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EDITORIAL COMMENT

Matching the NOAC to the Patient

Remember the Modifiable Bleeding Risk Factors*



Gregory Y.H. Lip, MD,^{††} Deirdre A. Lane, PhD[‡]

Approximately 5 years ago, when deciding on oral anticoagulation (OAC) for stroke prevention in atrial fibrillation (AF), we did not have a choice; only the vitamin K antagonists (VKA; e.g., warfarin) were available. In 2015, in addition to VKAs, we currently have 4 licensed non-VKA oral anticoagulants (NOACs), and therefore have the opportunity to fit the most appropriate drug to the patient's risk profile, and vice versa.

OAC confers a risk of bleeding, including gastrointestinal (GI) bleeding, as do antiplatelet drugs. In their respective randomized trials, an excess of GI bleeding compared with warfarin was seen with dabigatran 150 mg bid, rivaroxaban, and edoxaban 60 mg (1). No excess GI bleeding was seen with dabigatran 110 mg or apixaban 5 mg bid. Overall, a lower rate of major bleeding was seen with dabigatran 110 mg bid, apixaban, and edoxaban when compared with warfarin. The lower risk of bleeding has been confirmed by indirect comparisons of the NOACs against each other (2).

In this issue of the *Journal*, Sherwood et al. (3) present an ancillary analysis from ROCKET-AF (Rivaroxaban Once-daily Oral Direct Factor Xa

Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), which evaluated GI bleeding in the on-treatment population. There were significantly more major or nonmajor clinically relevant GI bleeding events on rivaroxaban (3.61 vs. 2.60 events/100 patient-years; hazard ratio [HR]: 1.42; 95% CI: 1.22 to 1.66), compared with warfarin-treated

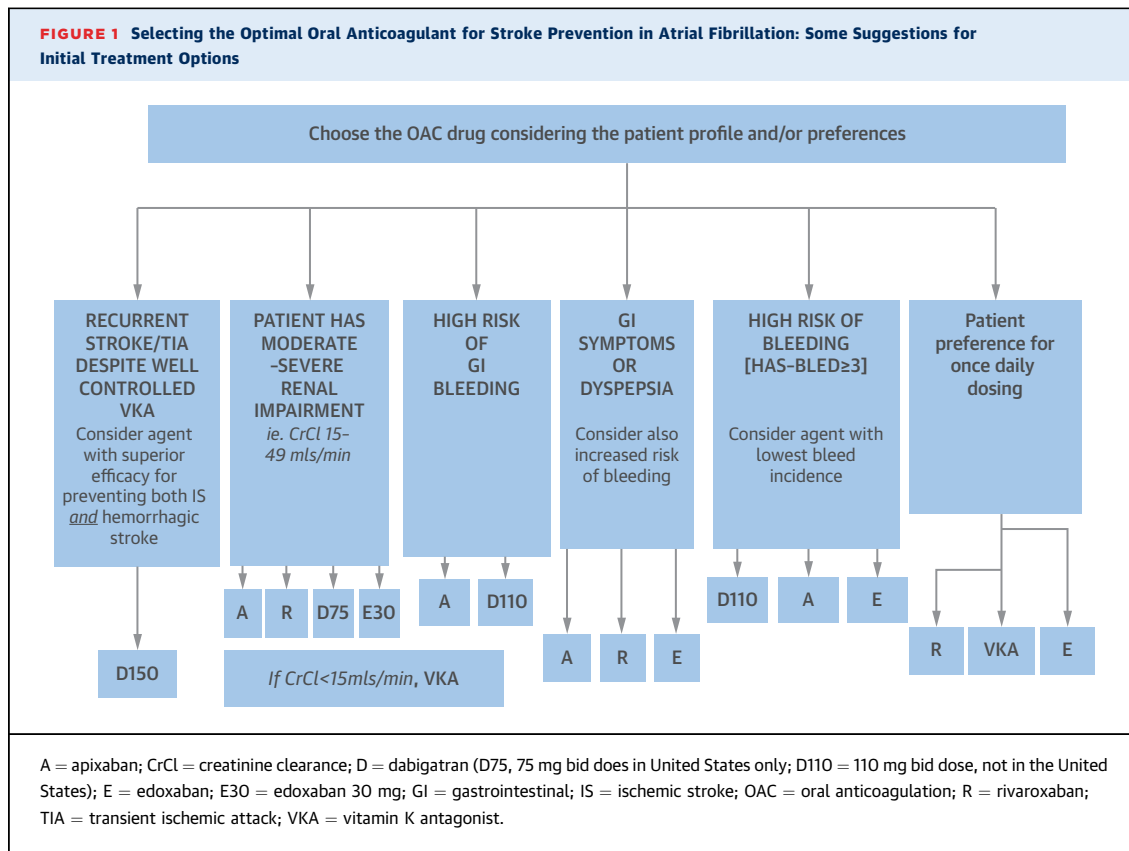
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patients. This increased risk of both major and clinically relevant nonmajor GI bleeding among patients taking rivaroxaban persisted in multivariable analyses. However, severe GI bleeding rates and location were similar between treatment arms (48% upper GI tract, 23% lower GI tract, and 29% rectal), with few fatal GI bleeding events.

Of note, the mean CHADS₂ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or TIA), CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age 65-74 years, sex category [female]), and HAS-BLED (uncontrolled systolic hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios [INRs], elderly [>65 years], concomitant antiplatelets, nonsteroidal anti-inflammatory drugs [NSAIDs], or excess alcohol) scores were similar in patients with and without GI bleeding. Stroke risk and bleeding risks track each other, and bleeding rates can rise with increasing CHADS₂ and CHA₂DS₂-VASc scores; however, the HAS-BLED score outperformed the 2 stroke risk scores for predicting clinically relevant bleeding (4,5). Attempts to derive a composite stroke and bleeding risk score offered additional complexity but minimal improvement in predictive value over the individual CHA₂DS₂-VASc or HAS-BLED scores (6,7). Thus, stroke risk should be assessed using

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a specific stroke risk score, that is, the CHA₂DS₂-VASc; and bleeding risk should be assessed using a specific bleeding risk score, HAS-BLED.

Clinical factors associated with GI bleeding in the ROCKET-AF cohort were anemia at baseline, prior history of GI bleeding, rivaroxaban (vs. warfarin use), and chronic aspirin or NSAIDs use. There was also a higher prevalence of renal impairment, diabetes, and hypertension among the patients with GI bleeding. Interestingly, many of these clinical factors are incorporated into the HAS-BLED score (8). The latter was proposed as a simple practical score to identify patients potentially at risk of bleeding for more vigilant follow-up and review, and to address the potentially reversible bleeding risk factors, that is, uncontrolled hypertension (the H in HAS-BLED), labile INRs (only applies if the patient is taking VKA, the L criterion), concomitant use of aspirin or NSAIDs with anticoagulation and/or alcohol excess (the D criterion in HAS-BLED), and so on (9).

The emphasis on correcting the potentially reversible bleeding risk factors is emphasized in guidelines from the European Society of Cardiology and the National Institute for Health and Care Excellence (10). Also, a high HAS-BLED score is not an excuse to withhold OAC. Indeed, Sherwood et al. (3)

emphasize the need for minimizing modifiable risk factors for GI bleeding in patients on OAC, which is a very sensible approach.

For example, a 55-year-old AF patient with poorly controlled hypertension, excessive alcohol intake, and taking warfarin with a time in therapeutic range (TTR) of 50% (i.e., poor anticoagulation control) would have a HAS-BLED score of 3 (i.e., high risk of bleeding). Consequently, the responsible physician would address that patient's risk factors by controlling blood pressure, reducing alcohol intake, and directing better efforts to improve the TTR or consider switching the patient to a NOAC. Thus, other bleeding risk scores that unduly simplify things by not incorporating parameters such as labile INRs (in a patient taking warfarin) or uncontrolled hypertension may erroneously categorize a patient as being at low risk, and potentially correctable bleeding risk factors may not be addressed.

Interestingly, some geographical variation was evident in GI bleeding. Quality of anticoagulation control in the warfarin arm, as reflected by the time in therapeutic range, was higher in North America (65.5%) compared with the rest of the world (55.7%). Patients in North America receiving rivaroxaban had

significantly higher GI bleeding hazard (1.89-fold) compared with warfarin. In this region, rivaroxaban was being compared with best managed warfarin (with a TTR of 65.5%) and bleeding on warfarin is very closely related to TTR (11,12). Hence, the 1.89-fold excess GI bleeding risk on rivaroxaban is perhaps unsurprising.

For the rest of the world, there was a 21% increase in GI bleeding risk on rivaroxaban compared with warfarin. In the rest of the world, the TTR was 55.7%, reflecting less optimal anticoagulation control on warfarin; despite this, there was still a 1.21-fold excess of GI bleeding. Inadequate time in therapeutic range is a continuing problem, and may be one explanation for the higher rates of thromboembolism and serious bleeding among Asians compared with non-Asians (13). Poor anticoagulation control (i.e., labile INRs) translates into an excess of thromboembolism, mortality, and bleeding (14).

Notwithstanding the issues with GI bleeding, we should not forget that, overall, the NOACs have changed the landscape for stroke prevention in AF. These drugs offer relative efficacy, safety, and convenience compared with the VKAs and, given the

availability of various NOAC drugs as well as VKAs (assuming good TTR), we are nowadays spoilt for choice, and have the opportunity to fit the drug to various patient characteristics (Figure 1). Even a single additional stroke risk factor confers a real increased risk of stroke and mortality that is significantly reduced by OAC (and with a positive net clinical benefit as well) (15,16). Thus, rather than a categorical approach to stroke risk stratification and treatment decisions, the initial step should be to identify those at “low risk” (i.e., CHA₂DS₂-VASc 0 in men, 1 in women) who do not need any antithrombotic therapy (9). The second step should then be to offer effective stroke prevention, which is OAC, to those AF patients with ≥1 additional stroke risk factors. Only such a proactive approach will help to reduce the burden of stroke associated with this common arrhythmia.

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