Abstracts from the CanVECTOR 2022 Annual Conference
October 14th, 2022

Conference Planning Committee Co-Chairs: Dr. Miriam Kimpton & Dr. Zachary Liederan
Scientific Abstract Review Committee Members: Dr. Shannon Bates, Dr. Ed Conway, Dr. Susan Kahn, Dr. Paul Kim, Dr. Sudeep Shivakumar, Dr. Deborah Siegal
Edited by: Nicole Langlois
Organized and Hosted by the Canadian Venous Thromboembolism Research Network

1 | Identifying Which Emergency Department Patients Should Be Tested for Pulmonary Embolism

Dennis Christopher; Keerat Grewal; Fabrice Mowbray; Somayeh Ghazalbash; Manaf Zargoush; Kerstin de Wit
1CanVECTOR Patient Partner, Canada; 2Schwartz/Reisman Emergency Medicine Institute, Mount Sinai Hospital, Toronto, Ontario, Canada; 3Ph.D. Candidate, Dept. of Health Research Methods, McMaster University, Hamilton, Ontario, Canada; 4Ph.D. Candidate, DeGroote School of Business, McMaster University, Hamilton, Ontario, Canada; 5Assistant Professor DeGroote School of Business, McMaster University, Hamilton, Ontario, Canada; 6Associate Professor, Department of Emergency Medicine, Queen's University, Kingston, Ontario, Canada

Background: Pulmonary embolism (PE) can be misdiagnosed when emergency physicians do not consider PE as a potential diagnosis. Little research has focused on who should be tested for PE.

Aim: To develop a predictive model which identifies underlying PE diagnosis in emergency department patients.

Methods: Using linked population-level administrative data from Ontario (Canada), we analyzed the first patient emergency department visit in each calendar year between 2015 and 2019. Patients were classified as presenting with PE if they were diagnosed with PE on that visit, within the following 30 days if there was no hospitalization, within seven days of hospitalization without surgery, or else prior to surgery within seven days. We collected patient data on age, sex, cancer, prior DVT and PE, pregnancy, coronary artery disease, COPD, diabetes, stroke, anticoagulant use, atrial fibrillation, recent hospitalization, recent surgery, presenting complaint and triage score. Logistic regression and 10-fold cross-validation were used to derive a model which predicts the diagnosis of PE for the year 2015, and subsequently validated the model performance on each calendar year 2016–2019.

Results: We analyzed 7,024,111 emergency department visits with 18,751 cases of PE. Mean age 48.6, 52% female, 3% history of cancer, 1.7% stroke, 1% prior PE, 1.6% prior DVT, 1.9% recent admission and 4.4% recent surgery. Our final model predicting a diagnosis of PE contained age, prior PE, prior DVT, presenting complaint and triage category. The area under the curve for the predicting PE was 82.8 in 2015, and 84.5, 81.3, 78.4 and 80.6 for each subsequent year. The optimal cut-off gave sensitivity estimates between 69.4%–74.4% and specificity estimates 73.7%–76.0% for each of the 5 years.

Conclusion: We derived a model which accurately predicts the diagnosis of PE in emergency department patients, with the potential to trigger PE testing in the emergency department.

2 | Improving Risk Stratification of Orthopaedic Trauma Patients with Suspected PE

Ashley Clarke; Leslie Skeith; Robert Kerley; Prism Schneider
University of Calgary, Calgary, Alberta, Canada

Introduction: Patients with major orthopaedic injuries, such as pelvic or acetabular fractures, have high incidences of life-threatening pulmonary embolism (PE). A local Pulmonary Embolism Response Team (PERT) developed risk stratification algorithms using previously validated tools (e.g., sPESI and BOVA score) to categorize patients based on their risk for decompensation (Low, Intermediate-Low, Intermediate-High, High) to assist with diagnosing and treating PE. The purpose of this study was to evaluate the addition of point-of-care thrombelastography (TEG) analysis to help confirm
individualized level of risk. TEG is a whole-blood test which provides an overview of an individual's clotting process, with initial results available within minutes. The maximal amplitude (MA) measures clot strength and can quantify increased thrombosis risk.

Methods: This is a planned sub-study of a prospective cohort of adult patients with surgically treated pelvic and acetabular fractures from a single Level I trauma centre. Consecutive patients who had a suspected PE and had TEG analysis performed within 24h prior to CTPA imaging were included. MA values from TEG analysis were captured for all patients and those with positive CTPA results were risk stratified as per the PERT algorithms. The primary aim was to compare MA values between patients with and without image-confirmed PE. We hypothesized that MA values would be higher in patients with image-confirmed PE. The secondary aim was to assess MA values between the different PERT risk stratification categories, where we hypothesized that MA values would increase with increasing PE risk category. Statistical analysis included two-sided t-tests to compare MA values and ages between those with and without image-confirmed PE, using a significance level of 0.05. Descriptive statistics were used to analyze MA values for different risk stratification categories.

Results: A total of 13 patients (four females, 31%) with suspected PE had CTPA imaging and TEG analysis performed where seven patients (54%) had image-confirmed PE. There was no difference in mean age between patients with PE (56.9 ± 22.0 years) and those without (44.3 ± 17.0 years). The difference between the average MA for positive (66.9 ± 4.9) and negative (62.0 ± 6.6) CTPA results approached statistical significance (p = 0.07). Patients with positive CTPA results were stratified as follows: one patient was Low Risk (MA = 65.2), four were Intermediate-Low (MA = 65.7 ± 5.8), one Intermediate-High (MA = 67.4), and one High Risk (MA = 72.7). MA values ascended with increasing PERT-defined severity and were associated with increased risk for decompensation due to PE.

Discussion & Significance: In this small sub-study of patients with pelvic and acetabular fractures, MA values from TEG analysis increased as the PERT-defined severity increased. There was also a trend towards higher MA values for those with image-confirmed PE. There may be a role for including TEG analysis to further inform risk stratification of the orthopaedic trauma patient suspected of PE, using MA. Utilization of TEG analysis could assist with determining the need for a CTPA, leading to reduced imaging costs, more rapid PE diagnosis, and safe use of thrombolytics.

3 | Characterizing Protease-Resistant ADAMTS13 Mutants

Veroncia DeYoung; Hasam Madarati; Colin Kretz
Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, ON, Canada

Background: ADAMTS13 is a metalloprotease that regulates the length, and thus the platelet-binding capacity, of von Willebrand Factor (VWF). ADAMTS13 activity must be regulated to allow for sufficient platelet recruitment to sites of vessel injury to achieve hemostasis while avoiding thrombosis. However, ADAMTS13 evades conventional mechanisms that regulate other metalloproteases. It is biochemically stable, secreted in an active form, and is resistant to natural protease inhibitors, leading to a long circulating-half life. Coagulation and neutrophil-derived proteases have been shown to cleave ADAMTS13 in vitro, impairing its ability to cleave VWF-multimers under flow. However, the significance of ADAMTS13 proteolytic degradation to its regulation in vivo remains unknown. We hypothesize that ADAMTS13 is degraded by proteases that are upregulated at sites of vascular injury, limiting its activity. We have identified two common cleavage sites within ADAMTS13 and have purified three mutants with one of each site or both sites mutated. These mutants will be characterized and used to study the importance of proteolytic regulation of ADAMTS13.

Objective: To investigate the importance of proteolytic degradation of ADAMTS13 as a regulatory mechanism in vivo using protease-resistant mutants.

Methods: Each ADAMTS13 mutant and wild-type (WT)ADAMTS13 (50nM) were incubated with purified coagulation, fibrinolytic, and neutrophil-derived proteases (50–100nM) for 0, 30, and 180 min. Cleavage patterns were visualized using western blotting.

Results: Coagulation and fibrinolytic proteases (thrombin, factor Xa, factor Xla, plasmin, and kallikrein) are capable of cleaving both predicted sites within WT-ADAMTS13. The double mutant is completely protected against cleavage by these proteases over 3h. Resistance to degradation by neutrophil-derived proteases, elastase, proteinase 3, and cathepsin G, is prolonged in the double mutant, but additional cleavage sites for these proteases are still present. WT-ADAMTS13 is not cleaved by factor Vlla, factor IXa, factor XIa, or activated protein C.

Conclusions: These findings validate the location of two protease-sensitive regions within ADAMTS13, and confirm that the double mutant is resistant to degradation by specific proteases in vitro. Subsequent investigation will characterize the kinetic properties of these ADAMTS13 mutants, examine their ability to cleave VWF-multimers under flow, and compare their antithrombotic capacity to WT-ADAMTS13 using mouse models of thrombosis.

4 | Use of Thromboprophylaxis in Hospitalized Patients with Cancer

Alex Dipierdomenico1; Anna Guo1; Indryas L. Woldie1; Grant Favel1; Abdulkadir Hussein3; Andrea Cervi1
1Windsor Regional Hospital, Windsor, Ontario, Canada; 2University of Western Ontario, London, Ontario, Canada; 3Mathematics and Statistics, University of Windsor, Windsor, Ontario, Canada

Introduction: Venous thromboembolism (VTE) is a known complication of hospitalization for acute medical illness; hospitalized patients with cancer represent a particularly high thrombotic risk population. However, there is significant underuse of thromboprophylaxis in medical inpatients with cancer.
Objective: The objective of this study was to characterize the use of thromboprophylaxis in hospitalized patients with cancer at Windsor Regional Hospital (WRH), a large, community-based hospital in Ontario, Canada. Specifically, we investigated use of both pharmacologic and mechanical thromboprophylaxis, along with clinical determinants relating to omission of VTE prophylaxis to better understand our local practice patterns.

Methods: This study was a retrospective, single center cohort analysis of 120 adult patients admitted to WRH with a primary solid tumor diagnosis (n = 57) and hematologic cancer diagnosis (n = 63) over a 3-month period (January 2018–March 2018). Chart review was performed for the first ten days of admission or until discharge. Multi-variate analyses were employed to determine clinical predictors of thromboprophylaxis use.

Results: Sixty-one (51%) medical inpatients with cancer received pharmacologic thromboprophylaxis during their hospitalization. The majority of patients (n = 39; 68.4%) with a solid tumor malignancy received prophylaxis, while only twenty-two (34.9%) patients with a hematologic malignancy were provided pharmacologic VTE prophylaxis. In total, 59 patients initially presented with contraindications to prophylaxis, with thrombocytopenia being the most cited contraindication (23 patients). In the subgroup of patients without contraindications to pharmacologic prophylaxis, 60% of patients with a primary hematologic diagnosis and 75% of patients with a primary solid tumor diagnosis received pharmacologic prophylaxis. A minority of patients (6.9%) who did not receive pharmacologic prophylaxis were prescribed mechanical thromboprophylaxis in the form of intermittent pneumatic compression device. Platelet nadir <25 × 10^9/L (OR = 0.12, 95% CI 0.0256–0.4087), active hormonal therapy (OR = 0.11, 95% CI 0.0055–0.6707) and pulmonary disease at baseline (OR = 4, 95% CI 1.0031–22.9064) were clinical predictors of use of pharmacologic thromboprophylaxis, although the number of patients receiving hormone therapy and with baseline pulmonary disease were relatively small (8 patients maintained on active hormonal therapy, and 14 patients with pulmonary disease at baseline).

Conclusion: In conclusion, thromboprophylaxis is an integral adjunct to the management of medical inpatients with active cancer yet may be neglected in clinical practice. In our population, nearly half of patients were not provided VTE prophylaxis. Severe thrombocytopenia and active hormonal therapy were negative predictors of pharmacologic thromboprophylaxis use while the presence of pulmonary disease favored prescription of prophylaxis on admission. Further studies are needed to better understand the rationale underlying omission of VTE prophylaxis in medical inpatients with cancer, and raise awareness of measures to prevent VTE in this patient population.
community hospitals. As well, our findings further support the need for development of concrete guidelines on indications for IVC filter use and monitoring practices.

6 | Clinical Benefits, Harms, and Cost-Effectiveness of Indefinite Anticoagulant Therapy for First Unprovoked Venous Thromboembolism: A Decision Analytic Modelling Study

Faizan Khan1; Doug Coyle1; Kednapa Thavorn2; Sasha van Katwyk3; Tobias Tritschler4; Brian Hutton2; Gregoire Le Gal2; Marc Rodger4; Dean Fergusson2

1University of Ottawa, Ottawa, Ontario, Canada; 2Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; 3University of Bern, Bern, Switzerland; 4McGill University, Montreal, Quebec, Canada

Background: Clinical practice guidelines suggest continuing anticoagulation indefinitely over discontinuing anticoagulation after completing 3–6 months of initial treatment for a first unprovoked VTE, except in patients who have a high risk for bleeding. However, the lifetime clinical benefits, harms, and cost-effectiveness of indefinite anticoagulation have not been formally assessed. While a randomized controlled trial (RCT) would be the optimal study design to provide evidence for or against continuing anticoagulation indefinitely in patients with a first unprovoked VTE, it is unlikely to be conducted due to the lifelong (i.e. until death) follow-up and extremely large sample size that would be required. Decision-analytic modelling can provide evidence to inform guidelines under circumstances in which RCTs are unfeasible.

Objective: The aim of this modelling study was to compare the clinical benefits, harms, and cost-effectiveness of continuing versus discontinuing anticoagulation indefinitely after completing initial treatment for a first unprovoked VTE.

Methods: We created a probabilistic Markov cohort simulation model [Figure 1] to simulate costs (adjusted to 2022 Canadian dollars) and outcomes (recurrent VTE, major bleeding, and quality-adjusted life-years [QALYs]) for two hypothetical cohorts of patients aged 55 years with a first unprovoked VTE that had completed 3–6 months of initial anticoagulant therapy - one cohort assigned to continue anticoagulation indefinitely with direct oral anticoagulants, and another assigned to discontinue anticoagulation indefinitely. The model adopted a cycle length of 1 month and a lifetime horizon. The economic analysis adopted a third-party payer perspective relating to the Canadian publicly-funded healthcare system.

Results: In a hypothetical cohort of 1000 patients, continuing anticoagulation indefinitely, compared to discontinuing anticoagulation, prevented 253 recurrent VTE events (number needed to treat = 4) and induced an additional 69 major bleeding events (number needed to harm = 15). Indefinite anticoagulation resulted in higher health system costs ($70,019.35 vs. $61,438.10 per person) and no improvement in QALYs (15.26 vs. 15.31 per person; incremental difference of -0.05 QALYs or -18.25 quality adjusted life-days). Model results were most sensitive to the annual risk of major bleeding and case-fatality rate of major bleeding during extended anticoagulation however, in all one-way sensitivity analyses, discontinuing anticoagulation remained economically dominant (i.e., lower costs and similar QALYs) over continuing anticoagulation indefinitely, at a willingness-to-pay (WTP) threshold of Can$50,000 per QALY. In probabilistic analyses, the probability of indefinite anticoagulation being the cost-effective treatment strategy was 0% at a WTP threshold of Can$50,000 or Can$100,000 per QALY.

Conclusions: Indefinite anticoagulation for a first unprovoked VTE is unlikely to either result in a net clinical benefit or be cost-effective. With no net gain in QALYs (albeit a small net loss), there is no rationale for continuing anticoagulation indefinitely in all (i.e., unselected) patients with a first unprovoked VTE. However, the clinical and cost-effectiveness of indefinite anticoagulation in subgroups of patients at high risk of recurrent VTE and low risk of major bleeding requires further investigation, and will be an important next step.

7 | Anything but Cookbook Medicine: Exploring the Influence of Supervisor Practice Variability on Resident Learning in Thrombosis Medicine

Shaheen Khattak1; Siraj Mithoowani2; Susan Lieberman3; Michelle Zeller4; Eric Tseng5; Jeroen van Merrienboer6

1Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada; 2Department of Medicine, McMaster University, Hamilton, Ontario, Canada; 3McMaster Centre for Transfusion Research, McMaster University, Hamilton, Ontario, Canada; 4Department of Medicine, McMaster University, Hamilton, Canada Canadian Blood Services, Ancaster, Ontario, Canada; 5Department of Medicine, University of Toronto, Toronto, Ontario, Canada; 6School of Health Professions Education, Maastricht University, Maastricht, The Netherlands

Introduction: Clinical practice variability is characterized by two or more expert clinicians who make different treatment decisions despite encountering a similar case. Thrombosis Medicine is an example of a specialty that has a large evidence base to support decision-making and where practice variability is common.

Objective: To explore how residents experience and interpret inter-supervisor clinical practice variability in Thrombosis Medicine, and how these variations influence learning.

Methods: Seventeen senior residents in Internal Medicine, Hematology or Thrombosis Medicine (PGY 3-6) participated in semi-structured interviews. All residents had completed one or more clinical rotations in Thrombosis Medicine. Data collection and analysis occurred iteratively and concurrently in a manner consistent with constructive grounded theory methodology. Variation theory was used as a sensitizing concept. A central tenet of this theory is that learning occurs by experiencing three sequential patterns of variation: contrast, generalization, and fusion. All transcripts were coded in duplicate by paired members of the study team. Participants
were recruited purposively with regard to their field of training until thematic saturation was reached. The primary investigator maintained an audit trail and reflexivity journal. Member checking was performed. Dedoose (version 8.0.35) was used for all analyses. The Hamilton Integrated Research Ethics Board reviewed the study.

**Results:** Clinical practice variability was common and generally viewed positively. Residents attributed clinical practice variability to supervisor personality differences, inter-institutional differences, availability and interpretation of evidence, differences in patient preferences and characteristics, and their own participation in the decision-making process. Inherent differences between supervisors, including personality traits, risk tolerance, and prior educational and clinical experiences were a major contributor. Clinical practice variability was felt to be most common when the clinical problem had scant or conflicting evidence to guide practice, for example, in the treatment of subsegmental pulmonary embolism or splanchnic vein thrombosis. Supervisor-learner discussions allowed residents to ask clarifying questions and supervisors to share tacit knowledge, elaborate on prior experiences and articulate their clinical reasoning. Observing practice variability was more helpful for senior learners and less so for junior learners as inexperience and knowledge gaps made it difficult to reconcile differences. Junior residents (PGY 2–4) were often assessment-focused and made note of practice patterns between their supervisors in order to predict their supervisors’ preferences for future cases. More experienced residents (PGY 5–6), especially those pursuing advanced training in Thrombosis Medicine, were more likely to view clinical practice variability as a means to improve their own decision-making skills in preparation for independent practice.

Consistent with variation theory, clinical practice variability helped residents discern critical aspects that influenced decision-making (contrast), group similar cases together so that the appropriate evidence could be applied (generalization) and weigh multiple variables to make a treatment decision (fusion).

**Conclusion:** Clinical practice variability helped residents discern critical aspects, group similar patients together and practice individualized medicine suggesting that it is a useful form of variation for learning in the workplace. Clinical supervisors and curriculum designers can promote learning from practice variability through role modeling, coaching, thinking aloud and promoting reflective practice.

---

**ABSTRACT**

**Background:** Limited data exists to guide the use of direct oral anticoagulants (DOACs) in patients with primary brain tumors and cancer-associated venous thromboembolism (VTE). While emerging data supports the use of DOACs in the management of cancer-associated VTE, there is concern that they may have a higher bleeding risk compared to traditional low molecular weight heparin (LMWH). This is particularly of concern in patients with primary brain tumors due to an increased risk of intracranial hemorrhage (ICH) with anticoagulation. DOACs are more convenient and significantly cheaper compared to LMWH, but due to safety concerns their use in this population remains controversial.

**Research Question:** In patients with primary brain tumors (WHO-classified gliomas (astrocytoma or oligodendroglioma)), what is the risk of ICH in those treated with DOACs compared to LMWH?

**Study Design:** This is a retrospective multi-center cohort study evaluating patients with primary brain tumors and VTE managed with anticoagulation followed at the Toronto General Hospital, Sunnybrook Health Sciences Centre and The Ottawa Hospital from April 2011 to April 2021. The study is being conducted through chart review from site-specific electronic medical records. The primary objective is to compare the risk of ICH in those treated with DOACs versus LMWH. Secondary objectives will compare the risk of major bleeding, VTE recurrence and all-cause mortality in those treated with DOACs versus LMWH.

**Inclusion Criteria:** (1) Age 18 or greater at cancer diagnosis; (2) Biopsy proven WHO-classified glioma (astrocytoma or oligodendroglioma); (3) Treatment with anticoagulation for VTE with a DOAC or LMWH at any dose.

**Exclusion Criteria:** (1) CrCl <30ml/min; (2) Concomitant use of strong inhibitors or inducers of both cytochrome P-450 3A4 and P-Glycoprotein if on DOACs.

**Sample Size and Analysis:** No formal sample size calculation will be performed. All patients who meet eligibility criteria during the
study time period will be included. Rates of outcomes will be described as events per 100 person-years and compared using Cox proportional hazards regression analysis with 95% confidence intervals. Adjustments for ECOG status, prior ICH, thrombocytopenia and tumor type will be conducted and a competing-risks model will be used to account for the high risk of mortality. Kaplan meier event-free survival curves will compare outcomes by anticoagulation group. Two-sided p values <0.05 will be considered statistically significant.

**Study Timeline:** REB approval has been approved at each site and provincially. Data is being collected at all sites. Data analysis and the written manuscript will be completed by August 2023.

**Relevance and Impact:** Given the paucity of evidence, further data on the risk of ICH, major bleeding and recurrent VTE in patients with primary brain tumors anticoagulated with DOACs, will help clinicians determine appropriate anticoagulation choices in this demographic.

**References**
1. Kabashneh S, Alkassis S, Shanah L, Alkofahi AA. Venous thromboembolism in patients with brain cancer: focus on prophylaxis and management. *Cureus*. 2020;12(6):e8771.
2. Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2018;16(9):1891-1894.
3. Kahale LA, Hakoum MB, Tsolakian IG, et al. Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. *Cochrane Database Syst Rev*. 2018;6:CD006650.
4. Mulder FI, Bosch FTM, Young AM, et al. Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis. *Blood*. 2020;136(12):1433-1441.
5. Giustozzi M, Agnelli G, del Toro-Cervera J, et al. Direct oral anticoagulants for the treatment of acute venous thromboembolism associated with cancer: a systematic review and meta-analysis. *Thromb Haemost*. 2020;120(7):1128-1136.
6. Khoury MN, Missios S, Edwin N, et al. Intracranial hemorrhage in setting of glioblastoma with venous thromboembolism. *Neurooncol Pract*. 2016;3(2):87-96.
7. Carney BJ, Uhlmann EJ, Puligandla M, et al. Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors. *J Thromb Haemost*. 2019;17(1):72-76.
8. Zwicker JI, Karp Leaf R, Carrier M. A meta-analysis of intracranial hemorrhage in patients with brain tumors receiving therapeutic anticoagulation. *J Thromb Haemost*. 2016;14(9):1736-1740.
9. Porfidia A, Giordano M, Sturiale CL, et al. Risk of intracranial bleeding in patients with primary brain cancer receiving therapeutic anticoagulation for venous thromboembolism: a meta-analysis. *Brain Behav*. 2020;10(6):e01638.

**9 | The Risk of Bleeding in Pregnant Women with Acute Venous Thromboembolism Treated with Anticoagulants**

**Camille Simard**1; Isabelle Malhamé2; Antonios Douros3; Kristian B. Filion3; Haim Abenhaim1; Vicky Tagalakis4

1Division of General Internal Medicine, Jewish General Hospital, Montreal, Quebec, Canada; 2Division of General Internal Medicine, McGill University Health Centre, Montreal, Quebec, Canada; 3Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Montreal, Quebec, Canada; 4Division of Obstetrics and Gynecology, Jewish General Hospital, Montreal, Quebec, Canada

**Introduction:** Venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), occurs during pregnancy in 1 to 2 per 1000 women annually. Women diagnosed with acute VTE during pregnancy receive a minimum of 3 months of low molecular weight heparin (LMWH) with treatment generally extended throughout pregnancy and for at least 6 weeks following delivery. There is a lack of reliable risk estimates of major bleeding associated with LMWH use in pregnancy. We sought to characterize LMWH use during pregnancy and to evaluate the risk of major bleeding among non-selected pregnant women with acute VTE treated with LMWH.

**Methods:** We conducted a retrospective, population-based cohort study using data from electronic healthcare databases from the province of Québec, Canada. From an inception cohort of Québec residents with a diagnosis of incident VTE between January 1, 1998, and December 31, 2015, we identified pregnant women diagnosed with VTE during pregnancy who received a prescription for LMWH within 15 days of the incident event. Women were followed until an inpatient diagnosis of bleeding within 30 days of delivery or censoring due to discontinuation of LMWH use, cessation of medication coverage eligibility, death, or the end of the study period, whichever occurred earliest. Major bleeding was defined as a hospitalization for bleeding at any time during pregnancy or the postpartum period and included pregnancy-related antepartum bleeding (vaginal and uterine bleeding, antepartum hemorrhage) and postpartum bleeding (postpartum hemorrhage, hysterectomy), and non-obstetric bleeding including intracranial hemorrhage, and gastrointestinal and genitourinary bleeding.

**Results:** From the inception cohort (n = 325,560), 259 pregnant women met criteria for inclusion and defined the study cohort. The mean age was 29.4 years (standard deviation (SD) 6.2), 202 (78.0%) women were diagnosed with DVT and 57 (22.0%) with PE. The majority of women (72.6%) received Dalteparin and 27.4% received Tinzaparin or Enoxaparin. Overall, 20 patients (7.7%) experienced major bleeding, 5 (1.9%) of which occurred during the antepartum period and 15 (5.8%) in the postpartum period. The incidence of major bleeding was 311 per 100 person-years (95% confidence interval (CI) 190–480). There were no deaths.

**Conclusion:** This study provides a population-derived estimate of major bleeding in pregnant women treated with therapeutic anticoagulation for VTE during pregnancy. Our results show a non-trivial
risk of major bleeding and that Dalteparin is the most used LMWH in pregnancy. Factors that may affect bleeding, which include timing of resumption of therapeutic anticoagulation in the postpartum period, need to be considered in the clinical setting. Whether the risk of major bleeding is increased in this patient population compared to the general obstetric population requires further study.

10 | Prolonged Platelet-mediated Hypercoagulability is Identified in Patients with Surgically Treated Metastatic Bone Disease

Lisa Yamaura; Leslie Skeith; Michael Monument; Prism Schneider University of Calgary, Calgary, Alberta, Canada

Background: Patients with metastatic bone disease (MBD) are at a 7-fold increased risk for venous thromboembolism (VTE) after orthopaedic surgery compared to patients without cancer. As the duration of post-operative hypercoagulability and the mechanisms that drive this hypercoagulable state are poorly defined, thromboprophylaxis guidelines for patients with MBD are unavailable. Thrombelastography (TEG) is a validated point-of-care tool which can measure clot strength (maximal amplitude, MA) and can be used to quantify VTE risk. We aimed to use TEG to evaluate the duration of post-operative hypercoagulability and activation of adenosine diphosphate (ADP) and thromboxane A2 (AA) platelet receptor pathways in patients with MBD who have undergone orthopaedic surgery. We hypothesized that MA values would remain elevated in some patients after discontinuing thromboprophylaxis, and that hypercoagulability would be platelet-mediated following orthopaedic surgery.

Methods: Consecutive adults (≥18 years) with a pathologic fracture due to MBD or haematological malignancy of bone were enrolled into this single-centre, prospective cohort study. Patients who were anticoagulated for acute VTE or who had primary bone tumours were excluded. Whole blood samples for serial TEG and platelet mapping (PLM) analyses were collected pre-operatively; on post-operative days (POD) one, three, and five; and 2-, 6-, and 12-weeks post-operatively. All patients received thromboprophylaxis (commonly low-molecular-weight heparin) post-operatively. Bilateral lower extremity Doppler ultrasound was performed on POD3 to screen for clinically significant proximal deep vein thrombosis (DVT), and incidence of image-confirmed DVT or pulmonary embolism (PE) was monitored. One-sample t-tests were performed to compare measured MA values with previously established TEG thresholds defining hypercoagulability (≥65 mm) and platelet hyperactivity (≥55 mm, PLM).

Results: Thirty-six patients (20 female, 55.6%) were enrolled, with a mean age of 67 ± 11 years. Primary breast (n = 10, 27.8%) or lung (n = 6, 16.7%) cancers were most common. VTE incidence was 13.9% (n = 5; one PE and four DVTs), and all events occurred by POD5. In patients who had VTE, TEG analysis demonstrated statistically significant hypercoagulability pre-operatively (mean MA: 69.5 ± 4.1 mm; p = 0.04), which peaked at the time of VTE diagnosis (mean MA: 70.3 ± 6.6 mm; p = 0.07). PLM analysis showed significant platelet hyperactivity at the time of VTE diagnosis (mean ADP MA: 69.5 ± 5.4 mm; p < 0.01; mean AA MA: 69.6 ± 5.6 mm; p < 0.01). In patients without VTE complications, hypercoagulability was most pronounced during the first two weeks post-operatively, with 90% of patients in a hypercoagulable state during this period. At 6-weeks post-operatively, 41% of patients remained hypercoagulable (mean MA 65.9 ± 5.0 mm; p = 0.22) after discontinuing thromboprophylaxis. In parallel with these findings, platelet hyperactivity was significantly elevated above the 55 mm threshold along both platelet receptor pathways, with more extensive stimulation along the ADP pathway (p < 0.001) compared to the AA pathway (p < 0.05).

Conclusion: Regardless of VTE incidence, orthopaedic surgery provoked increased hypercoagulability and platelet hyperactivity. Patients with VTE complications had significant platelet-mediated hypercoagulability. In patients without VTE, hypercoagulability and platelet hyperactivity persisted after thromboprophylaxis was discontinued. Further investigation into safety and efficacy of extended thromboprophylaxis and the use of antiplatelet agents that target the ADP (e.g., clopidogrel) and AA (e.g., aspirin) receptor pathways, is warranted.

11 | Studies of hyperglycemia-induced hypercoagulability in a murine model of sepsis

Sean Carlin; Erblin Cani; Neha Sharma; Dhruva Dwivedi; Patricia Liaw Thrombosis & Atherosclerosis Research Institute (TaARI), McMaster University, Hamilton, Ontario, Canada

Background: Venous thromboembolism (VTE), which most commonly manifests as deep vein thrombosis (DVT) or pulmonary embolism (PE), affects nearly 10 million people annually. The risk factors associated with VTE include major trauma, surgical or pharmacological interventions, and lifestyle. Alongside these risk factors, it has been shown that hyperglycemia, whether chronic (Diabetes Mellitus) or acute (stress-induced), can increase the odds ratio for VTE by up to 2-fold. Individuals with hyperglycemia also carry an additional risk of developing infections and sepsis. However, the precise mechanisms by which hyperglycemia induces a prothrombotic state remain unclear.

Objective and hypothesis: The overall objective of this study is to investigate time-dependent changes in markers of coagulation, anticoagulation, inflammation, and the formation of neutrophil extracellular traps (NETs) in a streptozotocin (STZ)-induced model of hyperglycemia using wildtype C57Bl/6 mice. We hypothesize that blood samples and organs collected from hyperglycemic mice will exhibit a more severe procoagulant and proinflammatory state compared to normoglycemic mice.

Methods: Five-week-old C57Bl/6 mice (both sexes) were administered a daily dose of 50 mg/kg of streptozotocin every other week
for three weeks. The mice were then aged to 12 weeks (short-term hyperglycemia) or 19 weeks (long-term hyperglycemia). Sepsis was induced via administration of rat fecal slurry which results in fecal-induced peritonitis (FIP). The fecal rat slurry was administered at either 0.6 mg/g or 0.75 mg/g. The study endpoint was set at either 8 h or 48 h post-FIP. The mice were treated with analgesics and antibiotics to emulate clinically relevant supportive therapy for sepsis patients. Plasma was collected from the mice to investigate changes in biomarkers of coagulation (thrombin-antithrombin (TAT) complexes), anticoagulation (protein C), inflammation (IL-6), and NET formation (cell-free DNA). We also measured levels of myeloperoxidase (MPO) in lung tissues.

**Results:** We observed a sustained hyperglycemic state in both male and female mice from week 8 to week 19. In contrast, blood glucose levels in the age-matched control mice remained in the normal range throughout the study. The 48-h survival rate in the short-term and long-term hyperglycemic mice were similar to normoglycemic age-matched mice. The glucose levels in non-surviving mice were below 1 mmol/L. In contrast, the glucose levels in mice that survived were similar to the pre-FIP levels. There were no differences in plasma levels of TAT, IL-6, cell-free DNA between hyperglycemic and normoglycemic mice. Interestingly, plasma levels of protein C were markedly decreased in the non-surviving mice exposed to long-term hyperglycemia compared to non-surviving normoglycemic mice ($p = 0.04$).

**Conclusions:** Our results suggest that STZ-induced hyperglycemia does not impact 48-h survival in a FIP model of sepsis. In addition, our data suggests that prolonged exposure to hyperglycemia impairs endogenous anticoagulation mediated by protein C. An acquired deficiency of protein C may contribute to a prothrombotic state associated with hyperglycemia.