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The Most Important Takeaways From the New ASH Guidelines for the Management of Venous Thromboembolism

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H&O How many recent guidelines focus on the management of patients with venous thromboembolism (VTE) that is not associated with cancer?

MS The guidelines we are discussing, from Ortel and colleagues for the American Society of Hematology (ASH), were published in late 2020. The American College of Chest Physicians (ACCP) released guidelines in this space in 2016 with Kearon as the first author, and the Anticoagulation Forum released a guidance document that same year. In addition, the European Society of Cardiology published guidelines on deep vein thrombosis (DVT) in 2018 and on pulmonary embolism (PE) in 2020.

H&O How do these guidelines differ from one another?

MS What sets the ASH guidelines and the ACCP guidelines apart is that they rely on systematic review with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework used to evaluate the evidence. I formerly referred primarily to the ACCP guidelines, but in recent years I would say that the ASH guidelines have replaced the ACCP guidelines in many areas.

H&O How do the 2020 ASH guidelines differ from previous ones?

MS The majority of the recommendations from the 2020 ASH guidelines are similar in many ways to the 2016 ACCP guidelines. The main difference in initial management is that ASH recommends using a direct-acting oral coagulant (DOAC) rather than warfarin for patients with VTE, but it does not suggest using one DOAC over another (Recommendation 4). Practitioners have a choice because we do not have any randomized comparisons of the 4 DOACs.

Regarding secondary prevention, the ASH guidelines contain several new recommendations. First, ASH suggests that a prognostic score (eg, the Vienna Prediction Model or the HERDOO2 [hyperpigmentation, edema, redness, D-dimer, obesity, older age, 2 scores] decision rule), D-dimer testing, or ultrasound not be used routinely to guide the duration of anticoagulation by detecting residual vein thrombosis (Recommendations 15-17). Second, ASH now suggests using a standard or lower DOAC dose for patients who are continuing with a DOAC for secondary prevention (Recommendation 22). This is an important change reflecting data from the AMPLIFY-EXT and EINSTEIN CHOICE studies, which examined standard- and low-dose apixaban (Eliquis, Bristol-Myers Squibb) and rivaroxaban (Xarelto, Janssen). Third, ASH also provides guidance for the management of patients in whom VTE has been provoked by a transient risk factor and who have a history of a previous unprovoked VTE or a VTE provoked by a chronic risk factor (Recommendation 24). The ASH guidelines suggest that these patients receive antithrombotic therapy indefinitely. They also suggest that patients with a history of a previous VTE triggered by a transient risk factor who experience a recurrent VTE due

to a transient risk factor should stop anticoagulation after the completion of primary therapy rather than continue with therapy indefinitely. This is important new guidance for the long-term management of VTE that was not provided in previous guidelines.

As far as additional management issues are concerned, ASH now provides suggestions for the management of patients with VTE who have stable cardiovascular disease in whom anticoagulation is initiated and who were previously taking aspirin for cardiovascular risk modification. They suggest that aspirin use be suspended rather than continued for the duration of anticoagulation therapy (Recommendation 26).

Other recommendations remain unchanged. For example, for the acute treatment of uncomplicated DVT or PE, the emphasis remains on treating most patients at home rather than keeping them in the hospital. Practitioners have the option of using either validated risk criteria or their clinical judgment to determine which patients are appropriate candidates for home treatment of PE. Thrombolytic therapy is recommended for patients with hemodynamically significant PE, and catheter-directed thrombolysis is suggested over systemic thrombolysis when thrombolysis is being considered for those with extensive DVT.

The ASH guidelines will be a tremendous resource for providers who care for a large variety of patients.

H&O Have you changed your approach at all to the management of patients with VTE on the basis of these guidelines?

MS I spend a significant amount of time caring for patients with VTE, so in most instances my practice already conformed to the recommendations outlined in the ASH guidelines. I think this true for anyone whose practice is similar to mine. However, having a panel of experts rigorously evaluate the evidence does increase my confidence that I am doing the right thing for my patients. The ASH guidelines will be a tremendous resource for providers who care for a large variety of patients. They provide a thorough review of the literature in this area and formulate evidence-based practical recommendations.

H&O What are the most important studies that have come out over the past few years that have changed treatment?

MS One of the most important studies is EINSTEIN CHOICE, which was published in the *New England Journal of Medicine* in 2017. As mentioned earlier, this study concluded that either standard- or low-dose DOACs can be used for secondary prevention—the basis for Recommendation 22. Before that, the most important study was AMPLIFY-EXT, which informed the recommendations regarding apixaban.

An important study that led to the recommendation for anticoagulation rather than catheter-directed thrombolysis for the treatment of DVT in most patients was the ATTRACT trial that Vedantham and colleagues published in the *New England Journal of Medicine* in 2017. This study was the basis for Recommendation 5, which suggests that anticoagulation therapy alone rather than catheter-directed thrombectomy is appropriate for most patients with proximal DVT. It also served as the basis for Recommendation 8, which suggests the use of catheter-directed thrombolysis rather than systemic thrombolysis for patients with extensive DVT who are appropriate candidates for catheter-based intervention. Before the ATTRACT trial, I think we were much more liberal in the use of catheter-directed thrombolysis.

A very important, somewhat older study is the SOX trial, a randomized double-blind study of graduated compression stockings for prevention of post-thrombotic syndrome. SOX found that graduated compression stockings did not prevent post-thrombotic syndrome. This study, which was published in 2014, provides the evidentiary basis for Recommendations 27 and 28, which advise against the use of graduated compression stockings to prevent post-thrombotic syndrome.

Another important study related to thrombolysis for PE is the PEITHO study by Meyer and colleagues, which was published in the *New England Journal of Medicine* in 2014. PEITHO found that systemic thrombolysis with tenecteplase (TNKase, Genentech) significantly increased the risk for bleeding complications compared with anticoagulation alone, without decreasing mortality. That study—in conjunction with the randomized trial of tissue plasminogen activator (tPA) published by Konstantinides and colleagues in the *New England Journal of Medicine* in 2002—has significantly influenced our use of systemic thrombolysis in acute PE, reserving it primarily for patients with hemodynamically significant PE. These studies led to Recommendation 6, which recommends the use of thrombolytic therapy followed by anticoagulation rather than anticoagulation alone in patients with PE and hemodynamic compromise, and to Recommendation 7,

which suggests anticoagulation alone rather than systemic thrombolysis for patients with non–hemodynamically significant PE.

H&O What questions remain regarding VTE that future guidelines might be able to address?

MS A number of important questions remain to be addressed by randomized trials. For example, are there any clinically important differences between DOACs for treatment of VTE? Randomized trials comparing DOACs and vitamin K antagonists for special patient populations, such as over- and underweight patients and those with severe chronic kidney disease, would also provide important information for management of these special patient populations.

Another important question regards the management of patients without cancer who have an isolated subsegmental PE without coexisting lower extremity DVT. Are the risks of anticoagulation worth the benefits in these patients? Two studies are currently looking at this question: SAFE-SSPE (NCT04263038) and SSPE (NCT01455818). Answering this question is important because anticoagulation carries a significant risk of bleeding, so we should avoid it in patients who do not stand to benefit. Additional study of patients with splanchnic vein thrombosis, which includes hepatic vein thrombosis, portal vein thrombosis, and mesenteric vein thrombosis, should be undertaken. Should all these patients receive anticoagulation, and if so, what is the appropriate duration of therapy? Cerebral venous sinus thrombosis is another important but less common form of venous thrombosis. Should these patients be treated in a similar fashion as patients with DVT or PE in regards to duration of therapy? The appropriate duration of therapy remains unclear.

Another important study is RENOVE, which is a large, randomized phase 3 study comparing low-dose with standard-dose DOACs (NCT03285438). I expect this study will provide important information that will influence practice and guide future recommendations.

Disclosure

Dr Streiff has received honoraria from and conducted a CME lecture for Bayer; has done consulting for Bristol-Myers Squibb and DisperSol Technologies; has done consulting, served on the advisory board, and received a grant from Janssen; has received grants from Novo Nordisk and Sanofi; has conducted a CME lecture, done consulting, and served on the advisory board for Pfizer; and has conducted a CME lecture and done consulting for Portola Pharmaceuticals.

Suggested Readings

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