Informal Highlights from the Thrombosis & Hemostasis Summit of North America
April 14-16, 2016

The 3rd annual Thrombosis & Hemostasis Summit of North America was held in Chicago April 14-16, 2016. The three-day program featured over 100 lectures on the latest research findings in the world of blood disorders. The following represents a few highlights selected by members of the board of the National Blood Clot Alliance.

John Heit MD - Thrombophilia Testing: Who?

On the opening day of the Congress, Thursday April 14, 2016, John Heit, MD, Emeritus Professor of Medicine, Laboratory Medicine and Pathology at the Mayo Clinic, discussed his approach to thrombophilia testing in his lecture entitled, *Thrombophilia Testing: Who?* At the outset, he reviewed the pathophysiology of clot formation. In the normal state, the proteins that promote clot formation are counterbalanced by those that oppose clot formation and promote dissolution of clots such that clots do not develop. The careful balance of these opposing systems ensures that blood clots form at the sites of vascular injury (e.g., a cut, an injury, a surgical incision) to prevent blood loss but do not grow to the point where they occlude the vessel cutting off blood flow to the surrounding tissues. Thrombosis occurs when this balance is disrupted and the summation of prothrombotic forces exceed those preventing blood clot formation. Both inherited (e.g., factor V Leiden, prothrombin gene mutation, antithrombin deficiency, etc.) and acquired (surgery, cancer, antiphospholipid syndrome, etc.) conditions can predispose individuals to excess clot formation. Inherited conditions that predispose toward clot formation are often called thrombophilic disorders or thrombophilia (Latin for "clot loving"). Thrombophilia has been associated with the development of deep venous thrombosis (DVT) and pulmonary embolism (PE).

Potent inherited thrombophilic states include antithrombin deficiency, protein C, and protein S deficiency. These disorders are often considered reasons to consider long term anticoagulation after an initial proximal DVT or PE. In contrast, patients who only have one copy of the factor V Leiden mutation or the prothrombin gene mutation are not considered at sufficient risk to warrant long term anticoagulation in most instances. Patients with one copy of both the factor V Leiden gene and the prothrombin gene, as well as patients with two copies of the prothrombin gene, are also considered to be at higher risk for recurrent blood clots, while a recent study indicates that patients with two copies of the factor V Leiden gene may not be at sufficient risk to warrant long term anticoagulation. For patients with a first episode of VTE, one could consider testing for antithrombin deficiency and antiphospholipid syndrome, since these conditions are associated with a substantial risk for recurrent VTE. Other characteristics associated with a significant risk for recurrence include unprovoked DVT or PE, cancer (especially metastatic disease), and male gender. Factors associated with a reduced risk for recurrence include clots associated with oral contraceptives, pregnancy or the postpartum period, or gynecologic surgery.

Among active cancer patients, those with metastatic pancreatic and lung cancer, brain tumors, polycythemia vera, ovarian cancer and those with progressive cancer are at increased risk for recurrent blood clots. Among patients with unprovoked VTE, there are several risk prediction models (HERDOO2, Vienna and DASH) that can be used in conjunction with D dimer tests to identify patients at lower risk for recurrence who might be eligible to safely discontinue anticoagulation. Dr. Heit also reviewed predictors of recurrent events among patients who are no longer on anticoagulation. These included a new diagnosis of cancer, a new hospitalization for a surgical or medical illness, a respiratory infection, and new pregnancy. Aspirin and warfarin use were associated with a reduced risk of recurrence in these patients. Presence of these risk factors should prompt providers to consider anticoagulant prophylaxis for these risk periods.

The presence of factor V Leiden and the prothrombin gene mutation have been associated with a modest risk for recurrent VTE, so in isolation they are not a reason for prolonged anticoagulation. Family studies have demonstrated that antithrombin, protein C and protein S deficiency are associated with a significant risk for

recurrence. Antiphospholipid syndrome has been associated with an increased risk of recurrence, as well although a recent metaanalysis found that this association has been inconsistent and further studies are warranted to further define the risk of recurrence with APS. Elevated homocysteine levels (> 90th percentile) have been associated with a moderate risk of recurrence that is not reduced by vitamin supplementation. Elevated factor VIII levels (> 90th percentile) have been associated with a 4-fold increased risk of recurrence but using factor VIII as a marker for recurrence risk is complicated by its role as an acute response protein. Despite the data showing the association of thrombophilia with an increased risk of recurrence, several prospective studies have not found that thrombophilia testing was helpful in predicting recurrence risk. Consequently, the role of thrombophilia testing in the routine management of patients is unclear. At this point the ACCP Guidelines do not recommend that thrombophilia testing be performed routinely in the management of patients with VTE. In patients who develop thrombosis in unusual locations, such as the abdomen or cerebral veins, physicians should consider paroxysmal nocturnal hemoglobinuria and polycythemia vera. In patients with renal vein thrombosis, it is important to look for the presence of acquired antithrombin deficiency associated with nephrotic syndrome. Since individual thrombophilia states are typically insufficient to warrant changes in management, Dr. Heit proposed that development of multivariate risk factor models that incorporate inherited and acquired thrombophilic risk factors (factor V Leiden, medical illness, oral contraceptive use, etc.) are likely to be the future role of thrombophilic testing in the management of VTE. Risk stratification models for identifying patients at risk for VTE during a hospital stay, assessing recurrence risk after an initial unprovoked VTE, and for incident VTE in patients with active cancer have already been developed and are in the process of being validated. Examples of the interaction between inherited and acquired risk factors for VTE include the synergistic interaction between factor V Leiden carrier status and total hip or knee arthroplasty or minor trauma or oral contraceptives and pregnancy. High throughput sequencing has allowed the discovery of new genetic risk factors that synergize with acquired risk factors in increasing VTE risk. While these findings are exciting, Dr. Heit cautioned that integration of this knowledge into routine care will require a careful balance of the cost of testing with value in management and independently validating new risk models.

Clive Kearon - Simplified Diagnosis of DVT/PE

The goal of VTE diagnostic testing is to identify patients who have a DVT or PE and are likely to benefit from anticoagulation. The Wells score is a validated check list of signs and symptoms of DVT and PE that has been demonstrated in multiple studies to be useful in identifying patients who are likely or unlikely to have VTE such that objectively radiologic testing is unnecessary to rule out DVT/PE. In patients deemed to be a high risk for VTE, the prevalence of DVT or PE is 75%. In those judged to be at moderate risk the prevalence is 25% and in those at low risk the prevalence is less than 10%. D dimer is a fragment of crosslinked fibrin clot that is a marker of active clot formation. D dimer testing is often done in conjunction with Weels criteria to determine if further radiologic testing should be performed. In patients judged to be at high risk for VTE using the Wells model, D dimer testing has little benefit as the test is rarely negative in this population so proceeding directly to duplex studies is appropriate. Since the level of D dimer increases with age, a number of retrospective studies and one prospective study have determined that the abnormal or positive D dimer threshold should be 500 ug/L for patients 50 years of age and younger, while among those older than 50 years, an adjusted threshold (age X 10ug/L) should be used as the threshold for a positive (abnormal) test. To reduce the number of abnormal D dimer studies and thus need for objective radiologic testing, some have advocated for using a D dimer threshold that is adjusted by the clinical probability of disease as judged by the Wells criteria. For patients with a moderate PTP the threshold would be 500ug/dL, while for those with a low PTP the threshold would be 1000 ug/dL. This approach has been demonstrated to be effective in several retrospective studies and one prospective randomized trial. Dr Kearon recommended that D dimer testing is not worthwhile in patients with a high PTP or the patient who has a condition such as a recent surgery or active cancer that are associated with a very high prevalence of abnormal D dimer results so very few patients would be excluded and the vast majority would need objective radiologic testing. In patients with a low PTP, a negative D dimer excludes a DVT. If using a highly sensitive D dimer test a

negative D dimer excludes DVT even if intermediate PTP. If imaging must be performed (high PTP or moderate PTP and negative moderate sensitive D dimer or positive D dimer any PTP, then imaging must be performed. Then compression ultrasound is the test of choice for DVT diagnosis. This test identifies DVT by imaging the vessel and using compression to demonstrate that the vessel walls can be compressed together. If there is a clot present then it will appear as a mass in the vessel lumen that blocks compression of the vessel walls together. Duplex ultrasound combines this with Doppler flow imaging which can detect blood flow and demonstrate the presence of clots as a static mass in the column of flowing blood. Both proximal leg and whole leg ultrasound are used for DVT diagnosis. Proximal leg ultrasound has high sensitivity and specificity for proximal DVT and picks up the most relevant events – proximal DVT. A limitation of proximal US is that it does exclude all DVT and so a second US in 1 week required to rule out progression of distal DVT that may progress into the proximal leg in the interim. In contrast, whole leg US more complex study that requires greater time to perform and higher degree of training and picks up some DVT (distal DVT of controversial importance that in some cases resolve without therapy and at low risk for embolisation. The advantage of whole leg US is that if negative it excludes all DVT and can be used as a standalone test to rule out DVT without requiring a second study.

In the event of a previous DVT, then US must demonstrate involvement of a new vessel or significant increase in thrombus in previously involved segment (> 4 mm diam > 10 cm length). If these criteria are not fulfilled, then serial duplex is required to rule out a new event or demonstration of no new findings on venography.

For PE, a negative good quality multi detector study rule out a PE. However, the positive predictive value of CT declines as clinical suspicion decrease such that main or lobar thrombus has a high positive predictive value of PE (97%) while segmental only have on average a 68% PPV (64% in low PTP patients!) and subsegmental findings only have a PPV on average of 25% . In patients with a contrast dye allergy or poor renal function, VQ scans may be preferred. Unfortunately, only 25% of V/Q scans are normal ruling out PE and only 10% are high probability so 65% are non-diagnostic. Single photon emission V/Q scanning has been reported as being superior for diagnosis but no large prospective studies have been performed and no studies have employed the gold standard of following patients with negative scans for 3 months without anticoagulation. These studies are warranted. In the vast majority of cases with a combination of pre-test probability assessment, D dimer and objective imaging sufficient diagnostic information can be obtained to implement a plan of care.

Bil Geerts - IVC Filters

Two different classes of IVC filters are currently available on the US market, permanent filters (ie, Greenfield filter) which are designed for permanent placement and can only be removed or excluded from vascular flow with significant expertise and retrievable filters (Denali, Celect) which are designed for retrieval and can be retrieved with considerable degree of success (>95%). Compared with the EU, the US places 25-fold more IVC filters (225,000 versus 9000). Since outcomes for VTE are similar between the US and the EU, this suggests that physicians in the US place many more filters than are required by the clinical situations faced by their patients. Dramatic differences in regional use inside the US also support this hypothesis. This dramatic increase in filter use coincides with the availability of retrievable filters which offer the option for removal at a later date. Filters are used for treatment (patients with acute DVT/PE who cannot be anticoagulated) and prophylactic (prevention of PE in patients at high risk for PE). Among several thousand publications regarding IVC filters, only two report randomized controlled trials. The PREPIC study published in 1998 by Decousus et.al. randomized patients with acute DVT and/or PE at high risk for PE to anticoagulation alone or anticoagulation plus a permanent IVC filter. They found that an IVC filter significantly reduced the incidence of PE at 12 days (from 4.8% to 1%) and 2 years (from 6.3% to 3.4%) at the expense of a significant increase in DVT (from 12% to 21%) with no impact on mortality. In conjunction with case series of patients treated with filters without anticoagulation, these data suggest that filters are effective in prevention of PE in patients who cannot be anticoagulated. In 2015, the second PREPIC trial was published. It randomized patients with acute high risk PE to anticoagulation alone or anticoagulation plus a retrievable IVC

filter. At 3 months, there was no difference in PE (AC 1.5% versus AC + IVCF 3%), DVT or death. There are no randomized controlled trials supporting IVC filters for prevent of PE in patient populations at high risk for PE. Therefore, IVC filters should only be used in patients who have an acute DVT/PE and cannot be treated with AC.

Nigel Makcman - Tissue Factor and Thrombosis in Cancer

Tissue factor is the only coagulation factor that normally is not in contact with blood. It is sequestered and highly expressed in the tissues just outside the inner lining of the blood vessels. This arrangement makes perfect biological sense, because tissue factor activates the first coagulation protein involved in the initiation of the coagulation cascade, factor VII. In this location it will not activate the clotting mechanism unless there is an injury to tissue/vessel wall that exposes tissue factor to the blood stream which activates factor VII and initiates the blood clotting response. Tissue factor is present in two forms; an encrypted form which does not readily activate factor VII and an unencrypted form which binds to activate factor VII forming a complex which activates the coagulation cascade. Abnormal cells including cancer cells, dying cells and immune cells activated by an infection or inflammatory stimulus can break up into small cellular particle that express tissue factor on their surface. These are known as tissue factor expressing microparticles and have been associated with an increased risk for clot formation. Cancer patients are 4-7 fold greater risk for thrombosis than patients without cancer. A number of intrinsic and extrinsic factors have been linked to an increased risk of clot formation in cancer patients including the primary site of cancer, its stage, cancer treatments, the presence of high platelets counts and anemia, inherited and acquired coagulation disorders and patients characteristics (age, comorbid medical conditions, immobility and obesity). The Khorana risk score is an evidence-based risk stratification tool that incorporates some of this risk factors and has been shown to predict a patient's risk for developing a blood clot during chemotherapy. Currently, guidelines do not recommend routine use of blood thinners to prevent cancer patients from developing a blood clot although several ongoing studies are assessing the efficacy of this strategy in patients predicted to be a t high risk of developing a blood clot using the Khorana score.

Why do cancer patients develop blood clots? One hypothesis is that cancers that expresses high concentrations of tissue factor release tissue factor bearing micro-particles into the blood stream which triggers activation of the coagulation proteins and blood clot formation. Animal studies have demonstrated that mice injected with human pancreatic cancer cells have a much higher rate of clot formation than mice injected with saline. Mice injected with pancreatic cancer cells induce activation of platelets that is dependent upon thrombin generation. Pre-treatment of mice with clopidogrel reduces clot formation when pancreatic cancer cells are injected into mice. These results suggest that anti-platelet agents may be useful in prevention of clot formation in cancer patients.

Tissue factor activity has also been linked to clot formation in pancreatic cancer patients. Increases in tissue factor activity were detected in patients prior to clot formation and was associated with reduced survival. However, this association was not noted for brain, stomach or colon cancers. The PHACS study randomized high risk patients starting chemotherapy to a low molecular weight heparin dalteparin or placebo for a 3 month course of therapy. LMWH was associated with a trend toward fewer blood clots at the cost of a 7 fold higher risk for bleeding complications although the study was too small to draw definitive conclusions. Larger studies testing the efficacy of new oral anticoagulants are now underway. Tissue factor activity was higher in the high risk cancer patients and particularly among patients with pancreatic cancer who developed a blood clot. This results suggest that blood tests of tissue factor activity may be useful for identifying pancreatic cancer patients at greater risk for blood clots.

Suresh Vedantham: Massive DVT and PE

Anticoagulation is good treatment for many blood clots but it may not be enough for large blood clots in the legs or the lungs in which rapid dissolution of the blood clot is necessary to prevent permanent long pasting damage

or death. Post-thrombotic syndrome is a common complication of blood clots (25-50% of patients) that causes chronic leg swelling pain and in a minority (5-10%) venous stasis skin ulcers that are difficult and expensive to treat. Post-thrombotic syndrome impairs quality of life therefore it is important to prevent. The only double blind randomized controlled trial of graduated compression stockings in the prevention of PTS, the SOX trial, showed that GCS had no impact on the frequency of PTS or any of its common manifestations. PTS is a sequelae of damage to venous valves caused by blood clots as well as the presence of residual blood clot in the vessel. These changes impede blood flow and cause reflux of blood in the vessel resulting in swelling in the damage of blood vessels venous obstruction caused by clots. The more clot that remains in the vessel the more likely that severe post-thrombotic syndrome will result. CAVENT, an open randomized controlled trial conducted in Europe that randomized patients with extensive proximal DVT to anticoagulation or anticoagulation plus catheter-directed thrombolysis found that clot lysis was associated with less PTS than anticoagulation alone. Real world studies of catheter-directed thrombolysis have noted increased intracranial bleeding (0.9% versus 0.3%), need for blood transfusions and greater hospital length of stay, and hospital charges. Ultrasound assisted thrombolysis, hypothesized to result in faster clot lysis and fewer complications, was found to be equivalent to thrombolysis alone in a open randomized controlled trial. The ATTRACT trial is a single blind randomized controlled trial of pharmacomechanical thrombectomy versus anticoagulation alone in patients with proximal DVT. Results from this large multicenter study should help resolve the questions surrounding the efficacy of CDT for extensive proximal DVT. Current indications for consideration of CDT include acute (within 4 weeks) limb threatening DVT or extensive proximal DVT (iliofemoral DVT) at low risk for bleeding. The benefit of thrombolysis is widely accepted for patients with massive PE. However, several randomized controlled trials of systemic thrombolysis in patients with submassive PE have not demonstrated any improvement in survival or recurrent PE compared with anticoagulation alone and have been associated with an increased risk of major bleeding. A meta-analysis of all the studies of systemic thrombolysis found a small survival benefit (2.17% versus 3.89%) that was offset by increased major bleeding and intracranial bleeding particularly among patients older than 65 years. Consequently, there has been limited enthusiasm for broad use of systemic thrombolysis in patients with submassive PE. Small studies of ultrasound catheter-directed thrombolysis for PE have demonstrated clinically significant reductions in clot burden with no increase in major bleeding. Larger randomized studies are warranted to confirm these findings.

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