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Case Time! V.T. Edwards: Management of Extended Thromboprophylaxis in the Medically Ill

Announcer:
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Dr. Spyropoulos:
Hello. I'm Dr. Alex Spyropoulos, professor of medicine at the Zucker School of Medicine at Hofstra/Northwell and professor at the Institute of Health System Science as part of the Feinstein Institutes for Medical Research in New York. I will be discussing extended thromboprophylaxis in medically ill patients.

Let's begin with a case study. We have a 75-year-old male with a prior history of stroke and relative immobility, history of hypertension, and history of New York Heart Association Class 3 congestive heart failure with a distant history of DVT, who's hospitalized with a CHF exacerbation necessitating a short 1-day stay in the Coronary Care Unit. He has a distant history of GI bleeding associated with H. pylori infection that has been treated approximately 3 years ago.

His meds include baby aspirin as well as others. His relevant labs include a hemoglobin of 11.1, elevated D-dimers at 700 ng/mL, and moderately reduced renal function with eGFR 45 mL/min. He's ready to be discharged after a 5-day hospital stay. For post discharge from prophylaxis, you would, A, tell patient to continuous his baby aspirin, B, add rivaroxaban 10 mg for approximately 35 days post discharge to his meds, or C, add graduated compression stockings.

Now, we have consistent longitudinal data that tells us that the risk of VTE extends well beyond hospitalization in medical patients. The risk rises dramatically in the first 4 to 6 weeks post discharge and plateaus at about 6 weeks post discharge. Indeed, the shortened hospital length of stay, which is now down to about 4 to 5 days both in the United States but also in advanced health systems, has dampened the treatment effects of in-hospital thromboprophylaxis, thus shifting to the disease burden from the inpatient to the outpatient setting. In high-risk elderly medical patients now, the vast majority, approximately 80%, of VTEs now occur in this immediate post-hospital discharge setting. And if we couple that to the fact that less than 4% of hospitalized medical patients receive any type of post-hospital discharge thromboprophylaxis, we can see how, if we concentrate all our efforts on VTE prevention in the inpatient setting, we will do very little to reduce the disease burden of hospital-acquired thrombosis, which now remains firmly both in the inpatient as well as extended post-discharge settings.

It is for this reason that the last 10 years have seen multiple trials of extended thromboprophylaxis mostly utilizing the direct oral anticoagulants, or DOACs, in medically ill patients. These trials had mixed results. The ADOPT trial showed no evidence of the treatment effect with apixaban and, conversely, a two-and-a-half-fold increased risk of major bleeding. The MAGELLAN trial was the first of the DOAC trials that met its primary efficacy endpoint, showing a 23% risk reduction of total VTE with rivaroxaban, but this came at a price of a nearly threefold increased risk of major bleeding. The APEX trial, with a relatively novel DOAC, betrixaban, that is no longer available, also showed in the modified intent-to-treat population a 24% risk reduction of total VTE with betrixaban, and for the first time showed no evidence of excess major bleeding. And the largest trial in the field, the MARINER trial, which I was privileged enough

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to be the co-principal investigator, did not meet its primary efficacy endpoint, although it showed a 24% reduction of both symptomatic VTE and VTE-related death with rivaroxaban, but prespecified secondary endpoints showed a 56% reduction in symptomatic VTE and a 27% reduction in symptomatic VTE and all-cause mortality. And much like APEX, there is no evidence of excess major bleeding.

So what does the totality of evidence of extended thromboprophylaxis in this population tells us? Well, it tells us that in unselected patients, a strategy of extended thromboprophylaxis essentially robs Peter to pay Paul. In other words, we can expect a 40% reduction in symptomatic VTE and VTE-related death with extended prophylaxis, but this comes at an expense of a twofold increased risk in major and fatal bleeding. And it was because of this that the most recent antithrombotic guideline recommendations, including those of CHEST and the American Society of Hematology, either suggested or recommended against routine extended post-discharge thromboprophylaxis in this patient population.

Now, since the publication of these guidelines, there have been multiple, multiple novel data that tells us we're able to now identify a low bleed risk in high-VTE-risk population that significantly benefits from extended thromboprophylaxis. In these 2 studies from the MAGELLAN database, we were able to identify 5 key bleed risk factors, namely active cancer, dual antiplatelet therapy at baseline, any bleeding or active gastroduodenal ulcer within 3 months of hospitalization or the presence of bronchiectasis or pulmonary cavitation. Overall, we excluded these bleed risk factors. We were able to identify a low bleed risk population. And if we incorporated the validated improved VTE score that is shown on the left, using 7 clinical risk factors and score thresholds of 4 or more, and/or an elevated D-dimer, which represents a novel biomarker to predict VTE, we were able to predict a nearly threefold higher VTE risk group of hospitalized medical patients that significantly benefited from extended prophylaxis leading to a 32% relative or 2.5% absolute risk reduction of total VTE. And importantly, this did not come with an expense of an increased risk of major bleeding.

Also, more recent data tells us that a strategy of extended thromboprophylaxis, in this case with a DOAC rivaroxaban 10 mg, is able to reduce not only symptomatic VTE but arterial thromboembolism including myocardial infarction, stroke, and cardiovascular death by about 28% in this patient population. Also, recent data tells us that clinical decision support science has improved dramatically in the last decade or so as part of implementation science. Whereas previous efforts using multifaceted approaches and passive alerts, either a human or electronic, has had some effectiveness in increasing appropriate prophylaxis. The use of now active clinical decision support for thromboprophylaxis has shown greater effect in this arena.

Towards this end, our informatics group at Northwell developed an EHR-agnostic active clinical decision support tool incorporating the IMPROVEDD VTE risk score in medical inpatients. We then designed a cluster randomized trial which randomized 2 hospitals to usual care and 2 hospitals using this novel tool, both at admission as well as in the novel workflow at discharge, as well during the medication reconciliation process. We found that this tool had high adoption in the intervention group with a nearly 78% tool adoption rate, which ultimately led to significant increases of inpatient-appropriate thromboprophylaxis by about 50%, as well as significant extended post-discharge prophylaxis at hospital discharge in high-VTE-risk patient groups, those with an IMPROVEDD score 4 or more. This ultimately led to a 29% reduction in total thromboembolism, which included a 20% reduction in venous thromboembolism, a 65% reduction in arterial thromboembolism, and just as importantly, there's no evidence of excess major bleeding. Now, all-cause mortality was increased in the intervention group, which happened to contain more COVID-19 patients as this trial was done during the COVID pandemic.

So because of this new recent data, the most updated 2024 International Consensus Statement on VTE prevention, which represents the most comprehensive and up-to-date VTE guidelines on the topic, have this to say with respect to extended post-discharge prophylaxis. Again, a mod recommendation based on moderate level of evidence that formalized VTE risk assessment should be considered at discharge, as well as at admission. Extended duration thromboprophylaxis either with low-molecular heparin, such as enoxaparin once daily or rivaroxaban 10 mg daily, for approximately 30 days may be considered on an individualized basis, especially in those patients who, using a validated VTE risk tool such as IMPROVE, exhibit high-risk features. Lastly, health informatics technology in the form of electronic alerts or clinical decision support tools may be considered to identify key populations that may benefit both from in-hospital as well as extended post-discharge thromboprophylaxis.

So to conclude, we're entering a new paradigm in medically ill thromboprophylaxis, what I'd like to call an individualized patient-level, risk-adapted approach utilizing clinical decision support and electronic health record interoperability. Formalized VTE risk assessment should be considered at discharge as well due to the fact that many thrombotic events in medically ill patients are now occurring in the immediate post-hospital discharge period. And especially in those advanced health systems with very short hospital durations or length of stays for these populations, if they exhibit high individual VTE risk factors, such as advanced age or history of VTE or cancer or, better yet, using formalized, validated VTE risk models such as IMPROVE, using established thresholds, such as 4 or more, and have high-risk features, they should be offered extended thromboprophylaxis, either with rivaroxaban that is approved in the United States or the low-molecular heparin such as enoxaparin.

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So to conclude in the case study, our patient should be offered rivaroxaban 10 mg for up to 35 days post discharge. The patient has high individual VTE risk features such as advanced age or history of VTE, has a high IMPROVE or IMPROVEDD score of 6 to 8 with a threshold risk score 4 or more, has no high bleed risk criteria. They would benefit from extended post-discharge prophylaxis. Again, there's no data using mechanical methods in this setting, and approximately 50% of patients in the extended DOAC trials were on aspirin concurrently.

Thank you.

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