In clinical practice, the need to add 1 or 2 antiplatelet agents to an oral anticoagulant (OAC) often arises in patients with atrial fibrillation (AF). The indications can be diverse, from primary prevention in patients at high risk for an ischemic atherosclerotic event to secondary prevention after an acute coronary syndrome (ACS) to prevention of stent thrombosis.\(^1\)\(^2\) Unfortunately, adding antiplatelet agents to OACs increases bleeding risk, and although this risk is highest early after initiation of combination therapy, there appears to be no safe therapeutic window.\(^1\) The difficulty lies in balancing thromboembolic risk and bleeding risk in the individual patient. Because many new agents have come on the market recently, there is a wide variety of possible strategies with regard to not only the number and type of agents but also the intensity of anticoagulation and duration of the combination treatment.

Although ample guidance is available for preventing thromboembolic events and bleeding complications related to anticoagulant therapy on the one hand and for preventing ischemic events with antiplatelet agents on the other hand, there are few data from prospective studies on the combined use of antiplatelets with warfarin or one of the new OACs. Because the wide variety of clinical scenarios in which combination therapy is indicated can hardly be studied prospectively in dedicated clinical trials, we have to turn to post hoc analyses from trials such as the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) to obtain a better understanding of the benefits and risk of adding 1 or 2 antiplatelet agents to an OAC.

In the RE-LY study, dabigatran at a dose of 110 mg twice daily reduced the risk of major bleeding and was noninferior to warfarin in preventing systemic emboli, whereas the 150-mg twice-daily dose reduced the risk of systemic emboli with a bleeding risk similar to that of warfarin. Both doses were associated with a significantly lower risk of intracranial hemorrhage.\(^1\) In this issue of Circulation, Dans and colleagues\(^4\) report on the efficacy and safety of 2 doses of dabigatran in combination with antiplatelet therapies. Use of antiplatelet agents was not randomized or stratified. At baseline, 40% of the patients were using an antiplatelet agent, and only 1 of 5 used it continuously throughout the study (median duration, 66% of the total study duration).\(^3\) Most of these patients were taking aspirin, whereas the use of clopidogrel only (1.9%) or dual antiplatelet therapy (4.5%) was infrequent. Other P2Y\(_12\) inhibitors such as ticagrelor or prasugrel were not used. In the present analysis, regardless of the allocated anticoagulant, any antiplatelet use increased the risk of major or minor extracranial bleeding. Intracranial hemorrhages were not more frequent, although the numbers were relatively low. Overall, antiplatelet therapy doubled the risk of bleeding, but the magnitude of risk increased with the number of antiplatelet agents used. The addition of a single antiplatelet agent (aspirin in most cases) significantly increased the risk of major bleeding by 60%, whereas the risk of major bleeding was 2.3 times higher after clopidogrel was added on top of aspirin. The noninferiority of the 110-mg twice-daily dabigatran dose in terms of efficacy was preserved with concomitant antiplatelet therapy. The lower risk of major and minor bleeding complications, including intracranial hemorrhage, as observed in the overall trial was also maintained in patients on concomitant antiplatelet therapy. As for the 150-mg twice-daily dose, the superior efficacy of dabigatran compared with warfarin tended to diminish to some extent in patients also taking antiplatelet agents. In contrast, the risk of major and minor bleeding complications remained similar to that of warfarin, but the risk of intracranial hemorrhage was still lower with this dose of dabigatran.

These results confirm previous findings and experience from daily practice: Combining antiplatelet and anticoagulant agents increases bleeding risk. This appears to be the case when an antiplatelet agent is added to a vitamin K antagonist or to a new OAC in AF patients, as shown in this analysis, and vice versa when an OAC is added to antiplatelet therapy in patients with clinical manifestations of atherosclerosis.\(^5\)\(^6\)\(^7\) In contrast, and less intuitively, stacking several antithrombotic agents does not necessarily improve outcome. In a large Danish registry in AF, aspirin on top of warfarin, a common combination strategy, not only increased the risk of major bleeding by 66% but also increased the risk of ischemic stroke compared with warfarin alone by 27%.\(^8\) Similarly, in the recently presented open-label What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulants and coronary StenTing (WOEST) trial, which included 70% patients with AF, combining dual antiplatelet therapy with warfarin after percutaneous coronary intervention resulted in higher mortality rates than with the combination of warfarin plus clopidogrel alone.\(^9\) This conundrum might be explained in part by complications triggered by the bleeding event but also by discontinuing 1 or more antithrombotic agents in case of a clinically important bleeding, resulting in an increased

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium.

Correspondence to Frans Van de Werf, MD, PhD, Department of Cardiovascular Sciences, KU Leuven, Herestraat 49, 3000 Leuven, Belgium. E-mail frans.vandewerf@med.kuleuven.be

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Peter R. Sinnaeve, MD, PhD; Frans Van de Werf, MD, PhD

Editorial

Do Ingredients Make the Difference?
Finding the Best Cocktail of an Anticoagulant With Antiplatelets
Combination of Anticoagulants and Antiplatelets

Sinnaeve and Van de Werf

risk for recurrent thrombotic complications. In the analysis by Dans et al, concomitant antiplatelet therapy tended to attenuate the advantage of dabigatran over warfarin in preventing systemic emboli in the 150-mg arm, but the noninferiority of the 110-mg dose remained unchanged. Of note, in patients on antiplatelet therapy, dabigatran 150 mg was associated with a significantly lower risk of cardiovascular death compared with warfarin, although a formal test for interaction was not significant. Taken together, dabigatran appears to maintain its overall favorable profile compared with warfarin in patients on antiplatelet therapy.

Although the RE-LY protocol recommended aspirin doses up to 100 mg, a sizeable proportion of patients received higher doses. There appeared to be no additional bleeding risk associated with incremental doses of aspirin, but only a very few patients took doses of $\geq 300$ mg. The latter observation does not justify the use of maintenance doses of aspirin $>100$ mg with or without an anticoagulant. Furthermore, there was an incremental risk of bleeding with dual antiplatelet therapy with single antiplatelet use regardless of the dose of dabigatran. This confirms what was observed in the Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome (RE-DEEM) trial: Both the 110- and 150-mg twice-daily doses had a similar 4-fold increase in bleeding risk compared with placebo when added to aspirin and clopidogrel in non-AF ACS patients. In aggregate and in view of the aforementioned WOEST trial, the need for adding a second antiplatelet agent should be carefully evaluated in each individual patient on an OAC.

The mean duration of antiplatelet use in RE-LY was 66% of the study follow-up period, and at any given time during the trial, only 27% of patients were on additional antiplatelet therapy. This suggests that the bleeding rates reported here probably underestimate the true risk associated with prolonged continuous combination therapy, as the authors correctly point out. On the other hand, it indirectly suggests that investigators want to keep combination therapies as short as possible. In the large Danish AF registry, for instance, the combination of warfarin plus aspirin and clopidogrel or warfarin plus clopidogrel alone was given during a much shorter period than warfarin plus aspirin alone (median, 83 or 64 days, respectively, versus 198 days). Even when this is probably driven by bleeding concerns and despite the shorter duration, the first 2 combinations were nevertheless associated with an $4$-fold risk in bleeding (relative risk, 3.6 and 4.0, respectively) compared with only a 75% increased risk with the more prolonged use of warfarin plus aspirin alone. These findings contrast to some extent with those of the WOEST trial, at least in terms of bleeding risk, underscoring that retrospective data such as those of the Danish registry ideally need to be verified in prospective, randomized trials. The present analysis from RE-LY does not provide solid guidance on the optimal duration of antiplatelet therapy on top of dabigatran. The duration of combination therapy depends largely on the clinical context, and as with a vitamin K antagonist, this treatment needs to be tailored to the individual patient after carefully balancing bleeding and thrombotic risk.

Does this subanalysis from RE-LY provide evidence to justify decreasing the dose of 150-mg twice daily in AF patients when there is an indication for additional antiplatelet therapy, for example, after an ACS or percutaneous coronary intervention? Because the absolute bleeding risk on antiplatelet therapy was the lowest with the 110-mg dose of dabigatran, regardless of the number of antiplatelet agents used, decreasing the dose of dabigatran from 150 to 110 mg for the duration of additional antiplatelet therapy, especially in patients at high bleeding risk, seems to be reasonable. Because both doses are still associated with a lower risk of intracranial hemorrhage, however, continuing the 150-mg twice-daily dose remains a defendable option in patients with relatively low bleeding risk and a high CHA2DS2-VASc score. It remains unclear whether the results of this study warrant a switch from warfarin to dabigatran in AF patients after an ACS or percutaneous coronary intervention. Although a recent percutaneous coronary intervention or an ACS and the need for dual antiplatelet therapy were not formal contraindications for enrollment in RE-LY, they were relatively uncommon; $17\%$ of patients had a history of myocardial infarction. On the other hand, the present analysis indicates that dabigatran retains its benefit over warfarin in patients on antiplatelet therapy. This suggests that dabigatran might be a safer alternative to warfarin in AF patients requiring antiplatelet therapy, especially with the use of the 110-mg twice-daily dose.

Do the results observed in RE-LY also apply to factor Xa antagonists? Unsurprisingly, the addition of aspirin or clopidogrel to either full-dose or reduced-dose factor Xa antagonist also increases bleeding risk. No interaction was observed in terms of safety with aspirin use at the time of randomization in AF patients in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trials, but there is currently no information on bleeding risk during prolonged use. Although lower doses of a factor Xa antagonist were used in a small subset of selected patients in trials, there was no prospective, randomized comparison of 2 doses as in the RE-LY trial. In addition, although in RE-LY antiplatelet therapy was left to the discretion of the physician, dual antiplatelet therapy was an exclusion criterion in ARISTOTLE and ROCKET-AF. In this respect, it remains uncertain whether the favorable risk/benefit profile observed with dabigatran 110 mg in combination with antiplatelet therapy can be translated to lower doses of factor Xa antagonists in AF patients. The significantly lower mortality rates with very low doses rivaroxaban (2.5 mg bid) on top of aspirin and clopidogrel compared with placebo in the Anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome 2 (ATLAS 2) trial in ACS patients should be mentioned here. Whether this regimen would be sufficiently protective against thromboembolic events in AF patients with atherosclerosis who need antiplatelet therapy is unclear and can be addressed only in a prospective trial.

In conclusion, combining dual or single antiplatelet therapy with chronic anticoagulation (new OAC and vitamin K antagonist) significantly increases bleeding risk. The present results suggest that in patients requiring (low-dose) aspirin,
dabigatran 110 mg might be a safer alternative to a vitamin K antagonist. It should be mentioned that no reliable clinical data are available in AF patients on the combined use of an OAC with the new P2Y12 antagonists (prasugrel or ticagrelor) either alone or with aspirin. Furthermore, the uncertainty with regard to level of anticoagulation, risk/benefit ratio of dual versus single antiplatelet therapy on top of OAC, and optimal duration of combination therapy means that, for the moment, this treatment needs to be highly personalized, taking into account the thrombotic and bleeding risk of each individual patient. More dedicated prospective trials are on this important clinical problem are definitely needed.

Disclosures
Dr. Sinnaeve has received honoraria from Johnson & Johnson for studies with rivaroxaban in ACS and speaker’s fees from Boehringer Ingelheim, Bayer, Pfizer, and BMS. Frans Dr Van de Wef has received a research grant and honoraria from Boehringer Ingelheim for a study on dabigatran in mechanical valves and honoraria from Johnson & Johnson for studies with rivaroxaban in ACS.

References

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