Antithrombotic Therapy After Coronary Artery Stenting in Patients With Atrial Fibrillation

Michiel Coppens, MD; John W. Eikelboom, MBBS

Dual antiplatelet therapy with aspirin and clopidogrel is highly effective for the prevention of stent thrombosis and other major ischemic cardiovascular events in patients undergoing percutaneous coronary intervention (PCI). However, in every 20 stented patients also has atrial fibrillation (AF) or another indication for oral anticoagulant therapy. Oral anticoagulant therapy is much more effective than dual antiplatelet therapy for the prevention of cardioembolic stroke in patients with AF, but when warfarin is coadministered with aspirin and clopidogrel (“triple therapy”), the rate of bleeding is as high as 15% during the first year. North American and European expert consensus statements recommend triple therapy in the majority of patients with AF undergoing PCI with stent insertion, but the efficacy and safety of this approach has not been rigorously evaluated.

In this issue of Circulation: Cardiovascular Interventions, Ruiz-Nodar et al further explore the benefits and risks of triple therapy in patients with AF undergoing PCI with stenting recruited between 2001 and 2008 from 2 Spanish centers. Of the 604 consecutive patients included in this study who received at least 1 coronary artery stent, 590 had an indication for oral anticoagulant therapy because of a CHA2DS2-VASC score of at least 1, and 420 were deemed to be at high risk of bleeding because they had an HAS-BLED score >3.7 The mean age of the 590 patients with an indication for oral anticoagulant therapy was 72.2 years, most of these patients (85.2%) were stented after presenting with an acute coronary syndrome (almost one half received a drug-eluting stent), and almost one half (44.6%) were discharged on triple therapy. The mortality rate at 1 year was 12.2%, possibly reflecting the advanced age and high rate of comorbidities (44.4% diabetes mellitus, 31.5% heart failure, 27.6% renal failure) of these patients. As previously reported, the mortality rate in this particular cohort is substantially higher than the 1% to 6% rate reported in contemporary cohorts of stented patients with AF. Compared with patients who had an HAS-BLED score of 1 to 2, those with a score >3 had substantially higher rates of mortality (14.1% versus 7.3%, P=0.04) and major adverse cardiovascular events (18.9% versus 8.8%, P<0.01) although bleeding was not significantly higher.

Despite the very high risk of patients with an HAS-BLED score >3, those discharged home on warfarin (most of whom were receiving triple therapy) had an 80% lower adjusted hazard of death (HR 0.20; 95% CI: 0.06–0.64) and a 79% lower adjusted hazard of major adverse cardiovascular events (hazard ratio: 0.21; 95% CI: 0.08–0.57) than those not discharged home on warfarin. Patients discharged home on warfarin also had a higher rate of bleeding than those not discharged on warfarin but this is not unexpected, and the increased hazard of bleeding was no longer statistically significant in the adjusted analyses (hazard ratio: 2.31; 95% CI: 0.55–9.71).

The apparently large benefit of warfarin in stented patients with AF who have an HAS-BLED score >3 is consistent with the benefit of triple therapy reported in unselected patients undergoing stenting who were treated with warfarin. We believe, however, that these data should be very cautiously interpreted. Historic trials of warfarin compared with placebo or no warfarin for stroke prevention in AF demonstrated a 20% to 30% mortality reduction and a 60% to 70% stroke reduction,2 and these trials were conducted during a time when other effective secondary prevention studies were not widely used. The absolute benefits of warfarin compared with no warfarin might be expected to be greater in higher-risk populations, such as those with an HAS-BLED score >3, but it seems very unlikely that the relative mortality benefits would be 2 to 3 times larger than previously reported. In the study by Ruiz-Nodar et al, the rates of statin and angiotensin-converting enzyme inhibitor therapy are not reported, but warfarin was administered on a background of dual antiplatelet therapy, which is also effective for the prevention of major thrombotic cardiovascular events. Ruiz-Nodar et al also do not report the effects of warfarin on cause-specific mortality, but an 80% relative (10% absolute) reduction in total mortality implies an even greater reduction in cardiovascular mortality. Despite adjustment for baseline characteristics, confounding can never be reliably excluded in an observational study, and it remains possible that systematic differences between patients treated with warfarin and those not treated with warfarin contributed to the apparently very large treatment effects.

Notwithstanding the aforementioned caveats, the results of the study by Ruiz-Nodar et al contain several important lessons for
clinical practice. First, the 1-year outcome data provide a sobering reminder that preexisting AF in patients undergoing PCI with stenting identifies a population at high risk of death and major cardiovascular events. Vigorously targeting these patients with effective secondary cardiovascular prevention strategies would seem appropriate. Second, although the HAS-BLED score was developed to assess bleeding risk in patients with AF, the results by Ruiz-Nodar et al demonstrate that this risk-prediction scheme is also a powerful predictor of nonhemorrhagic outcomes and mortality in patients with AF who undergo PCI with stenting. Third, the favorable outcomes with warfarin reported by Ruiz-Nodar et al raise the possibility that even in patients at high risk of bleeding, triple therapy may offer substantial benefits for patients. The evidence is, however, of low quality because of the observational study design and, until confirmed by rigorous randomized comparisons, we believe that clinicians should continue to minimize exposure of patients at high risk of bleeding to triple therapy, as also currently recommended by expert consensus guidelines.5,6

What are the implications of these results for future research? Consistent evidence from observational studies indicates that triple therapy is associated with an increased risk of bleeding compared with other less intensive antithrombotic regimens,3,4 and there is still no high-quality evidence that triple therapy reduces the risk of major cardiovascular events. Several randomized-controlled trials testing the effectiveness and safety of different antithrombotic regimens in patients with AF undergoing coronary artery stenting are currently ongoing (WOEST, ISAR-TRIPLE, and MUSICA-2, see www.clinicaltrials.gov), but collectively involve only modest numbers of patients, and are substantially underpowered to reliably evaluate efficacy. Until triple therapy is adequately tested in large randomized-controlled trials, we believe that clinical practice concerning the choice and duration of antithrombotic regimens in AF patients undergoing PCI with stenting will continue to be based on expert opinion and an assessment of the tradeoff between benefits and risks in individual patients.

Disclosures
None.

References

Key Words: aspirin ■ clopidogrel ■ stent ■ triple therapy ■ warfarin ■ Editorial

Table. North American and European Guidelines for Antithrombotic Therapy in Patients With AF and a Moderate-to-High Risk of Stroke (CHADS2 score >1) Undergoing PCI

<table>
<thead>
<tr>
<th>Bleeding Risk</th>
<th>Stent Type</th>
<th>North American Guideline</th>
<th>European Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low to intermediate</td>
<td>Bare metal stent</td>
<td>Low stent thrombosis risk: Triple Rx 1 month, then OAC + single agent antiplatelet Rx for 12 months</td>
<td>Elective: Triple Rx 1 month, then OAC alone</td>
</tr>
<tr>
<td></td>
<td>Drug-eluting stent</td>
<td>High stent thrombosis risk: Triple Rx 6 months, then OAC + single agent antiplatelet Rx to 12 months</td>
<td>ACS: Triple Rx 6 months, then OAC + single agent antiplatelet Rx to 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACS: Triple Rx 6 months, then OAC + single agent antiplatelet Rx to 12 months</td>
<td>ACS: Triple Rx 6 months, then OAC + single agent antiplatelet therapy to 12 months</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Low stent thrombosis risk: Triple Rx 6 months, then OAC + single agent antiplatelet Rx to 12 months</td>
<td>Elective: Triple Rx 3 months (-olimus stent) or 6 months (paclitaxel stent), then OAC + single agent antiplatelet Rx to 12 months</td>
</tr>
<tr>
<td></td>
<td>Drug-eluting stent</td>
<td>High stent thrombosis risk: Triple Rx to 12 months</td>
<td>Elective: Triple Rx 2-4 weeks, then OAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not recommended</td>
<td>ACS: Triple Rx 4 weeks, then OAC + single agent antiplatelet Rx to 12 months</td>
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<tr>
<td></td>
<td></td>
<td>After 12 months</td>
<td>OAC alone in all</td>
</tr>
</tbody>
</table>

The North American Guideline recommends considering continued single antiplatelet Rx and OAC in those at high risk for atherothrombotic events. ACS indicates acute coronary syndrome; AF, atrial fibrillation; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; and Rx, treatment.
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