A RESEARCH REVIEW™
SPEAKER SERIES

GPCME 2020: Thromboembolism Highlights

Making Education Easy 2020

About the speakers

Dr Gordon Royle

Gordon is a graduate of Otago Medical School. After moving to Auckland, he undertook a Masters in Molecular Biology, and went on to train in Haematology. He works as a Haematologist and researcher at Middlemore Hospital, and is a senior lecturer with Auckland University's School of Medicine. He has a particular interest in coagulation haematology. His clinical research experience includes the role of principal investigator in several new oral anticoagulant trials.

Dr Laura Young

Laura is a haematologist specialising in thrombosis and haemostasis. She trained at the University of Auckland, then completed training in haematology in Auckland, followed by research at the University of Auckland as part of a PhD focusing on coagulation inhibitors. Dr Young is now employed at Auckland Hospital as part of the Thrombosis Unit and Haemophilia Centre and is involved in hospital-based clinical trials. She also lectures at the Auckland University School of Medicine.

Daryl Pollock

Daryl is a clinical nurse specialist at MidCentral District Health Board, Palmerston North. She has been working in the role of clinical nurse specialist in thrombosis/haemostasis for approximately 10 years. In 2011, Daryl obtained a Master of Nursing and in 2018 became a RN Specialty Team prescriber.

The Haematology and Thromboembolism plenary sessions at both the Rotorua GPCME and South GPCME Virtual Conference were supported by Leukaemia and Blood Cancer NZ and Bayer NZ. This publication summarises the VTE highlights from these sessions. The talk by Dr Gordon Royle provided a general update on managing thrombosis. The talk by Dr Laura Young from Auckland Hospital presented data on the link between cancer and thrombosis, and on the various treatment options available. Also included are excerpts from the talk by Clinical Nurse Specialist Daryl Pollock on managing VTE in the community. This publication has been created with funding from Sanofi.

UPDATE ON TREATING VENOUS THROMBOSIS

Dr Gordon Royle - Haematologist

Why do we have a clotting system?

The clotting system works to spot weld holes in the circulatory system; without a coagulation system a person can spontaneously bleed to death. However, *with* a coagulation system comes vulnerability to venous thromboembolic events (VTE) such as DVT and pulmonary embolism (PE).

Diagnosing VTE

To diagnose a suspected VTE, the Wells score is generally used and, depending on the score, often a D-dimer test.[1] When a clot is broken down, D-dimers are one of the degradation products released into the circulation. The usefulness of measuring the D-dimer level is that a normal level almost completely excludes DVT/PE. However, an elevated level can be caused by many things, such as infection, inflammation, malignancy, or recent surgery – and these are often the exact contexts in which you might suspect somebody does have VTE, so *elevated* D-dimer levels are often unhelpful.[1]

Calculating the Wells score for a patient with a suspected VTE may mean an ultrasound can be avoided or (for the PE Wells score) a CT pulmonary angiogram (CTPA) can be avoided. In women who are pregnant, rather than CTPA, a ventilation-perfusion (V/Q) scan can be performed, to ensure less radiation risk to breast tissue, without unacceptable radiation risk to the foetus; it is reliable in younger people with good lungs (and CTPA is less interpretable in pregnancy). However, this test is not available everywhere.

Prior to starting anticoagulation treatment, basic checks that are needed include determining if the patient is already on some form of blood-thinning treatment such as an anti-platelet agent (e.g. aspirin, NSAIDs, clopidogrel, etc), and undertaking blood tests such as a full blood count, renal function tests, a basic coagulation screen and liver function tests.

What do I treat the VTE with?

The ideal anticoagulant prevents thrombosis without impairing haemostasis - that is, it prevents clotting without causing bleeding. That ideal drug does not exist yet, but we are getting closer with some of the options currently available. These options include enoxaparin, which is funded for use in malignancy, where it is more effective and straightforward than warfarin, and in pregnancy, where no oral anticoagulants are known to be safe. There is warfarin, which can be used in renal failure and is the preferred anticoagulant in antiphospholipid syndrome (APS). However, it can cause fetopathy (with a main risk period between 6 and 12 weeks' gestation), and drugs, diet and alcohol can destabilise the INR. There are also venous access issues to consider with warfarin for INR testing.

The DOACs are generally preferred over warfarin, not just for convenience but also for their safety and efficacy. The DOACs have short half-lives and, unlike warfarin, do not need to be stopped for a week pre-surgery, however, they may be associated with higher GI bleeding rates than warfarin, and they are contraindicated in renal failure.

Rivaroxaban does not require 5 days' enoxaparin prior to starting, it is only 30% dependent upon renal clearance and has a single daily dose, but some patients experience menorrhagia. It can be used down to a lower creatinine clearance (15 mL/min).

Dabigatran has a specific reversibility agent, and a low intracranial bleed rate, but it can exacerbate GI tract symptoms - especially upper GI. Of note, it is important to use ideal body weight and not actual body weight in calculating Cockroft-Gault creatinine clearance - or eGFR can be used.

How long should I treat my patient's VTE for?

The question behind this is, what will happen if I stop treatment? Is my patient likely to experience a recurrence? The answer depends on whether the VTE was provoked or unprovoked. If a VTE is going to resolve on anticoagulation it will generally have done so by 3 months. So, if the clot was provoked, after 3 months of treatment if the cause has gone, you can generally stop anticoagulation. However, for an unprovoked clot, if there is no obvious cause, it should be assumed that whatever caused the clot could cause another clot if anticoagulation is stopped. In those cases, treatment is continued, but it is now to prevent a clot rather than to dissolve a clot; we are now treating the risk, not the clot. Importantly, long-term anticoagulation carries a bleeding risk - this must be balanced against the risk from clot recurrence. Unfortunately, some risk factors for bleeding are also risk factors for clotting.

The next table summarises the situation nicely. For example, you break your leg while skiing and undergo surgery, following which you develop a big DVT. Once your leg is healed, your chance of a clot recurrence at 1 year (without continuing anticoagulation) is only 1%, and is only 3% at 5 years, because it was a clearly provoked event, which could have happened to anyone.[1] On the other hand, if the VTE was less strongly provoked, such as following a long-haul flight or medical admission to hospital, it should be assumed that the person has some degree of built-in clotting tendency and, correspondingly, their risk of recurrence (off anticoagulation) at 1 and 5 years is 5 times higher. Where a clot is completely unprovoked, i.e. when there is not even a transient minor provoking factor, the recurrence risk is twice as high again. Distal clots are different; they only have half the risk in unprovoked cases compared to proximal clots. Patients with persistent risk factors such as cancer or antiphospholipid syndrome are at the highest risk of recurrence, almost 50% at 5 years, with the same high level of recurrence risk in a person who has had two unprovoked VTEs.

Table 2. Types of venous thromboembolism (VTE) and associated VTE recurrence rates.[1]

Type of VTE	Recurrence rate at 1 year after stopping AC	Recurrence rate at 5 years after stopping AC
First provoked by major surgery or major trauma	1%	3%
First VTE provoked by transient risk factor (non-surgical)	5%	15%
First unprovoked proximal DVT or PE	10%	30%
First unprovoked distal VT	5%	15%
Provoked VTE with persistent risk factors (e.g. active cancer)	15%	45%
Second episode of unprovoked VTE	15%	45%

AC, anticoagulation; DVT, deep vein thrombosis; PE, pulmonary embolism

In summary, well provoked VTEs should be treated for 3 to 6 months, usually 3 months for DVT and up to 6 months for PEs. However, for unprovoked events, the recurrence risk does not disappear entirely with time; even at 10 years there is significant recurrence risk. Distal DVTs have a lower recurrence risk and a lower complication rate: these are generally treated with 6 weeks' anticoagulation or with 2 weeks and then a rescan.[2]

The HERDOO2 rule

In spontaneous proximal DVT and in PE, "men continue and HERDOO2".[3] The HERDOO2 rule means that for men, due to their higher recurrence risk, they just continue taking anticoagulants, but if the patient is female, anticoagulant treatment can be stopped unless two or more specific risk factors are present (**figure 2**), in which case it is considered safer to continue.[3]

HERDOO2 rule

Risk factor		Scoring
H	Hyperpigmentation	1 point total, if any one of these criteria is present
E	Edema	
R	Redness of either leg	
D	D-dimer ≥ 250 µg/L while anticoagulated	1
O	Obesity with BMI ≥ 30 kg/m^2	1
O	Older age, ie, ≥ 65 years	1

Decision making:		
Women:	0-1	Discontinue anticoagulation
	≥2	Continue anticoagulation
All men		Continue long-term anticoagulation

Figure 2. HERDOO2 clinical decision rule.[3]

There may also be other factors not taken into account by HERDOO2, such as a very strong family history of VTE or the presence of antiphospholipid syndrome or cancer, and patient preference should also be considered, particularly where a case could be made either way, for stopping versus continuing.

What next?

Assume your patient had a provoked clot and you have stopped anticoagulation, what do you do next? They will need to be protected at future times when they are temporarily at increased VTE risk, including major injury, major surgery, major medical illness, while taking oestrogens, and maybe international air travel (especially if the initial clot followed air travel). If the patient asks how effectively their anticoagulant protects them against a further VTE, the generally accepted figure is approximately 80% to 90%. Therefore, if a breakthrough clot does occur, compliance should be questioned.

Note, postphlebitic syndrome is relatively common, occurring in approximately 20% of patients, and even after the clot has resolved, the leg may still be painful.

For superficial vein clots, if there is clinical suspicion that the great saphenous vein is involved, an ultrasound is recommended, because in about 25% of cases, DVT may coexist. If the clot is greater than 8 cm long or is less than 5 cm from the deep system, it should be treated with therapeutic anticoagulation for 6 to 12 weeks. For other superficial thrombosis, treatment is generally with enoxaparin for 10 to 14 days at an intermediate dose of 1 mg/kg once (not twice) a day, assuming normal renal function; alternative options are NSAIDs and analgesia or hirudoid cream. A rescan is not routinely performed if, after two weeks' enoxaparin, symptoms have resolved.

Thrombophilia testing is not routinely indicated if there is an obvious cause, such as in the case of hip joint replacement, but may be indicated for unexplained VTE in a young person (< 45 years), or with a strong family history, or with thrombosis at an unusual or unexpected site. However, it may be prudent to screen for antiphospholipid syndrome, particularly if there is a history of autoimmune disease.

What about…. ?

Enoxaparin and heavy patients: If my patient is over 150 kg can I just put them on 150 mg twice daily? Yes, this is the usual approach, and there is some evidence to support this, including measured levels in patients up to 180 kg.[4]

Can my patient with a VTE resume the combined oral contraceptive pill (COCP)? Our first instinct is to stop the COCP, but patients are actually well protected while on therapeutic-dose anticoagulation. Suitable alternative contraceptives include Jadelle and progestogen-only medications (and barrier methods). Note, tranexamic acid may be reasonably safe to add, for example in the case of menorrhagia, if other options are not available.[5]

Bleeding on DOACs: Remember some of your patients, maybe 20%, will not be compliant with their DOAC medication, so when treating bleeding, you need to do everything you would have done if they weren't prescribed a DOAC. Tranexamic acid may be very effective in GI bleeding.

Pulmonary hypertension: This is relatively rare after PE (approximately 3% of patients), but it may take up to 6 months to develop. So, if dyspnoea has not returned to baseline (or is getting worse) by the 6-month point, the patient should be referred for an echo to check for pulmonary hypertension. Some patients may require clot excision, but this is a rare scenario.

CANCER-ASSOCIATED THROMBOSIS

Dr Laura Young - Haematologist

Cancer and thrombosis are strongly linked, with around 20% of venous thromboembolism (VTE) cases associated with known cancer.[6] At Auckland Hospital, which has a tertiary cancer unit, around 30% of the cases through the thrombosis unit are active cancer patients. Risk factors for cancer-associated thrombosis include being relatively early in relation to diagnosis, with a relative risk approximately 5-fold higher within 3-6 months of diagnosis, certain cancer types, advanced cancer stages, certain types of chemotherapy, and also to some extent comorbidities such as obesity, a past history of VTE or a known history of haemophilia.[7,8]

Why do we have this relationship?

The mechanisms that the tumour cell uses to develop a blood supply, grow and metastasise, result in activation of the blood clotting cascade (**Figure 1**).[9]

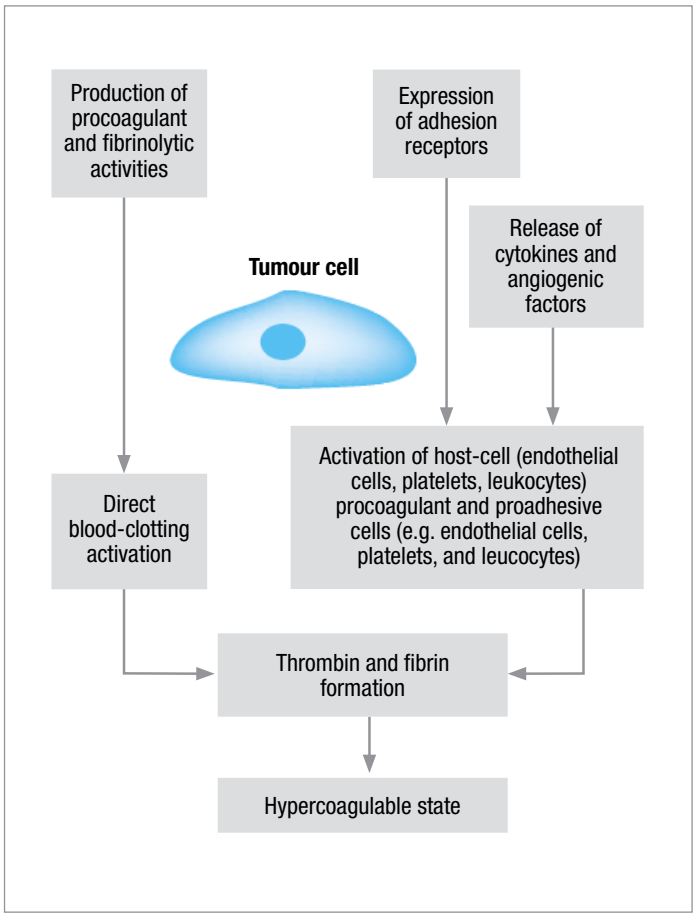

Figure 1. Tumour-cell prothrombotic properties.[9]

The frequency of cancer-associated thrombosis is increasing due to many factors, such as older patients (increased VTE prevalence with age), more intense cancer therapies, improved survival with cancer, and more frequent use of imaging techniques that pick up incidental VTE (notably PE).[10-12]

Rates of cancer-associated thrombosis vary for different cancers

Common cancers such as breast and prostate have been shown to have a venous thrombosis rate of around 2-3 per 100 patient years, compared with 1 per 100 patient years in controls, but other cancers with strongly procoagulant effects like lung and brain cancers, and particularly upper gastrointestinal (GI) malignancies, have even higher rates of thrombosis.[13] In an analysis comparing the incidence of VTE with 1-year relative mortality, the cancer types with the worst overall mortality tended to have much higher rates of VTE.[10] Importantly, cancer-associated thrombosis is associated with increased mortality. The directionality of this relationship remains unclear, but it is certainly clear that if you compare people who have not had any thrombosis with people who have thrombosis without cancer there is an increase in mortality, and when you put the two things together, cancer and thrombosis, there is an exponential increase in risk of death (**Table 1**).[10,14]

Table 1. Crude mortality rates and age- and sex-adjusted hazard ratios of death in patients with venous thrombosis and/or cancer.[10]

Exposure	Person years	Deaths (n)	Mortality rate per 100 person years (95% CI)	Hazard ratio (95% CI)
None	277713	1750	0.63 (0.60-0.66)	1.0 (reference)
VT only	1317	67	5.1 (4.0-6.4)	2.6 (2.0-3.3)
Cancer only	5650	721	12.7 (11.9-13.7)	7.4 (6.8-8.2)
Cancer-related VT	131	72	55.0 (43.6-69.3)	31.2 (24.6-39.6)

CI, confidence interval; VT, venous thrombosis

What about treatment?

In New Zealand, the standard treatment for cancer associated thrombosis has been enoxaparin, but there are different low molecular weight heparins (LMWH) used around the world for cancer-associated thrombosis. In the seminal CLOT study,[15] it was shown that LMWH was associated with significantly less recurrent VTE than warfarin, since which time smaller studies have shown similar trends.[16] Overall, the bleeding rate in these trials was similar between LMWH and warfarin; the advantage of LMWH is in the prevention of VTE, although it is worth noting that none of these studies have shown a significant effect on survival.[16]

In the last 15 years, enoxaparin has been the standard of care for patients in NZ with VTE and active cancer. However, many patients struggle with the daily injections and bruising, and the concept of indefinite therapy to reduce recurrence risk. A number of studies have shown compliance is less than 50%.[17]

What do the guidelines say?

International guidelines are homogeneous regarding major therapeutic recommendations.[1,12,18,19] If VTE occurs with adjuvant chemotherapy, guidelines generally recommend stopping anticoagulation therapy after 6 months. But with active ongoing malignancy, most patients need continued treatment. Many guidelines do not even mention minor venous thromboses, but we tend to extrapolate the thrombosis risk as similar to more significant events, and this is confirmed in observational cohorts.[20] For VTEs related to central lines, which are very common in cancer, we generally treat for 3-6 months for anticoagulation, but many patients tend to have catheters for longer, so they need to stay on anticoagulation until the catheter comes out.

Direct-acting oral anticoagulants

Dabigatran

When the direct-acting oral anticoagulants (DOACs) arrived on the scene in New Zealand around 2011 with dabigatran, naturally patients wanted to consider a novel oral alternative to LMWH, given that it did not need to be injected. Dabigatran is still widely used in New Zealand, although rivaroxaban has been funded in the last two years. The only evidence available for dabigatran in terms of cancer is from the standard VTE trials, in which the comparator was warfarin.[21,22] In these trials, the number of patients with active cancer who were included was very small, but these trials do show that for patients with or without cancer, in terms of outcome, dabigatran was no better than warfarin.[21] By extrapolation, this would suggest that dabigatran is worse than LMWH, because we know LMWH is better than warfarin. Therefore, we tend to avoid using dabigatran for the treatment of VTE diagnosed during cancer therapy.

Factor Xa inhibitors in cancer-associated thrombosis

For the factor Xa inhibitors, we do have direct evidence for their use in cancer-associated thrombosis.[23,24] In the first trial providing such evidence, patients received once-daily edoxaban (not registered in NZ), an oral factor Xa inhibitor similar to rivaroxaban, with a dose reduction for renal function, or the comparator, subcutaneous dalteparin; there were approximately 500 patients in each arm.[23] The second study was the SELECT-D pilot study, using rivaroxaban (fully funded in New Zealand).[24] In this study, patients received rivaroxaban as used for VTE with a dose adjustment for creatinine, and dalteparin was again the comparator. Finally, the CARAVAGGIO study of apixaban, which was published in 2020, and was a larger trial with roughly 1200 patients, (a substantial sample size for cancer thrombosis studies), which again used dalteparin as a comparator, against twice-daily apixaban, and didn't include brain tumours or leukaemia.[25]

These individual trials, along with a recent meta-analysis of all three trials,[26] showed that these factor Xa inhibitors do appear to be very effective in preventing VTE, but the confidence intervals do cross 1.0. The prevention rate favours the DOACs, so efficacy is clear, but there is also a tendency to more bleeding, with the exception of apixaban with a more favourable profile in terms of bleeding rates, and would be the preference if it was funded in New Zealand. Of note, all three trials, all with similar designs with the same comparator, failed to show a survival difference between DOACs and LMWH.

Sounds good… so any differences?

The oral Xa inhibitors edoxaban (not registered in NZ) and rivaroxaban result in higher rates of bleeding with GI and genitourinary cancer, compared with LMWH (12% vs 4% and 36% vs 11%, respectively).[23,24] For this reason, we avoid giving rivaroxaban to anybody with a GI/GU tumour still in situ, for example during preoperative adjuvant chemotherapy or for patients with metastatic disease at diagnosis who do not have a primary tumour excision. Additionally, in the atrial fibrillation (AF) trials, GI bleeding was more common with DOACs than warfarin,[27] but apixaban was not associated with a particularly significant rate of bleeding complications.[25] In the large AF pharma trials with warfarin as a comparator, apixaban appeared to be the best choice for the frail elderly.[28] Overall, if there is a high risk of bleeding (see box text), then we go with a LMWH, but if not then we can use a DOAC.

Patients at high risk of bleeding

- GI or GU tumour in situ
- Thrombocytopenia (likely platelet count of <50)
- Recent bleeding
- Very recent surgery
- Brain malignancy (excluded from some of the DOAC malignancy trials)

Our treatment approach

In our current practice, we most often start with enoxaparin, which we give for 2 weeks to 3 months. For patients with a very high bleeding risk (for example primary brain cancer) we give enoxaparin with dose reductions (such as 0.5 mg/kg twice daily as a starting point, or prophylaxis only if the thrombotic load is less with a high-risk tumour). If a patient has had bleeding, we would start with a low dose of enoxaparin and escalate, although as our experience with these agents grows we are going straight to rivaroxaban where the thrombotic load is moderate or low and there are no bleeding risk factors. Other circumstances where this is relevant include moderate renal dysfunction and reduced platelets with chemotherapy.

Prevention is better than cure

We know from several trials comparing LMWH to placebo that it does prevent VTE in the setting of active cancer.[29] However, the number needed to treat is still relatively high, particularly for a therapy which is challenging to self-administer that does modestly increase bleeding risk. There is a scoring system called the Khorana score, including multiple clinical variables to identify those who are at higher risk of thrombosis.[30] The question then arises, of whether we could use DOACs for prophylaxis in high-risk patients. Two recent trials published in the NEJM, one with rivaroxaban[31] and one with apixaban,[32] have looked at this. Together, these trials do show a benefit in terms of prevention of VTE, but despite only treating those with a high Khorana score, the best scoring system available to date, the number needed to treat remains relatively high.[33] We still have not really worked out who are the best patients to give DOACs to, but they are certainly a potential option in very high-risk malignancy or people with other issues like previous VTE who do not have particular risk factors for bleeding.

In summary, this is a problem that is increasing, and while the arrival of the DOACs is helping us, we usually still start with enoxaparin and patients remain on it indefinitely, unless their cancer is cured.

MANAGING VTE IN THE COMMUNITY

Daryl Pollock – Clinical nurse specialist

Anticoagulation management and superficial thrombophlebitis

Phlebitis is the presence of inflammation within a vein, whereas thrombosis indicates the presence of a clot within the vein. Thrombophlebitis is diagnosed after confirming the presence of a thrombus within an inflamed vein. Phlebitis and thrombosis of the lower extremity is generally a benign and self-limiting disorder, affecting the superficial veins of the lower extremity. It is a relatively common condition, and the incidence may be much more than previously believed. Thrombosis of the great or small saphenous vein appears to be more prevalent than DVT.

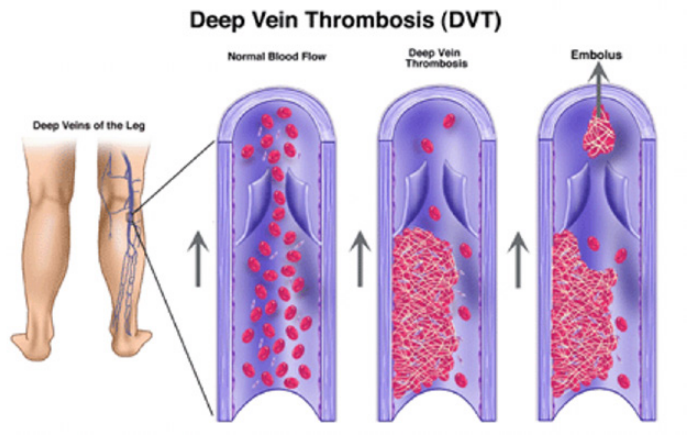

Figure 3: Deep vein thrombosis

Risk factors for superficial thrombophlebitis

Risk factors for superficial thrombophlebitis are the same risk factors associated with conditions that increase the risk of clotting:

- Varicose veins
- Vein excision/ablation
- Pregnancy/oestrogen therapy
- Prior vein thrombosis
- Malignancy and hypercoagulable states
- IV catheter use

Clinical presentation

Uncomplicated thrombophlebitis presents with tenderness, induration, pain and/or erythema along the course of a superficial vein. Complicated thrombophlebitis, is thrombophlebitis that is recurrent or migratory, and involves long segments of the greater saphenous vein (for example 30cm), may be suppurative (accompanied by fever, fluctuance and/or purulent drainage) and may be accompanied by thromboembolism.

Diagnosis

Diagnosis of thrombophlebitis is generally based on the patient's physical examination and complaints, and it is really important to look at the individual clinical scenario. Diagnosis is confirmed with duplex ultrasound, which identifies the presence, location and extent of superficial thrombophlebitis and DVT. Of note, the risk of DVT progressing from the great saphenous (saphenofemoral junction) or small saphenous (saphenopopliteal junction) vein is greater with the perforating veins. If the isolated uncomplicated phlebitis is not affecting the great or small saphenous vein and there are no other risk factors for DVT, then the likelihood of DVT is low and no other testing is required.

Superficial veins in obese patients can be several centimetres deep, therefore it is important to image these people. Patients with significant lower limb swelling should also have an ultrasound.

Treatment options

For uncomplicated thrombophlebitis, treatment involves elevation of the limb, warm or cool compresses and nonsteroidal anti-inflammatories (NSAIDs); no one NSAID been found to be more effective than the other. Treatment may also include compression, but it is important to remember that these people have veins that are very painful, and they may not want to have compression. It is very important that patients remain ambulatory. If thrombophlebitis is more extensive, but still uncomplicated, treatment should also include anticoagulation, and for recurrent thrombophlebitis, the patient should be referred to vascular services as they may require vein excision to prevent recurrence. For suppurative thrombophlebitis, empiric systemic antibiotics should be given, but only for proven infection not for suspicion of infection.

Available treatments include topical agents, for which there is limited data that these alleviate symptoms and hasten resolution, and compression therapy, which can be very painful for the patient and contraindications such as heart failure and anticoagulation must be considered. In patients at low risk for VTE (venous segment >5cm, remote from the junction) NSAIDs are the treatment of choice, and for patients at high risk (clot <5cm from the junction particularly the upper part of the leg), anticoagulation therapy should be given. This is generally LMWH for 30 days, but this can be discussed with the local haematology team. LMWH, especially enoxaparin, seems to have a bit of an anti-inflammatory effect as well and this helps alleviate the pain. To get LMWH for one month, a Special Authority is required.

Community Pharmacy Anticoagulant Management Service

The Community Pharmacy Anticoagulation Management Service (CPAMS) enables pharmacists to manage patients on warfarin using near patient testing and decision support software. CPAMS was developed in December 2010, and a 6-month pilot was carried out in 15 pharmacies, with 693 patients recruited. The mean time in therapeutic range (TTR) was 78.6%, rising to 79.4% and 80.2% for patients who had been in CPAMS for 16 and 26 weeks, respectively. All pharmacy sites achieved a mean TTR in excess of 70% (range 71.4% to 84.1%), which is great, well above the recommended target of 60%. Subsequently, the Ministry of Health has funded this service for some centres.

More information on the Community Pharmacy Anti-Coagulation Management Service (CPAMS) can be found here:

http://inronline.net/

How does CPAMS work?

- Patient visits your pharmacy
- The patient has a finger prick blood test
- The results are automatically transferred to INR online
- The computer recommends a dose and prints out a calendar
- The results are sent to the GP
- The patient receives an email reminder for the next test

CPAMS has been provided in New Zealand for 10 years and there are more than 6000 patients currently using the service. More than 10 000 patients have used the service over the last 5 years, with the service provided by more than 160 pharmacies, 48 of which are in the South Island, with these pharmacies well distributed geographically.

A recent review of CPAMS over the last 5 years in May 2020,[34] showed that in January 2015, approximately 4000 patients were registered, with over 6600 patients registered currently, and approximately 10 000 tests performed by January 2020. Of registered patients, at least 60% were on warfarin for stroke prevention in AF. Of the 10 075 patients who had at least 4 tests and were included in the analysis, TTR was 73%, time below range was 16.24%, and time above range was 10.76%.

When the patient goes into the pharmacy and they are out of range, the pharmacist can discuss with the patient whether they may have missed any doses, started any new medications or anything else that might have taken them out of range. If the INR is between 1.8-3.2, for a target of 2.5, it is suggested that the treatment is safe within this range and the dose does not need adjusting. For individual patients, 79.4% had INR results in range more than 60% of the time, and when limited to patients who had been on treatment for at least 6 months, this increased to 83.2%. In conclusion, CPAMS provides an efficient safe anticoagulant monitoring service giving a consistent high level of anticoagulant control. There is scope to expand CPAMS, which could become the standard of care for warfarin management in NZ.

Interrupting warfarin for surgery and other invasive procedures

A person on warfarin may require interruption of their treatment to cover invasive procedures such as bowel screening (especially now as patients are coming in for polyp removals as bowel screening has been extended to those aged over 60 years), orthopaedic surgery, urological procedures and all other surgeries. The approach depends on risk categories.

- Low risk is defined as those with a bileaflet aortic valve with no risk factors for stroke, or AF with a $CHADS_2$ score of ≤2.
- Patients considered to be at intermediate risk are those with a bileaflet aortic valve and one of AF, hypertension, diabetes and congestive heart failure, or with a $CHADS_2$ score of 3 or 4, or VTE (more than 3 months since VTE), recurrent thromboses, or active cancer.
- High-risk patients are patients with any mitral valve prosthesis, a bileaflet aortic valve with a prior history of cerebrovascular accident or with multiple risk factors, or AF patients with rheumatic valvular disease, AF with prior cerebrovascular accident or transient ischaemic attack within the last 3 months, a $CHADS_2$ score 5 or 6, or patients with VTE, recent VTE < 3 months, severe thrombophilia if known, ATIII protein C or S deficiency, lupus anticoagulant/APS, or homozygous FV Leiden.

Example high-risk protocol

Most surgical departments will refer high-risk patients to the Haemostasis Department

Protocol for a procedure on **28.8.20**

- Stop warfarin 5 days prior to procedure (**last dose 23.8.20**)
- After 36 hours commence SC enoxaparin 1 mg/kg/bd (if poor renal function, with eGFR <30, reduce to 1 mg/kg/od)
- Last dose would be 8am, 24 hours prior to surgery (**8am 27.8.20**)
- Day prior check INR, if >1.7 give oral Vit K 1mg
- Day of procedure if INR >1.5 previous day then retest, if >1.5 either give Prothombinex 25 IU/kg or postpone the surgery
- At 12-24 hours post-procedure give SC enoxaparin 40 mg/day and restart warfarin at the usual dose
- At 48-72 hours post-procedure increase SC enoxaparin to 1.5 mg/kg/day
- Day 4 INR generally monitored by continued community dosing, but may be monitored by the Haemostasis Department, working in conjunction with the patient's GP.

Perioperative management of DOACs

There are apps available for both dabigatran and rivaroxaban.

Dabigatran - available on the APP store

Rivaroxaban - available on the APP store

These have both been designed by HealthObs Ltd.

Dabigatran

For a 68-year-old female, with a weight of 68kg, creatinine clearance of 95, who is undergoing elective surgery that carries a standard bleeding risk, the app would advise stopping dabigatran 36 hours prior to surgery. For the same patient at a high bleeding risk, the app would advise stopping 6 doses prior.

Rivaroxaban

In a patient at standard bleeding risk with normal renal function, the rivaroxaban app advises stopping 24 hours prior to surgery, and then resuming 24 hours post-surgery. In a patient with a creatinine clearance of 30-50 ml/min you would stop 36 hours prior to surgery and resume 24 hours post-surgery. The rivaroxaban app tells you when to restart, whereas the dabigatran does not.

These patients do not need bridging enoxaparin.

From the panel discussion:

"After we stop anticoagulation after 3 months you mentioned protecting patients against certain risks, how do we do this?"

Dr Gordon Royle answered that if there is a transient risk factor such as a moonboot for a sprained ankle, then while the risk is present either a prophylactic dose of enoxaparin (which in normal renal function is 0.5 mg/kg/day, rounded up to the nearest 20 mg), or rivaroxaban 10 mg/day or dabigatran 220 mg/day is appropriate. In all cases, this must be balanced against any bleeding risk and renal function must be checked. Dr Laura Young noted that for active cancer patients, post thrombosis therapy will generally be continued if the malignancy persists.

"Those on lifelong anticoagulation for VTE find it restrictive to avoid alcohol at all costs due to the risk of bleeding, is there some compromise or guidance on how much alcohol could be allowed?"

Dr Young and Dr Royle agreed that, with warfarin, heavy drinking can cause the INR to be unstable. This does not apply to DOACs. Heavy drinking can also raise the bleeding risk for other reasons, e.g. by lowering the platelet count, by causing portal hypertension, or causing gastritis. The risk of bleeding is not high if alcohol intake is within the WHO range for safe alcohol intake. People should not be encouraged to indulge heavily, but within reasonable limits it is not an issue with anticoagulation.

TAKE-HOME MESSAGES

Diagnosing VTE

- Diagnosis of thrombophlebitis is based on the individual clinical scenario.
- The Wells score and often a D-dimer test can be used to aid diagnosis.
- Diagnosis is usually confirmed by ultrasound.

Treatment and management of VTE

- Provoked VTEs should be treated for 3 to 6 months.
- Unprovoked events carry a continued recurrence risk, and thus long-term treatment may be necessary.
- The ideal anticoagulant prevents thrombosis without impairing haemostasis.
- This ideal drug does not yet exist, but some of the currently available options, such as enoxaparin and the DOACs, are bringing us closer.

Cancer-associated VTE

- Cancer and thrombosis are strongly linked, with around 20% of VTE cases associated with known cancer.
- Cancer-associated VTE is an increasing problem, and while the arrival of the DOACs is helping, initial treatment is usually still enoxaparin, which patients remain on indefinitely, unless their cancer is cured.

REFERENCES

1. Tran HA, Gibbs H, Merriman E, et al. New guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism. Med J Aust. 2019;210(5):227-35.
2. Merriman E, Chunilal S, McRae S, et al. Two Weeks of Low Molecular Weight Heparin for Isolated Symptomatic Distal Vein Thrombosis (TWISTER Study): Final Analysis of 242 Patients [abstract]. Res Pract Thromb Haemost. 2020;4(Suppl 1).
3. Rodger MA, Le Gal G, Anderson DR, et al. Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study. BMJ (Clinical research ed). 2017;356:j1065.
4. McCaughan G, Crowther H, Chen V, et al. Australian and New Zealand Registry of Anticoagulation in the Obese. ISTH; July 6-19; Melbourne2019.
5. Klok FA, Schreiber K, Stach K, et al. Oral contraception and menstrual bleeding during treatment of venous thromboembolism: Expert opinion versus current practice: Combined results of a systematic review, expert panel opinion and an international survey. Thromb Res. 2017;153:101-7.
6. Fernandes CJ, Morinaga LTK, Alves JL, Jr., et al. Cancer-associated thrombosis: the when, how and why. Eur Respir Rev. 2019;28(151).
7. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med. 2012;9(7):e1001275.
8. Hisada Y, Geddings JE, Ay C, et al. Venous thrombosis and cancer: from mouse models to clinical trials. J Thromb Haemost. 2015;13(8):1372-82.
9. Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. The Lancet Oncology. 2005;6(6):401-10.
10. Timp JF, Braekkan SK, Versteeg HH, et al. Epidemiology of cancer-associated venous thrombosis. Blood. 2013;122(10):1712-23.
11. Fuentes HE, Tafur AJ, Caprini JA. Cancer-associated thrombosis. Dis Mon. 2016;62(5):121-58.
12. Di Nisio M, Lee AY, Carrier M, et al. Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2015;13(5):880-3.
13. Horsted F, West J, Grainge MJ. Risk of Venous Thromboembolism in Patients with Cancer: A Systematic Review and Meta-Analysis. PLOS Medicine. 2012;9(7):e1001275.
14. Braekkan SK, Borch KH, Mathiesen EB, et al. Body height and risk of venous thromboembolism: The Tromsø Study. American journal of epidemiology. 2010;171(10):1109-15.
15. Lee AYY, Levine MN, Baker RI, et al. Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer. New England Journal of Medicine. 2003;349(2):146-53.
16. Lee AY, Peterson EA. Treatment of cancer-associated thrombosis. Blood. 2013;122(14):2310-7.
17. Mahe I, Chidiac J, Helfer H, et al. Factors influencing adherence to clinical guidelines in the management of cancer-associated thrombosis. J Thromb Haemost. 2016;14(11):2107-13.
18. Key NS, Khorana AA, Kuderer NM, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2020;38(5):496-520.
19. 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):1891-4.
20. Valerio L, Ambaglio C, Barone M, et al. Recurrence Risk after First Symptomatic Distal versus Proximal Deep Vein Thrombosis According to Baseline Risk Factors. TH Open. 2019;3(1):e58-e63.
21. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism. New England Journal of Medicine. 2009;361(24):2342-52.
22. Goldhaber SZ, Schellong S, Kakkar A, et al. Treatment of acute pulmonary embolism with dabigatran versus warfarin. A pooled analysis of data from RE-COVER and RE-COVER II. Thromb Haemost. 2016;116(4):714-21.
23. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. New England Journal of Medicine. 2017;378(7):615-24.
24. Young AM, Marshall A, Thirlwall J, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). Journal of Clinical Oncology. 2018;36(20):2017-23.
25. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. New England Journal of Medicine. 2020;382(17):1599-607.
26. Fuentes HE, McBane RD, 2nd, Wysokinski WE, et al. Direct Oral Factor Xa Inhibitors for the Treatment of Acute Cancer-Associated Venous Thromboembolism: A Systematic Review and Network Meta-analysis. Mayo Clin Proc. 2019;94(12):2444-54.
27. Feagins LA, Weideman RA. GI Bleeding Risk of DOACs Versus Warfarin: Is Newer Better? Dig Dis Sci. 2018;63(7):1675-7.
28. Abraham NS, Noseworthy PA, Yao X, et al. Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study. Gastroenterology. 2017;152(5):1014-22 e1.
29. Di Nisio M, Porreca E, Candeloro M, et al. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database of Systematic Reviews. 2016(12).
30. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111(10):4902-7.
31. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. New England Journal of Medicine. 2019;380(8):720-8.
32. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. New England Journal of Medicine. 2018;380(8):711-9.
33. Agnelli G. Direct Oral Anticoagulants for Thromboprophylaxis in Ambulatory Patients with Cancer. New England Journal of Medicine. 2019;380(8):781-3.
34. Harper P. Community Pharmacy Anticoagulant Management Service: CPAMS at 10 years 2020 [Available from: http://inronline.net/wp-content/uploads/2020/05/CPAMS-at-10.pdf.

SANOFI

This publication has been created with an educational grant from Sanofi. The content is entirely independent and based on published studies and the speaker's opinions. It may not reflect the views of Sanofi. This review may contain unapproved products or unapproved uses of approved products. Before prescribing any of the prescription medications mentioned in this article please consult the full Product Information. These are available at www.medsafe.govt.nz. Treatment decisions based on these data are the full responsibility of the prescribing physician.