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SPEAKER SERIES

World Thrombosis Day Webinar Review

"Advances in Reducing the Disease Burden of Thrombosis"

Making Education Easy 2017

On World Thrombosis Day (13 October 2017), a webinar was co-hosted by the International Society on Thrombosis and Haemostasis (ISTH) and the Centers for Disease Control and Prevention (CDC), Professor Gibson provided a general overview of the advances in reducing the disease burden of thrombosis.

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WORLD THROMBOSIS DAY
OCTOBER 13

World Thrombosis Day is focused on venous thromboembolism (VTE) and hospitalisation as a leading risk factor for VTE. Through education and outreach, WTD hopes to reduce VTE-related death - the majority of which is hospital-associated. WTD is a timely opportunity to discuss, update or establish your organisation's VTE policy. Preventing clots is a patient safety issue and should be a standard of care for all hospitalised patients. Policies should engage all staff involved in patient care and strive for high compliance.

Abbreviations used in this review:
ACS = acute coronary syndrome
AF = atrial fibrillation
CAD = coronary artery disease
CI = confidence interval
CV = cardiovascular
CVDs = cardiovascular and cerebrovascular disease
DAPT = dual antiplatelet therapy
DVT = deep vein thrombosis
MI = myocardial infarction
NOACs = novel oral anticoagulants
PCI = percutaneous coronary interventions
PE = pulmonary embolism
RR = relative risk
TIMI = thrombolysis in myocardial infarction
VKA = vitamin K antagonists
VTE = venous thromboembolism

The International Society of Thrombosis and Haemostasis, through World Thrombosis Day (WTD), has championed global awareness of thrombosis, paticularly venous thromboembolism (VTE).

In NZ we estimate VTE events occur in 4,000-4,500 individuals annually. Of these anywhere between 25-50% maybe hospital associated and therefore potentially preventable. Importantly fatal episodes may result in 50-75 deaths / year due to hospital associated pulmonary embolism (PE). The literature suggests for a country like NZ that VTE associated disability adjusted life-years exceed life-years lost secondary to the effects of hospital-acquired pneumonia, catheter-related sepsis and adverse drug effects combined. It is an important problem.

In 2012 a National Policy Framework was developed for VTE prevention in adult inpatients by the NZ VTE Prevention Steering Group. This initiative has been supported by the Health Quality Safety Commission NZ and the Health and Disability Commissioner. The aim was for a routine standardised risk stratification to complement prophylactic guidelines and education. Risk assessment is now incorporated as standard practice in many of our hospitals. The issue, as with any guideline, is how well it is applied at an individual patient level. This remains a work in progress.

The "take-home messages" in this excellent webinar review are very relevant to all NZ clinicians. There is also an emphasis on public awareness and empowering patients to ask about personal thrombotic risk prior to surgery or during hospital admission.

Pharmac data indicates an increasing utilisation for dabigatran, corresponding with a drop in warfarin prescriptions, suggesting more patients are also accessing safer anticoagulation for atrial fibrillation (AF).

Paul Ockelford, Clinical Haematologist

The global burden of thrombosis

Thrombosis, an abnormal life-threatening blood clot that forms in the artery or veins, was responsible for one in four deaths globally in 2010.[1] Venous thromboembolism (VTE) accounts for about 1 million deaths each year worldwide. VTEs are represented by pulmonary embolisms (PE) and by deep vein thrombosis (DVT) and despite the danger of these conditions, the public are less aware of PE or DVT than a heart attack or stroke.[2]

What is a blood clot?

A thrombus, or blood clot, is composed of platelets or fibrin.[3] In order to prevent a thrombus forming, the focus for the last 25 years has largely involved the development of agents that prevent platelets from:

- adhering to the lining of the endothelium (no currently approved drugs),
- being activated (aspirin, thienopyridines),
- being amplified (thienopyridines), or
- aggregating via the cross-linking of fibrin molecules (glycoprotein IIb/IIa inhibitors).

Thrombin is the chemical that proceeds the formation of fibrin and has more recently become a target for diminishing the risk of blood clots.

During bleeding, two positive feedback loops are quickly activated causing the platelet to change shape and initiate the formation of a clot. Both these feedback loops can be targeted to prevent the formation of a blood clot (**Figure 1**).

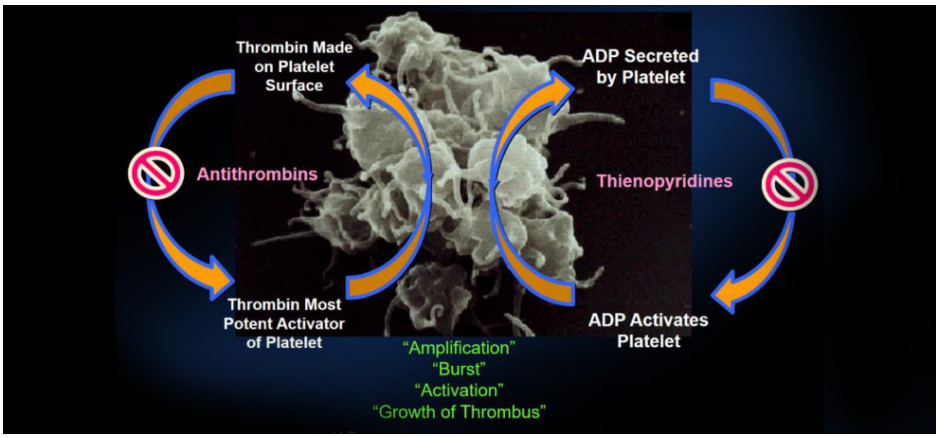

Figure 1. Two positive feedback loops operating during platelet amplification

Cardio- and cerebro-vascular disease

Cardiovascular and cerebrovascular diseases (CVDs) are the leading cause of death globally.[4] An estimated 17.7 million people died from CVDs in 2015, representing 31% of all global deaths; an estimated 7.4 million deaths were due to coronary heart disease and 6.7 million were due to stroke. Most CVDs can be prevented by addressing behavioural risk factors such as smoking, unhealthy diet and obesity, and physical inactivity. However, people with CVD or who are at high risk of CVD (due to the presence of one or more risk factors such as hypertension, diabetes, hyperlipidaemia, or already established disease) need early detection and management using counselling and medicines, as appropriate.[4]

Coronary artery disease

Various pharmaceutical agents, and combinations of these agents have been available to treat patients with coronary artery disease (CAD), including vitamin K antagonists (VKA; e.g. warfarin), aspirin, and aspirin plus thienopyridine. More recently, the role of anti-thrombins has been investigated in both the acute and chronic setting.

While a stent may treat the problem of a blockage in an artery at the point where it was placed, CAD is a chronic disease that affects the other arteries that are not stented. The patient needs to be treated not only by lowering blood pressure and cholesterol, but also by lowering their risk of clotting.

Focus on atrial fibrillation

Atrial fibrillation (AF), also known as arrhythmia, can potentially place individuals at increased risk of thromboembolic stroke. Approximately 33.5 million people globally had AF in 2010, with 4.7 million new cases reported each year.[5] This percentage is increasing as the world-wide population ages. Approximately 44% of disabling or fatal strokes have been shown to be AF related.[6]

In the past, warfarin was used to treat AF, but this drug requires close monitoring. A new class of drugs called novel oral anticoagulants (NOACs; e.g., factor Xa inhibitors and direct thrombin inhibitors) have significantly reduced the risk for haemorrhagic stroke by 51%, and all-cause mortality by 10%, compared with the use of warfarin (**Figure 2**).[7]

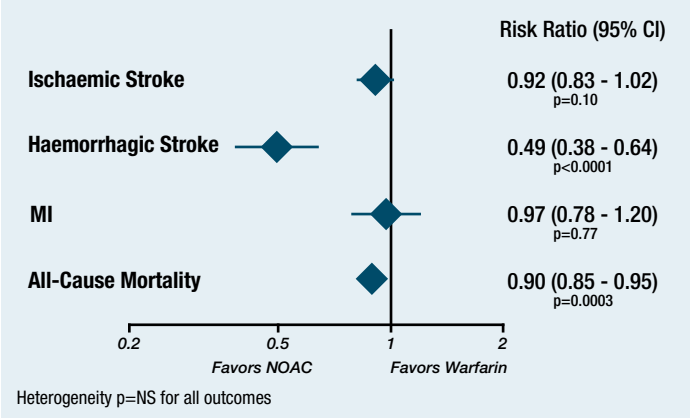

Figure 2. Efficacy outcomes associated with the use of NOACs, compared with warfarin, in patients with atrial fibrillation[7]

An increasing number of people have both AF and CAD, placing them at risk of stroke and MI. It is estimated that about 1-2 million people with AF and CAD in both the US and Europe are candidates for coronary revascularization, often in the form of percutaneous coronary interventions (PCI).[8] However, the optimal management for AF and ACS differs. In the ACTIVE W study, the combination of aspirin and clopidogrel was not as effective as warfarin in patients with AF.[9] However, in the STARS study, the combination of aspirin and a thienopyridine was more effective than warfarin in patients with coronary stents.[10]

In patients with AF undergoing PCI with placement of stents, standard anticoagulation with a VKA plus a dual antiplatelet therapy (DAPT) with a P2Y12 inhibitor and aspirin (triple therapy) reduced the risk of thrombosis and stroke, but was associated with an incidence of bleeding of about 27%.[11] However, treatment with a very low-dose NOAC (rivaroxaban) plus DAPT (aspirin and a thienopyridine) or low-dose NOAC (rivaroxaban) plus a single thienopyridine was associated with lower rates of clinically significant bleeding than with standard therapy with a VKA plus DAPT.[11]

Venous thromboembolism

An estimated average of 547,596 hospitalizations with VTE occurred each year among those aged ≥18 years in the United States during 2007-2009.[12] Worldwide, VTE is a leading cause of hospital-associated premature death and disability.[13, 14] Prevalent or incident VTE events are estimated to cost $US7 to 10 billion each year in the US alone.[15]

In general, there is low public awareness of the risks associated with VTE.[2] A worldwide survey showed awareness of the fact that cancer, hospitalization or surgery were risk factors for VTE was low (16%, 25%, and 36%, respectively).

Virchow's triad

Virchow, who was born on the same day as World Thrombosis Day, highlighted three main risk factors for VTE, namely a hypercoagulable state, endothelial injury and venous stasis (**Figure 3**).[16, 17] Both patients and doctors should assess their risk of a VTE based on the risk factors shown in Figure 3.

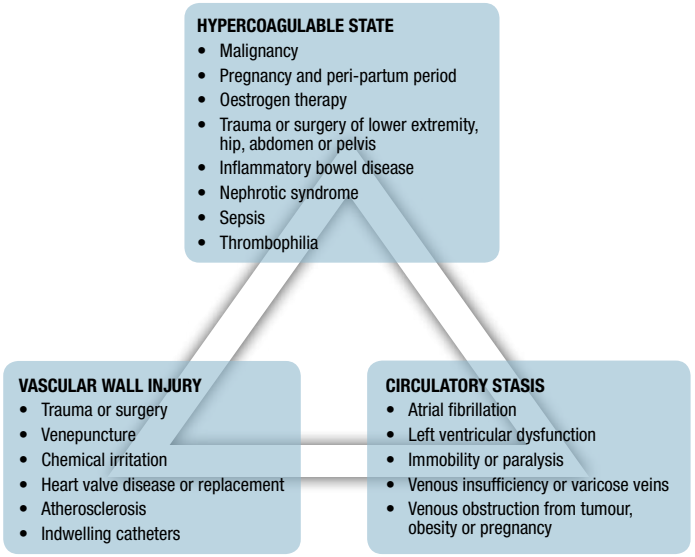

Figure 3. Virchow's triad of VTE risk factors[17]

Provoked or unprovoked VTE

There are two general ways that patients will present with a VTE, namely provoked or unproved. Clinical presentations of VTE that are provoked occur in about 70% of patients. Provoked VTE is associated with known risk factors, such as hospitalisation, surgery, cancer or medical illness. If the risk factor is removed, then there is about a 2% per year recurrence rate after 3 months of anticoagulation therapy.[18] However, about 30% of patients present with unprovoked VTE, where the risk factor cannot be identified (also called idiopathic). In these patients, there is a higher risk of a clot forming of 7-11% per year recurrence for a DVT or PE after the anticoagulant is stopped after 3-24 months.[19]

Most new cases of VTE are mostly associated with recent hospitalisation.[20] Thus, a stay in hospital provides an important opportunity to significantly assess the risk of VTE, and then provide treatment for those at risk.

Hospital-Associated VTE

- Age, hospitalisation, surgery, prior VTE and cancer are major risk factors
- 60% of all new VTE cases are associated with recent hospitalisation
- Hospital is a key access point for prevention
- Risk period often extends beyond the hospital stay
- Effective prophylaxis is available
- VTE risk assessment is indicated for all

Assessment tools for VTE

Various VTE risk assessment tools are available, including the Caprini score (used in non-orthopaedic surgical patients), the IMPROVE VTE score[21] (for medical patients) and more recently, the new IMPROVEDD score developed by Professor Gibson in 2017.

The IMPROVEDD score incorporates measurements of D-Dimer into the risk score, as well as the other variables shown in Figure 4.[22] D-dimer is a biomarker for fibrinolysis (and therefore a measure of clotting activity) that has been associated with heightened VTE risk among patients hospitalized for an acute medical illness. If D-Dimer is ≥2 times the upper limit of normal then 2 points are added to the IMPROVE score (**Figure 4**) to arrive at the IMPROVEDD score. Patients with an IMPROVEDD score ≥2 are at risk of developing a VTE (**Figure 4).**

Variable	Score
Prior episode of VTE	3
Thrombophilia	2
Paralysis of the lower extremity during hospitalisation	2
Current malignancy	2
Immobilization for at least 7 days	1
ICU or CCU admission	1
Age >60 years	1

If D-Dimer ≥ 2 X ULN then add 2 points to the above IMPROVE score to arrive at the IMPROVEDD score.

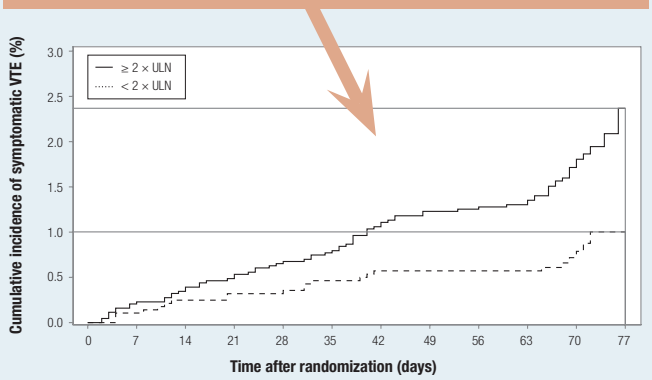

Figure 4. Kaplan–Meier curves for symptomatic VTE stratified by the IMPROVEDD risk category.[22] The risk for symptomatic VTE was compared between the at-risk warranting prophylaxis (≥IMPROVEDD 2 points) and low-risk (IMPROVEDD 0–1 points) categories [Adapted from Gibson CM, et al. TH Open. 2017]

Public health impact of mandated VTE assessment in hospitals

In 2010, a mandated, incentivised VTE risk assessment program was introduced in England in the National Health Service (NHS). The assessment, which uses a standardised tool, takes place when a patient is admitted to an NHS hospital.[23] Across hospitals who assessed 90% or more of hospitalised patients (screening target), there was a 15% reduction in VTE-associated 90-day mortality (relative risk [RR] 0.85, 95% CI 0.75, 0.96; p=0.011). This effect occurred across both surgical and non-surgical patients. It is estimated that 900 VTE-associated deaths were avoided in England during 2011 and 2012 as a result,[24] representing a big improvement from a public health perspective.

Prophylaxis after hospitalisation

The use of blood thinners has reduced the risk of thrombosis after patients have left the hospital; however, two NOACs, rivaroxaban and apixaban, have also been associated with an increased risk of bleeding (**Figure 5**). Consequently, physicians have been hesitant about their use. Encouragingly, research is continuing to develop drugs with a lower risk of bleeding and provide new choices in the armamentarium against VTE.

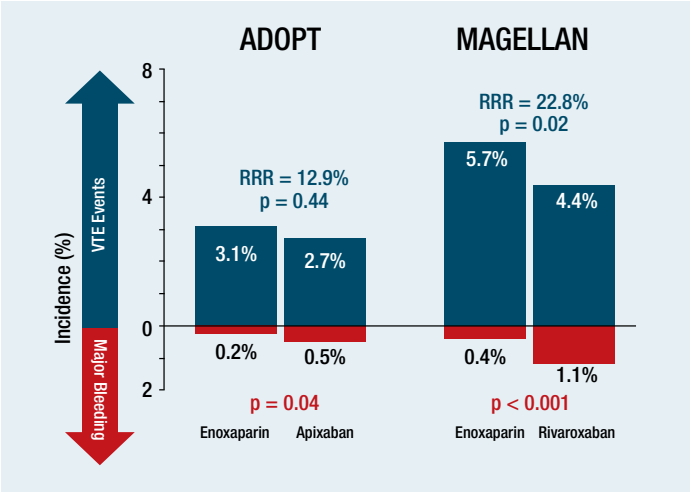

Figure 5. NOACs trials of extended prophylaxis of VTE in acute medically ill patients in the ADOPT[25] and MAGELLAN[26] trials

Treatment of VTE

Various pharmacological options are available for the treatment of blood clots once they have formed (**Figure 6**), including those that work over the short-term (5-10 days), the longer term (3-6 months), or over an extended period (>6 months).

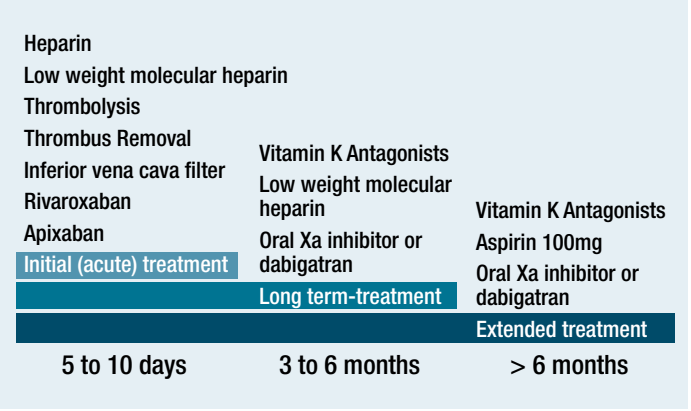

Figure 6. Strategies for treating blood clots

There are also techniques and strategies for removing the clot, and catching the clot within the vein using a filter. Of importance are the Pulmonary Embolism response teams, who facilitate patient-focused decision making, and the efficient and orchestrated use of these clinical strategies.[27] Such teams are composed of specialists such as haematologists, respiratory physicians, cardiologists, radiologists, and interventional radiologists, as well as the patient and their family.

Patients should also be encouraged to become aware of what thrombosis is, how it is prevented and treated, and how they can reduce their individual risks including when in hospital.

TAKE-HOME MESSAGES

- Thrombosis is the leading cause of death worldwide
- The risk associated with thrombosis can be reduced by making the public more aware of their risk factors, how their risks can be assessed, and how they can prevent thrombosis occurring
- Patients who are hospitalised or having surgery should be encouraged to ask about VTE risk and prevention
- VTE risk assessment should occur in all hospitalised patients
- Clinical leaders, hospital systems and payers (such as the insurance companies, employers, or the government) should work together to reduce the risk of thrombosis
- AF is an important opportunity to intervene to prevent stroke
- Various pharmaceutical agents are available to prevent and treat thrombosis
- "Feel the pulse" each time a patient visits a health professional to check for pulse regularity

RESOURCES ON THROMBOSIS

World Thrombosis Day Website
www.worldthrombosisday.org

Tools for Healthcare Professionals

Materials include infographics, posters and flyers
http://www.worldthrombosisday.org/campaign-materials/healthcare-professionals/

www.vtematters.co.nz

NZ VTE Prevention Programme National Policy Framework:
https://www.researchreview.co.nz/getmedia/a19ddf40-5c4b-4a9e-9003-f1fe89800b30/NZ-National-Policy-Framework-Summary-on-VTE-Prevention.pdf.aspx?ext=.pdf

Educational Series: Prevention and management of cancer-associated thrombosis
https://www.researchreview.co.nz/nz/Clinical-Area/Internal-Medicine/Haematology/Haematology/Educational-Series-Prevention-and-management-of-ca.aspx

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