ASH 2011: Clinically Relevant Highlights Regarding Venous Thromboembolism and Anticoagulation

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The annual meeting of the American Society of Hematology took place in San Diego from Dec 10-13, 2011. The listing below is my personal view of what I thought were the interesting and clinically relevant abstracts on thrombosis and anticoagulation. I thought only one abstract was clinical-practice-changing – abstract #543: "Aspirin after oral anticoagulants for prevention of recurrence in patients with unprovoked VTE. The WARFASA study". Below are brief summaries of the abstracts. It is, of course, important to keep in mind that these are only abstracts, not peer-reviewed full publications. Thus, interpretation of the presented data is limited.

A. ASPIRIN PREVENTS RECURRENT VENOUS THROMBOEMBOLISM

Summary: Fascinating news. In patients with a history of unprovoked VTE treated for 6-18 months with warfarin, subsequent aspirin was much more effective than placebo in preventing recurrent VTE (abstract #543).

Details: There has been some evidence over the years that aspirin protects against VTE, but the effect observed has been mild. The WARFASA study presented at ASH 2011 investigated patients with a history of unprovoked VTE, enrolling them after they had been treated with warfarin for 6-18 months. They were then randomized to aspirin 100 mg /day or placebo and followed for an average of 2 years. It was a double-blind design. Primary endpoints were symptomatic VTE and fatal PE. 403 patients were enrolled: 205 received aspirin, 198 placebo. Recurrent VTE occurred in 11.0 % of patients treated with placebo, and in 5.9 % on aspirin. Aspirin lead to a 40 % risk reduction. Major bleeding and clinically relevant non-major bleeding occurred similarly in both treatment groups.

Perspective: The study findings are remarkable. Aspirin can prevent some DVTs and PEs, with no detectable increase in bleeding risk. Consequences for my practice:

- Does this study change my clinical practice? Yes. I used to tell patients who came off warfarin after treatment for an appropriate length of time (often 3-6 months) that there was no strong reason to take aspirin. I will now tell them that, once they stop warfarin, it is worthwhile to take aspirin long-term.
- What dose will I recommend? I will tell the patient that here in the U.S. where we do not have 100 mg tablet sizes, either a baby aspirin (81 mg) or an adult aspirin (325 mg) would be appropriate.
- Would I recommend that patients who are on long-term warfarin now stop warfarin and switch to aspirin instead? No. Clearly not. Warfarin is much more effective than aspirin. Aspirin is not a replacement for warfarin.

A few limitations of this study need to be highlighted: (a) It has not yet been published in a peer-reviewed journal; and (b) a follow-up study is needed to see whether the results can be confirmed.

B. NEW ORAL ANTICOAGULANTS

a. ***Dabigatran in acute venous thromboembolism (VTE)***

Summary: A relevant phase 3 study was presented at ASH 2011 (abstract # 205). May be this study will lead to FDA approval of Pradaxa® (Dabigatran) for the VTE indication.
Details: At present, Dabigatran is FDA approved in the U.S. for atrial fibrillation, but not for VTE. The large RECOVER I trial in the past had shown that Dabigatran and warfarin taken for 6 months for acute VTE were equally effective in preventing recurrent VTE and were equally safe [Schulman S et al, NEJM 2009]. The FDA had mandated a follow-up study before considering approval of the drug. The RECOVER II trial now presented was a replica study; a large phase 3 randomized double-blind trial of patients with acute VTE. As in RECOVER I, Dabigatran was not given right off the bat, but only after 5 to 11 days of LMWH or heparin therapy. Dabigatran dose: 150 mg twice daily; length of treatment: 6 months. 2.4 % of 1,279 patients randomized to Dabigatran had a recurrent symptomatic VTE, compared with 2.2 % in the warfarin arm. Conclusions: (a) Dabigatran and warfarin were equally effective, and (b) there was no difference in major bleeding between the two groups.

b. **H*ow to manage major bleeding on the new oral anticoagulants?***

Summary: No data on this topic helpful for patient management were presented at ASH 2011. Clinical strategies how to manage major and life-threatening bleeding on Dabigatran have recently been published: (a) by ASH: "2011 Clinical Practice Guide on Anticoagulant Dosing and Management of Anticoagulant-Associated Bleeding Complications in Adults" [http://www.hematology.org/Practice/Guidelines/2934.aspx].) and (b) by Clot Connect [http://professionalsblog.clotconnect.org/2011/04/26/pradaxa-dabigatran-hospital-guideline/].
Details: Abstract #2316 showed that in a rat-tail bleeding model non-activated and activated prothrombin complex concentrates (PCC) and recombinant factor VIIa (rVIIa) reversed the Dabigatran-induced bleeding, even though the coagulation test prolongations did not correct. Abstract #1252 showed that in *ex vivo* plasma spiking studies coagulation test prolongations induced by the new (non FDA approved) oral anticoagulant Edoxaban were reversible. No conclusions from these *ex vivo* and animal studies can be drawn that would help with clinical decision making in bleeding patients.

c. ***How to monitor Dabigatran or Rivaroxaban, if need be?***

Summary: Data on two monitoring tests were presented at ASH 2011: (a) The Hemoclot® test, a dilute thrombin clotting time test (TCT or TT), appears to be useful in monitoring Dabigatran (abstract #2307); (b) The PiCT test (Prothrombinase induced Clotting Test) may be useful for monitoring of Dabigatran, Rivaroxaban or Apixaban (abstract # 3363). However, neither test is widely available in routine clinical practice.
Details: In case of bleeding or thrombosis in the patient on Dabigatran or Rivaroxaban, the clinician may want to have available a monitoring test to determine whether a patient is supra- or sub-therapeutic on the anticoagulant drug. In addition, prior to major surgery that has a high risk for bleeding, a physician may want to make sure that no residual drug is circulating in the patient. Limited published date exist as to which coagulation test is best used to determine drug overdose or residual levels of anticoagulant. The Hemoclot® test (abstract #2307) appears to be useful in monitoring Dabigatran (b) The PiCT test (Prothrombinase induced Clotting Test) may be useful for monitoring of Dabigatran, Rivaroxaban or Apixaban (abstract # 3363). At this time, for Dabigatran monitoring the

Ecarin clotting time (not widely available either) and may be the aPTT and thrombin time (limited availability) may be the most useful tests to obtain, depending on the purpose of testing. For determination of Rivaroxaban overdose or residual circulating drug activity the monitoring, the PT may be most suitable.

C. LENGTH OF ANTICOAGULATION IN VENOUS THROMBOEMBOLISM

a. ***Should family history of VTE influence length of anticoagulation in a patient with first unprovoked VTE?***
Summary: No. At least based on this study (abstract #2299), even though it was limited by relatively small numbers of relatives with VTE.
Details: Many physicians assume that a strong family history of VTE indicates that a patient who has had VTE is at high risk of recurrence if he/she comes off anticoagulation. However, it is not known whether that is true. Abstract #2299 presented data from a large multicenter prospective study, in which 669 patients with unprovoked VTE were enrolled. Detailed family histories were obtained. Findings and conclusions were that a family history of VTE is not a predictor for recurrent VTE and should, therefore, not be used to determine length of anticoagulation therapy.

b. ***How to predict which patient with unprovoked VTE needs long-term anticoagulation and which patient does not?***
Summary: The DASH score (details described below) can separate patients with unprovoked VTE into those with a low risk of recurrence in whom anticoagulation can be discontinued after few months of treatment, and those who should be on long-term anticoagulation because of a high risk of recurrence (abstract #544). However, at this point I would not use the DASH score for clinical decision-making.
Details: The authors performed a meta-analysis of 7 prospective studies of patients with unprovoked DVT who had been treated for at least 3 months with vitamin K antagonists, and determined what characteristics were indicators of a high risk of recurrent VTE. Main predictors of recurrence were abnormal D-dimer after stopping anticoagulation, age < 50 years, male gender, and VTE not associated with hormonal therapy. A predictive recurrence score was then created – "DASH score" (D-dimer, Age, Sex, Hormones) -, with the following points: (a) +2 for abnormal post-anticoagulation D-dimer, (b) +1 for age < 50 years, (c) +1 for male gender, (d) -2 for hormone use. The annual recurrence rate was: 3.1 % for DASH score ≤1; 6.4 % for DASH score of 2; 12.3 % for score of ≥ 3. As the risk of recurrence is low with a DASH score of ≤1, these are patients with unprovoked VTE in whom long-term anticoagulation is not needed. These are about 50 % of patients with unprovoked VTE. The DASH score needs to be validated. In addition, a discrepancy with another existing scoring system - the HERDOO-2 score (also not validated) - needs to be resolved. The discrepancy is that in the DASH score a younger age (< 50 years) is a predictor of recurrence, whereas in the HERDOO-2 score age > 70 years predicts a higher risk of recurrence. So, it is not clear at this point whether it is worse to be young or old when it comes to VTE recurrence risk.

D. CANCER AND VENOUS THROMBOEMBOLISM

a. ***VTE prevention with LMWH in outpatient cancer patients receiving chemotherapy***
Summary: The once daily s.c. ultra-LMWH Semuloparin given for VTE prophylaxis in

cancer patients receiving chemotherapy decreases the occurrence of symptomatic VTE, without increasing major bleeding. The benefit is particularly seen in patients at moderate and high risk for VTE as assessed by the Khorana score [Khorana A et al. Blood 2008;111:4902-7].
Details: The phase 3 SAVE-ONCO trial investigated once daily ultra-LMWH Semuloparin (by Sanofi) versus placebo for VTE prevention in cancer patients receiving chemotherapy. 3212 patients were randomized and treated for a median of 3.5 months. Patients' baseline VTE risk was assessed by the Khorana score to determine which risk-category of patients may benefit most from VTE prophylaxis. Endpoints were symptomatic VTE or VTE-related death. In the overall study population, the primary endpoint occurred in 1.2 % of patients, compared to 3.4 % of the placebo-treated patients. A reduction of VTE occurrence with Semuloparin was seen in all VTE-risk groups, but particularly, to no surprise, in the high VTE risk patients: 1.5 % and 5.4 % in the Semuloparin and placebo groups had VTE in this high-risk group. The incidence of major bleeding was similar: 1.2 % and 1.1 % in the Semuloparin and placebo groups.

b. ***How long should cancer patients with VTE due to major surgery be treated?***
Summary: It is recommended by ASCO, ACCP, and NCCN guidelines that cancer patients with DVT or PE should be treated with anticoagulants "indefinitely or until the cancer is resolved". However, it is not known whether cancer patients with major surgery associated VTE truly have a high risk of recurrent VTE that would justify long-term anticoagulation therapy.
Details: This was a single-center cohort study (abstract #3342). Of 220 cancer patients with symptomatic VTE, 42 had had major surgery within 3 months of the diagnosis of VTE, and thus, were classified as having had surgery-associated VTE The majority of these patients were treated with anticoagulation for only 6 months, whereas the other VTE patients remained on longer-term anticoagulation. The risk of recurrent VTE was much lower in the surgery-associated VTE patients than in the non-surgical cancer patients: 2.8 % versus 11.3 % at 6 months, 3.0 % versus 16.2 % at 1 year, and 9.3 % versus 27.5 % at 2 years. Thus, clearly, the risk of recurrent VTE was lower in the surgery-associated VTE cancer patients. However, whether the risk is low enough to warrant time-limited anticoagulation for only 3 or 6 months only, is not clear at this point.

E. OTHERS

a. ***Subsegmental PE – is it really a PE? Is it clinically relevant? Should we anticoagulate?***
Summary: A patient who is said to have "isolated subsegmental PE" by CTA may actually not have a PE – there is only moderate agreement in CTA interpretation between radiologists when it comes to such PEs. In addition, it is not clear whether patients with isolated subsegmental PE benefit from anticoagulant therapy – the risk-benefit ratio is unclear.
Details: 70 patients who had presented with suspected PE and had been diagnosed by CTA with isolated subsegmental PE were retrospectively studied: (a) The CTA images were reviewed by a blinded thoracic radiologist. In only 44 % of cases did the radiologist agree with the original diagnosis. (b) Of the70 patients, 26 % did not receive anticoagulation and none had a recurrent VTE during 3 months of follow-up. One of the patients who did receive anticoagulation had a major bleed.

b. ***Are progestin contraceptives save from a VTE point of view?***
Summary: Progestin-only oral formulations used for contraception do not appear to increase the risk for VTE, but injectable progestins do.
Details: A review of the published literature identified 7 studies investigating the risk of VTE associated with various progestin-only contraceptives (abstract # 3344). A table in the abstract lists the 7 studies, the study designs, the drug formulations, and the adjusted risk ratio for VTE. The overall risk for VTE with injectable progestins was 2.67 (CI 1.29-5.53) compared to individuals not taking hormonal contraceptives, whereas oral progestin-only contraceptives did not increase the VTE risk (RR 0.87; CI 0.53-1.42).