows that the risk of bleeding without them at older ages is high, and the consequences significant. In other words, this new data should provide reassurance that the benefits of PPI use at older ages will outweigh the risks.

The authors conclude that older people who take ASA to prevent a recurrent cardiovascular event should take a PPI to lower their risk of serious bleeding complications, and this should be considered for future secondary prevention guidelines.
Do We Need Both OAC and ASA Therapy with AF?

There is an increased risk of stroke in patients with atrial fibrillation (AF). Additionally, there is an increased risk of coronary artery disease (CAD) in AF (a systemic disease) or it already coexists. Oral anticoagulants (OACs) are indicated for CVA prophylaxis in AF to prevent formation of fibrin due to activation of the coagulation system in states of hemodynamic stasis and are far superior to ASA. Antiplatelet drugs like ASA are used to prevent atherothrombotic events like MI in patients with CAD. The question is, do we need both?

A recent report in JACC by Lee et al. should prompt clinicians to rethink the approach to antithrombotic therapy for patients with AF, particularly when anticoagulation is indicated in those at more than minimal thromboembolic risk. Although the risk of stroke in patients with AF generally exceeds their risk of MI, the latter is not negligible, even when the diagnosis of CAD has not been established.

A total of 71,959 patients were identified (median 75 years of age; females: 47%). At baseline, 37,539 patients (52%) were treated with vitamin K antagonist (VKA) monotherapy, 25,458 (35%) with acetylsalicylic acid (ASA) monotherapy and 8,962 (13%) with dual-therapy (VKA + ASA). The incidence of MI was 3% (n = 2,275). Relative to the VKA-treated group, the associated risk of MI was significantly higher for ASA (incidence rate ratio [IRR]: 1.54; 95% confidence interval [CI]: 1.40 to 1.68) and dual-therapy (IRR: 1.22; 95% CI: 1.06 to 1.40). The bleeding risk was significantly higher for dual-therapy (IRR: 1.93; 95% CI: 1.81 to 2.07). The risk of stroke relative to that of VKA therapy was significantly higher for both ASA (IRR: 2.00; 95% CI: 1.88 to 2.12) and dual-therapy (IRR: 1.30; 95% CI: 1.18 to 1.43).

The risk of MI seems lowest when patients are treated with an anticoagulant—specifically a VKA—highest among those treated with ASA alone and intermediate for those treated with both. But combination therapy carries a greater risk of major bleeding than either form of monotherapy does. Stroke risk was greatest in those taking ASA either alone or with warfarin. (There are questions about why ASA and a VKA together did not lower risk of stroke or MI.)

Obviously, the risk of MI is higher for patients with AF and known CAD, and the question of whether to add an antiplatelet agent to an anticoagulant is a little more challenging. But we’ve known for years that anticoagulation alone has been associated with low rates of MI (generally <1%/year) in randomized trials—we use ASA because it’s easier. So we think the answer is the same—no need to add ASA to warfarin.

In the era of direct-acting oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban and edoxaban, it is worth noting that no significant differences in MI rate, which ranged from 0.5%/year to 1.1%/year, were observed in the five randomized trials comparing DOACs against warfarin for patients with AF, in which the prevalence of prior MI ranged from about 14% to 18%. Based on this data, we believe there is reason to believe that efficacy rates for MI would be similar, while rates of major bleeding, particularly intracerebral hemorrhage, would be lower. But further research in prevention of CAD events with DOACs is warranted in high-risk patients with AF compared with VKA treatment.

Under Treatment and Inappropriate Treatment of AF

Editorialists and Dr. Valentin Fuster agree that much ground needs to be covered before all eligible patients with AF, especially those at high risk of stroke (CHA2DS2 Vasc score > 2), receive appropriate guideline-directed anticoagulant therapy. Many were receiving inappropriate antithrombotic treatment (ASA) or no treatment based upon review of the Gloria-AF study. Introduction of DOACs in routine practice has been associated with improved rates of overall OAC use for AF, but significant gaps still remain. In this situation, it is appropriate to remind ourselves that “an ounce of prevention is worth a pound of cure.”
Overdosing and underdosing of DOACs for AF was common in a large U.S. cohort study, including inappropriate dosage reductions when there weren’t renal indications for them, and failures to drop the dosages when renal dysfunction called for it. Such practices can lead to DOAC overdosing and underdosing that can compromise the drugs’ safety without improving their effectiveness (i.e. increased stroke or bleeding risk).

We recommend calculating the creatinine clearance (CrCl) in all patients with a glomerular filtration rate (GFR) < 60ml/min/1.73m2 and dose accordingly, allowing for better dose adjustment in this patient group—as per algorithm below. Use the Cockcroft-Gault method (in the Qx Calculate app on your phone), which gives a more accurate assessment of renal function by not resulting in overestimation of renal function in elderly patients or those with lower GFR. This should be done bi-annually.

**Take Homes**

**Proposal #1:** In elderly patients older than 75 years, add PPIs to ASA for secondary CVD prevention to decrease major GI bleed risk.

**Proposal #2:** In patients with high-risk AF who are appropriately treated with OACs, it is not necessary to add aspirin for primary prevention of MI as it only increases bleeding risk without decreasing MI risk.

The Lancet study authors and we believe this is also true for secondary prevention in stable CAD. We believe it is reasonable to assume this is also true for DOACs, but more data is needed for confirmation.

**Proposal #3:** Anticoagulate high-risk AF patients with high-risk Has-Bled scores, the very elderly and those with increased fall risk. The benefit (decreased CVA risk) outweighs the downside. Add a PPI and take appropriate measures to decrease bleed and/or decrease falls.

**Proposal #4:** Use appropriate doses of DOACs based on calculated CrCl if GFR less than 60ml/min/1.73m2.

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