Clear evidence supports the value of oral anticoagulation (OAC) with vitamin K antagonists in preventing stroke and thromboembolism in patients with atrial fibrillation (AF) who have well-established risk factors. For this indication, vitamin K antagonists have been shown to be superior to single or dual antiplatelet agents in reducing thromboembolic complications (1). Yet, up to 30% of patients with AF also have indications for antiplatelet therapy because of coronary artery disease (2). Dual antiplatelet therapy with aspirin and a P2Y₁₂ receptor inhibitor (e.g., clopidogrel) is usually recommended after stent implantation or acute coronary syndrome (3). Thus, patients with both AF and coronary events typically receive combination OAC and antiplatelet therapy. There has been concern that withholding antiplatelet therapy in these patients could expose them to higher rates of stent thrombosis and myocardial infarction (MI), and P2Y₁₂ inhibitors seem to be particularly important in this regard. Yet, the combination of OAC with antiplatelet drugs clearly increases the risk of major hemorrhages and fatal bleeding in both AF and coronary populations (4–6). European guidelines from 2010 suggest triple therapy after stent implantation, with the duration depending on the type of stent implanted, the presence of an acute coronary syndrome, and the bleeding risk of the patient. (7) An earlier guideline document from the American College of Cardiology, American Heart Association, and European Society of Cardiology de-emphasizes the use of aspirin and favors OAC + clopidogrel after stent implantation in AF patients, because “the addition of aspirin to the chronic anticoagulant regimen contributes more risk than benefit” (8). For patients with both AF and coronary disease, there is a paucity of information to guide rational decisions and very little evidence to support intensive anticoagulation with triple therapy.

In this issue of the Journal, Lamberts et al. (9) used national databanks and registries in Denmark to explore the safety and efficacy of different anticoagulation regimens in patients with AF who also had MI and/or percutaneous coronary intervention (PCI). Because patients in Denmark have unique identifiers, the investigators could link national databases of hospital stays, procedural treatments, drug prescriptions, and causes of death. This analysis has the advantage of studying outcomes in a large “real world” population, not one highly selected by rigorous inclusion criteria of a randomized trial. It also illustrates the power of nationwide registries to explore clinically important questions that might prove difficult to approach in randomized trials. As with any retrospective registry, some important data might not be available. For example, this study does not inform us how many PCI patients had drug-eluting stents. Also, registry studies that use hospital diagnosis codes depend heavily on the accuracy of the coding. Fortunately, the codes employed in this study have been previously validated with relatively high specificities and predictive values.

With this approach, 12,165 AF patients were identified who were hospitalized for MI and/or PCI. Anticoagulation regimens were monotherapy in 38% (aspirin, clopidogrel, or OAC), dual therapy in 47% (dual antiplatelets or OAC + 1 antiplatelet), and triple therapy in 15%. Outcomes assessed after 1 year included MI, ischemic stroke, mortality, and bleeding, as judged from hospital stay and death records. In this analysis, OAC + clopidogrel emerged as the favored overall strategy. Compared with triple therapy, this dual combination showed no excess of MI or coronary death, and there was no difference in ischemic stroke or overall mortality. In terms of bleeding, OAC + clopidogrel showed a nonsignificant benefit compared with triple therapy. Other regimens (OAC + aspirin; dual antiplatelet therapy without OAC) were associated with less bleeding but at the cost of higher all-cause mortality rates. Not surprisingly, there were also more strokes among those treated with dual antiplatelets compared with any regimen that used an OAC. Those who had PCI without MI had a lower coronary event rate, but there was still a benefit for OAC + clopidogrel compared with the other regimens in these lower-risk patients. Other interesting findings were high subsequent mortality, MI, and stroke among those hospitalized for bleeding compared with those without. The higher rates of thrombotic events among those with nonfatal bleeding suggest that bleeding is dangerous not only because of the hemorrhage itself but also because it forces discontinuation of needed anticoagulation.

A limitation of this study design is the possibility that treatment decisions were confounded by many clinical features that cannot be captured from the national databases. The authors acknowledge this important limitation and report that baseline characteristics—such as CHADS₂ and
HAS-BLED scores—seem not to have influenced the choice of anticoagulation prescriptions. But it should be acknowledged that even this analysis does not control for other comorbidities that might lead physicians to choose a particular anticoagulation regimen (clopidogrel alone vs. the combination of aspirin + clopidogrel) after a new cardiac event. Finally, the number of patients who were initially prescribed the “optimal” regimen of OAC + clopidogrel was relatively small (548 of 12,615 subjects).

The question of dual versus triple anticoagulation has recently been addressed in a prospective, randomized trial (WOEST [What is the Optimal Antithrombotic and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting] trial) (10). This trial tested OAC + clopidogrel versus triple therapy in patients undergoing coronary stenting who also needed OAC (for AF in 69%). After 1 year of follow-up, OAC + clopidogrel was associated with significantly less overall bleeding, and there was no increase in stent thrombosis, although this relatively small study of 573 patients was underpowered to exclude excess stent thrombosis. In composite, these 2 studies suggest dual anticoagulation with OAC + clopidogrel as a safer and perhaps equally effective strategy compared with triple therapy.

But a myriad of questions remain unanswered. Could there be even higher-risk patients in whom coronary protection with triple therapy outweighs the bleeding risks? For example, patients with recurrent coronary events within 1 year would be considered at elevated risk, but patients with MI in the previous year were excluded from the Danish study. Also, this study does not address the time course of triple or even dual therapy after MI or PCI. Current guidelines suggest that monotherapy with warfarin might be sufficient 1 year after stenting in lower-risk patients (7,8), an issue that is not addressed in the present study. Even more perplexing is how to treat patients with resistance to clopidogrel. These patients might be candidates for other P2Y12 inhibitors, but sparse data are available on the combination of OAC with newer P2Y12 receptor inhibitors (prasugrel, ticagrelor), which are shown to reduce coronary endpoints but at the expense of more bleeding (11,12). Preliminary evidence suggests more bleeding occurs in triple therapy patients receiving prasugrel compared with clopidogrel (13). Finally, these results cannot necessarily be extrapolated to the newer direct thrombin and factor Xa inhibitors, but it is probable that combining these new agents with dual antiplatelets would cause more bleeding than benefit (14).

The implication here is that physicians should have confidence to curtail triple therapy when OAC is needed for AF. One method to minimize the need for combination therapy is to use bare-metal stents whenever possible in AF patients. New stent designs are likely to reduce the need for triple therapy in the future. Ultimately, the clinician must exercise judgment and integrate bleeding and thrombotic risks in prescribing anticoagulation regimens in such situations.

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