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EDITORIAL

More Bleeding With the Newer Anticoagulants?

Antonis S. Manolis, MD

First Department of Cardiology, Evagelismos Hospital, Athens, Greece

The new oral anticoagulants that are currently available are dabigatran (Pradaxa, Boehringer Ingelheim), a direct thrombin inhibitor, and the activated factor X (Xa) inhibitors, apixaban (Eliquis, Pfizer) and rivaroxaban (Xarelto, Bayer), with several other agents in the pipeline.[1-3] These new oral anticoagulants are supposed to have a wider therapeutic window than warfarin, leading to a lower incidence of major bleeding. However, the results of large randomized trials indicate that *bleeding remains a major concern even with the new agents*. Studies with rivaroxaban, edoxaban and dabigatran showed that these drugs have incidences of severe bleeding comparable to those of enoxaparin and warfarin. The number of bleeding events is rising due to the ageing of the population and the increasing need for interventional therapies. The shorter half-life of the new agents might facilitate the management of bleeding events and the control of anticoagulation during interventions or emergency circumstances. If bleeding occurs, the lack of specific antidotes limits the therapeutic options. Due to the selection bias in the initial randomized studies, the absolute bleeding risk might be underestimated. This can only be measured after exposure of the drugs to larger populations with close post marketing surveillance within registries, a strategy that would be very helpful in defining the actual bleeding risk for the new drug classes. In case of bleeding occurrence, supportive care should be sufficient for most patients because of the short duration of action of the new agents. Some have suggested the use of prothrombin complex concentrates as a reversal agent for the new agents, but the data are limited.[4]

RE-LY demonstrated a higher rate of gastrointestinal bleeding with a higher dose of dabigatran, whereas ROCKET-AF had a higher rate of major gastrointestinal bleeding and epistaxis with rivaroxaban.[3] Postmarketing surveillance is most critical in further assessing safety in the real world. To date, there have been several fatal bleeding events reported worldwide with dabigatran (in RE-LY, life-threatening bleeds did occur but were significantly fewer than with warfarin). Whether these events are happening at a higher rate than what was expected on the basis of clinical trial data will need to be further explored; however, the FDA has issued a re-assuring statement.[5]

One major concern with the new anticoagulants relates to kidney function. The new drugs differ from the old agents with respect to their elimination through the kidneys. These drugs may potentially cause bleeding complications in patients with reduced drug excretion due to impaired renal function. Dabigatran etexilate and rivaroxaban carry the highest risk due to a high degree of renal excretion, whereas the risk for apixaban seems

lower. Thus, patients with renal insufficiency are at increased risk for bleeding complications. This was further emphasized in a recent report from the ROCKET-AF study, whereby patients with AF and moderate renal insufficiency receiving rivaroxaban had higher rates of stroke and bleeding.[6] Specifically, among the 2950 (21%) patients with creatinine clearance (CrCl) 30–49 mL/min, although they received a reduced dose of rivaroxaban (15 mg qd instead of 20 mg qd), the principal safety endpoint (major and clinically relevant nonmajor bleeding) occurred more frequently in those with renal insufficiency than in those without. In patients with moderate renal insufficiency, rivaroxaban-treated patients had more frequent gastrointestinal bleeding (4.1 vs. 2.6%; P = 0.02). Fatal bleeding (0.28 vs. 0.74% per 100 patient-years; P = 0.047) occurred less often with rivaroxaban.

In a recent study in patients undergoing ablation of atrial fibrillation (AF), periprocedural use of *dabigatran* increased the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy.[7] Specifically, in 145 patients receiving periprocedural dabigatran, the dose was held on the morning of the procedure, while another 145 patients received uninterrupted warfarin therapy. Both groups had a similar CHADS2 score, left atrial size, and left ventricular ejection fraction. A total of 3 thromboembolic complications (2.1%) occurred in the dabigatran group and none in the warfarin group (p = NS). Dabigatran led to a higher major bleeding rate (6% vs 1%; p = 0.019), total bleeding rate (14% vs 6%; p = 0.031), and combined bleeding and thromboembolic complication rate (16% vs 6%; p = 0.009) compared with warfarin. Dabigatran use was an independent predictor of bleeding or thromboembolic complications (odds ratio: 2.76; p = 0.01) on multivariate regression analysis. The authors concluded that in patients undergoing AF ablation, periprocedural dabigatran use significantly increases the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy.

Although, it was hypothesized that the new anticoagulant, *apixaban*, would be safe and perhaps more effective than short-term prophylaxis with enoxaparin for prolonging prophylaxis for venous thromboembolism in medically ill patients after hospital discharge, this did not pan out in the ADOPT trial.[8] Specifically, In this placebo-controlled trial, 4495 acutely ill patients who had congestive heart failure or respiratory failure or other medical disorders and at least one additional risk factor for venous thromboembolism and who were hospitalized with an expected stay of at least 3 days were randomized to receive oral apixaban (2.5 mg bid) for 30 days (n=2211), or subcutaneous enoxaparin (40 mg qd) for 6 to 14 days (n=2284). Among the participants, 60 (2.71%) in the apixaban group and 70 (3.06%) in the enoxaparin group met the criteria for the primary efficacy outcome (30-day composite of death related to venous thromboembolism, pulmonary embolism, symptomatic deep-vein thrombosis, or asymptomatic proximal-leg deep-vein thrombosis). This translates into a relative risk with apixaban of 0.87 (P = NS). By day 30, major bleeding had occurred in 0.47% of the patients in the apixaban group (15 of 3184 patients) and in 0.19% of the patients in the enoxaparin group (6 of 3217 patients) (relative risk, 2.58; P = 0.04). The investigators concluded that in medically ill patients, an extended course of thromboprophylaxis with apixaban was not superior to a shorter course with enoxaparin. Apixaban was associated with significantly more major bleeding events than was enoxaparin.

A most difficult group of patients are those with atrial fibrillation who also have coronary artery disease and are submitted to percutaneous coronary intervention and stenting, which necessitates triple antithrombotic therapy.[9] The risk of bleeding in this subset is very high with current use of aspirin, clopidogrel and warfarin. However, with regards to combining antiplatelet therapy with the new oral anticoagulants, there currently exist no data.

Finally, a beacon of light has emerged in the management of acute coronary syndromes with the use of the newer anticoagulant, bivalirudin.[10-13] Bivalirudin is a direct thrombin inhibitor, used an as intravenous anticoagulant. Its efficacy has been demonstrated in the management of patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) or ST-segment elevation myocardial infarction (STEMI). In the ISAR-REACT 4 trial,[12] two antithrombotic regimens were compared, the combination of abciximab and unfractionated heparin with bivalirudin alone. Bivalidurin reduced the risk of bleeding in patients undergoing PCI for non–ST-segment elevation myocardial infarction without compromising efficacy. Major bleeding occurred in 4.6% of the patients in the abciximab group as compared with 2.6% in the bivalirudin group (relative risk, 1.84; P = 0.02). Similarly, in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction trial (HORIZONS-AMI), bivalirudin was superior to a glycoprotein IIb/IIIa inhibitor and heparin in patients undergoing primary PCI for ST-segment elevation myocardial infarction.[11] Patients experiencing periprocedural vascular complications after percutaneous coronary interventions, particularly those with severe bleeding, have an increased one-year mortality rate; the use of bivalirudin together

with closure devices has been shown to reduce the risk of such complications. [14]

Another intravenous direct thrombin inhibitor is argatroban.[15] The efficacy of argatroban has been demonstrated among patients with acute coronary syndromes and stroke. However, this drug is currently approved by the FDA only for the treatment of patients with heparin-induced thrombocytopenia. Although newer intravenous direct factor Xa inhibitors have been developed, they are still in the testing phase.[16] Fondaparinux is a long-acting indirect factor Xa inhibitor,[17] but its use was associated with a high rate of catheter-related thromboses and thus has not been well received.

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The Electrocardiogram in the Athlete

John Kapelakis, MD, Hector Anninos, MD

Department of Cardiology, Evagelismos Hospital, Athens, Greece

The electrocardiogram (ECG) is crucial in diagnosing a variety of cardiovascular conditions in the athlete and has been established as an important tool for pre-participation screening. However, several ECG abnormalities may be present even in competitive athletes which may increase with age and level of exercise and one should discern those which are common and related to training from those that are uncommon and training-unrelated. These issues and the recommendations of several authorities for the utility of ECG in this important group will be herein reviewed.