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Editorial

New Options for the Extended Treatment of Venous Thromboembolic Disease in Primary Care: Risk Stratification and Direct Oral Anticoagulants

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EDITORIAL

Venous Thromboembolism is the third most common cause of vascular death following acute myocardial infarction and stroke [1]. Men appear to have a 2 fold higher incidence of VTE after correcting for estrogen as a confounder [2] and an individual's lifetime risk approaches 8% from the age of 45. Without ongoing prophylaxis, almost 30% of all VTE patients will have a recurrent episode within ten years [3].

Patients presenting with so-called unprovoked or idiopathic VTE represent almost one third of all episodes of VTE and have a much higher risk of recurrence approaching 10% at 1 year and 30% at five [4]. The decision to extend anticoagulation beyond the typical 3 to 6 month mark in this group hinges on an accurate estimation of the risk of recurrence balanced by the risk of bleeding. Here we examine contemporary risk algorithms and review results of the four major VTE extension trials published to date.

Several algorithms have been established to assess an individual's risk of recurrent VTE. The DASH [5], Vienna [6], and HERDOO2 [7] prediction rules use various clinical parameters together with D-dimer levels, off treatment, to predict recurrence risk. Of these, only the HERDOO2 rule has been validated prospectively in a large cohort [8]. In a cohort of 2785 patients, Rodger et al. have recently shown that low risk women (HERDOO2 score < or = to 1) who discontinue anticoagulation have a 3% per year (CI 1.8% to 4.8%) recurrence risk. High risk women (HERDOO2 score > 1) and men who discontinue anticoagulation have a significantly higher recurrence rate of 8.1% (CI 5.2% to 11.9%). Such rules offer the hope that we will be able to predict a patient's individual risk and limit ongoing anticoagulation to those who will benefit most.

Historically, VTE has been managed with a combination of Heparin and a Vitamin K antagonist. Recently, four landmark trials have demonstrated efficacy and safety of two new classes of oral anticoagulants in the treatment of VTE [9]. Of these, Apixaban, Dagiatran, and Rivaroxaban have been assessed in randomized controlled trials enrolling patients with VTE where there exists clinical equipoise as to whether anticoagulation should be extended beyond the typical 3 to 6 month window [10-13].

Einstein-Extension [10] provided the first indication that extended treatment with a novel anticoagulant would be both safe and efficacious. 1196 patients were enrolled in this 6 to 12 month double-blind follow up study to assess the superiority of rivaroxaban 20 mg od versus placebo. The average age of trial participants was 58 years and 90% of these patients had a GFR > 30 ml/min. Almost three quarters of the study group (74%) entered the trial following an unprovoked VTE. The primary efficacy outcome (recurrent VTE) occurred in 1.3% of the rivaroxaban arm and 7.1% of the placebo arm, representing superiority. The principal safety outcome (major bleeding) was met in 0.7% of the rivaroxaban arm versus 0% in the placebo control. It would be appropriate to exercise caution if extrapolating these results to an older population with higher bleeding risk and with less robust measures of renal function.

The Amplify-Ext trial enrolled 2486 patients in a double-blind placebo controlled comparison of apixaban 5 mg bid versus 2.5 mg bid versus placebo. The mean age of trial participants was 56, 92% of whom had a GFR > 30 ml/min. Further, 93% of this study population had entered the trial following an unprovoked VTE. After 12 months 1.7%, 1.7% and 8.8% of patients receiving the 5 mg, 2.5 mg and placebo dose respectively, suffered a recurrent VTE. Corresponding rates of major bleeding were 0.1%, 0.2% and 0.5%, and of clinically relevant non-major bleeding were 4.2%, 3.0% and 2.3%. Overall, apixaban provided for significant reductions in recurrent VTE rates at virtual placebo-like bleed risk.

The RE-SONATE trial [12] enrolled 1343 patients in a double-blind fashion to dabigatran 150 mg bid or matching placebo. Trial participants had an average age of 55.5 years and an average GFR of 100 ml/min. This group was followed for a further 12 months

and assessed for recurrent VTE and non-fatal major bleeding. Dabigatran reduced subsequent VTE to 0.4% versus 5.6% seen with placebo. Bleed rates favored placebo at 1.8% versus the 5.3% seen in the dabigatran arm. There was no appreciable increase in myocardial infarction rate. Again, caution should be exercised in extrapolating these outcomes to an older population with less robust renal status and a higher bleed risk.

Finally a look at Einstein-Choice, the most recent VTE extension trial [13]. This is the largest extension trial to date enrolling 3396 patients. This is a more novel trial recognizing the importance of ASA in reducing the risk for recurrent VTE [14]. Accordingly, patients were randomized in a double blind fashion to receive rivaroxaban at either 20 mg or 10 mg od or ASA at 100 mg od and followed for up to 12 months. Recurrent VTE was documented in 1.5%, 1.2% and 4.4% of patients receiving 20 mg rivaroxaban, 10 mg rivaroxaban and 100 mg ASA respectively whereas major bleeding occurred in 0.5%, 0.4% and 0.3% correspondingly. Clinically relevant non-major bleeding occurred in 2.7% of those receiving 20 mg of rivaroxaban, in 2.0% of those receiving the 10 mg dose and in 1.8% of those receiving ASA. Overall, approximately 40% of the study population had entered the trial following an unprovoked VTE. The mean study age was approximately 58 years and 95% of the participants had a GFR > 50 ml/min. As observed in the Amplify-Ext trial we see virtually placebo-like bleeding complications and Factor Xa efficacy in Einstein-Choice. Again we must be cautious about extrapolating these results to a less clinically robust group with higher innate bleeding risks.

In summary, exciting new developments exist to more accurately predict an individual's risk for VTE recurrence. In addition, primary care physicians now have several new options for ongoing VTE prophylaxis that are evidence-based and supported by trials that have enrolled over 8400 participants. Specifically, we see placebo-like bleed risks using Factor Xa inhibitors in properly selected cohorts. We must continue to select our VTE prophylaxis patients carefully as we look forwards to further developments.

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