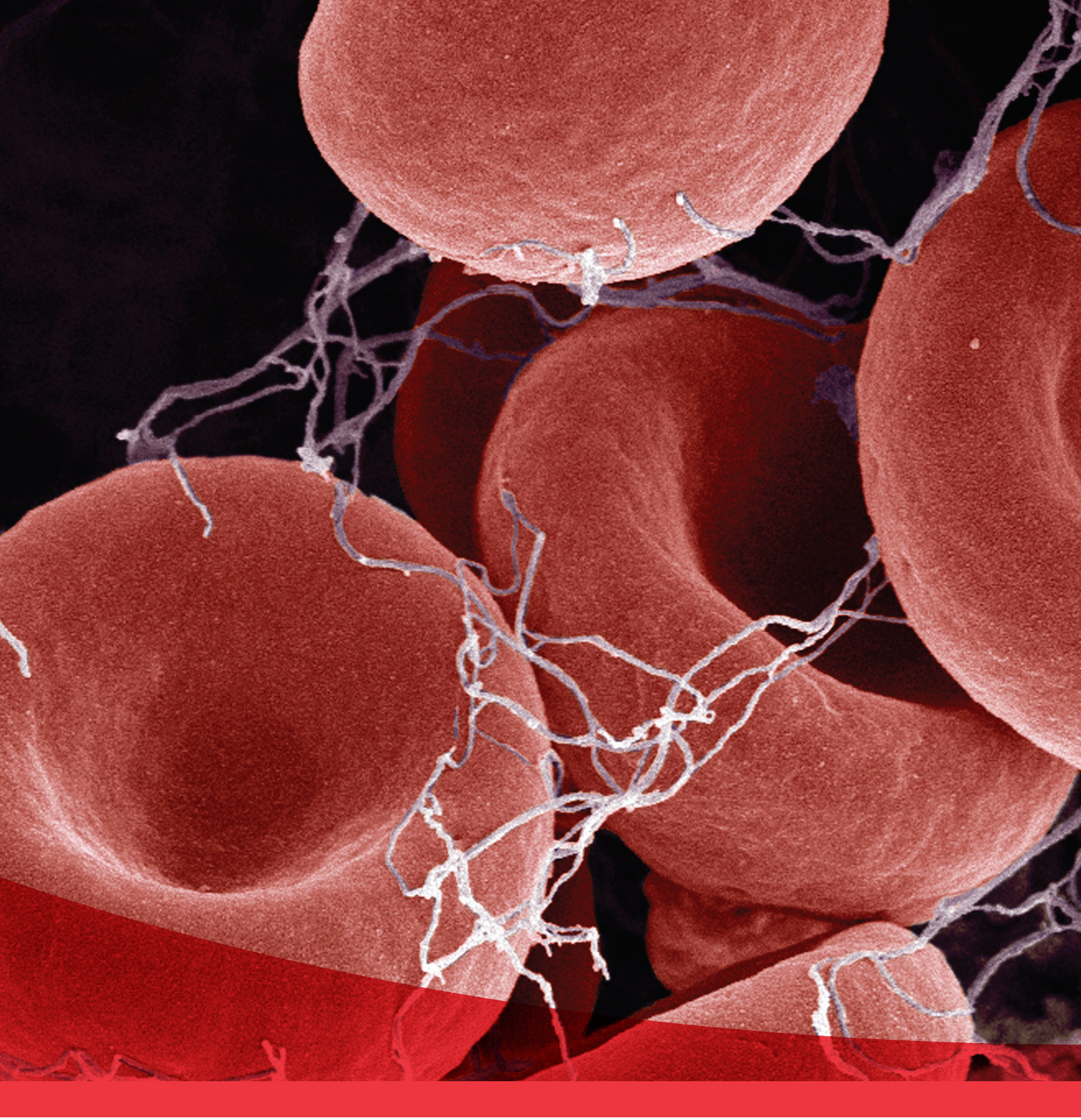


Preventing Venous Thromboembolism:

A Healthcare Professional Guide to Intervention

CardinalHealth

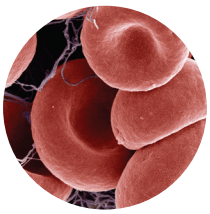
Participant Handbook

Contents

Definitions.

Anticoagulants	An agent used to prevent the formation of blood clots. These include oral agents, such as warfarin, and others which are injected into the vein or under the skin, such as heparin.
Deep-Vein Thrombosis (DVT)	Venous thrombosis that occurs in the "deep veins" of the arms, legs, thighs or pelvis.
Distal	Refers to the part of the body that is further away from the centre of the body than another part.
Foot Impulse Technology (FIT)	The foot impulse system is designed to provide the advantages of ambulation to patients who are immobilised.
Graduated Compression Stockings (GCS)	Also known as anti-embolism stockings. Stockings are manufactured to provide compression around the legs at gradually decreasing pressures from ankle to thigh.
Heparin-Induced Thrombocytopenia (HIT)	Low blood platelet count resulting from the administration of heparin (or heparin like agents). Despite having a low platelet count, patients with this condition are at high risk of blood clotting.
Intermittent Pneumatic Compression (IPC)	A method of prophylaxis that comprises of the use of inflatable garments wrapped around the legs, inflated by a pneumatic pump. The pump provides intermittent cycles of compressed air that alternately inflates and deflates the chambers on the garments, administering controlled pressure to the limbs, enhancing venous return.
Post Thrombotic (Post Phlebitic) Syndrome	Chronic pain, swelling, and ulceration of the skin of the leg that occurs as a consequence of previous venous thrombosis.
Prophylaxis	A measure taken for the prevention of a disease.
Proximal	Refers to a part of the body that is closer to the centre of the body than another part.
Pulmonary Embolism (PE)	A blood clot that breaks off from the deep veins and travels via the venous circulation to block the pulmonary arteries (arteries in the lungs). Most deaths arising from DVT are caused by PE.
Thrombophilia	The genetic or acquired prothrombotic states that increase the tendency to form venous thromboembolism. It is a condition that leads to a tendency for a person's blood to clot inappropriately.
Thromboprophylaxis	Chemical and or mechanical measures taken to reduce the risk of thrombosis.
Venous Thromboembolism (VTE)	Formation of blood clots in the vein. A clot that forms in a deep vein usually in the leg is called a Deep Vein Thrombosis (DVT). If that clot breaks loose and travels to the lungs it is called a Pulmonary Embolus (PE). Together DVT and PE are known as VTE.
Venous Thrombosis (VT)	A condition in which a blood clot (thrombus) forms in a vein.

What is VTE?



When a clot develops and persists in a deep vein it is a deep vein thrombosis (DVT).
A thrombus that breaks away from a vein wall and floats freely in the blood stream is an embolus. An embolus that travels via the venous system to the vessel that carries blood from the heart to the lungs (pulmonary artery) is called a pulmonary embolism (PE).
A PE is a very serious and potentially fatal complication. DVTs also have long term complications. These are known as post thrombotic syndrome and may include chronic pain, swelling and or ulceration of the skin.

Clot Formation.

A blood clot is a coagulation of red and white blood cells, platelets and clotting factors localised within an insoluble fibrin network.

- The haemostatic system maintains the balance between coagulation and lysis with three processes:
  - clot formation
  - anticoagulation
  - fibrinolysis
- When a blood vessel is injured, it constricts to minimise blood loss.
- Then, platelets adhere to the exposed sub endothelium and release substances that attract additional platelets, creating a feedback cycle that continues to adhere and attract platelets.
- Circulating fibrinogen binds to the platelets and forms a soft plug composed of platelets and fibrin.

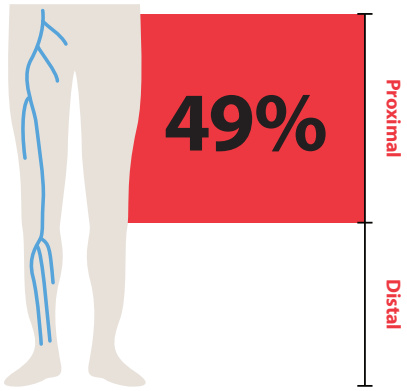
This initial response of soft plug formation is followed by a cascade of events activating clotting factors that interact to further activate the coagulation cascade.

- Fibrinogen is converted to fibrin resulting in a stable clot made up of fibrin, platelets and red blood cells.

If the process of clot formation continues unchecked by anticoagulation and fibrinolysis, it can cause thrombosis.

Where Do Clots Form?

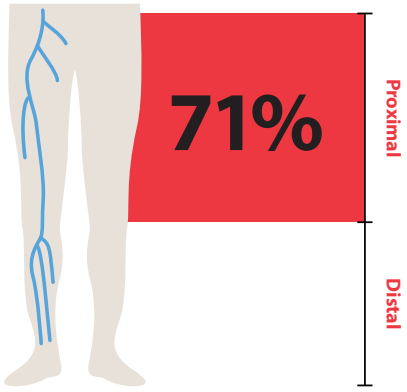
- In DVT a blood clot forms in the deep veins of the peripheries, most commonly in the legs, including the popliteal vein (behind the knee), femoral vein (of the thigh), and iliac veins of the pelvis.
- PE generally arise from proximal thromboses[1].
- Femoral DVTs are responsible for 75% of fatal PE[2].



49% OF THROMBI OCCUR IN THE VEINS OF THE THIGH AND POPLITEAL SPACE WITHOUT CALF INVOLVEMENT[1]

Maternity - Where Do Clots Form?

- When DVT occurs during pregnancy, it is more likely to be proximal, massive, and in the left lower extremity[3].
- Up to 90% of DVTs in pregnant women occur in the left leg, most are ileo-femoral[4].
- Pulmonary emboli generally arise from proximal thrombosis[1].



71% OF DVTS IN MATERNITY PATIENTS WERE PROXIMAL WITH NO CALF INVOLVEMENT[4]

Prevalence & Cost.

Why Focus on Venous Thromboembolism?

VTE is estimated to be one of the leading preventable causes of death in hospital with modelling of healthcare statistics showing that PE accounts for 7% of all deaths in Australian hospitals every year. In almost 25% of people affected, sudden death is the first clinical sign of PE.[5]

Incidence.

The silent nature of VTE prevents precise prevalence reporting.

- Estimates suggest that symptomatic VTE affects about 1 per 1,000 Australians per year.[5]
- Based on epidemiological evidence, VTE was estimated to be responsible for 5,285 deaths in Australia in 2008.[6]
- DVT occurs in over 50% of some categories of hospitalised patients if prophylaxis is not used.[7]

Cost.

In 2008 the financial cost of VTE was $1.72 billion (0.15% of GDP).[7] Of this:

- 1.38 billion (80%) was productivity lost primarily due to premature death of Australians with VTE.
- 162 million (9.4%) was the efficiency loss from taxation forgone and government health expenditures.
- 146 million (8.6%) was direct health care expenditure.
- 22 million (1.3%) was bring-forward of funeral costs.
- 12 million (0.7%) was the value of the informal care of people with VTE.

VTE costs $116,000 per case per annum. Including the loss of wellbeing, the cost approaches 1.5 million per person.[6]

Mortality.

- VTE deaths represent some 7% of all deaths in Australian hospitals.[6]
- In Australia VTE causes more deaths than all transport accidents and falls combined. It is a bigger killer than bowel or breast cancer and over 40 times more deadly than AIDS.[6]
- VTE is the largest preventable cause of death in hospitalised patients.[8]
- Death occurs in approximately 6% of DVT cases and 12% of PE cases within one month of diagnosis.[9]
- 10% of maternal deaths are due to VTE.[10]
- VTE is the most common cause of 30 day mortality in patients who underwent surgery for cancer.[11]
- In stroke PE accounts for 5% of deaths and is the 3rd most common cause of death after Stroke.[12]
- Obese patients have a significantly higher frequency of PE as the immediate cause of death.[13]

In Australia, 30,000 cases of hospital-associated Venous Thromboembolism (VTE) occur every year.[5]

30,000

Affected Per Year.

Recurrence.

- History of VTE is the largest predictor of a patient having another VTE event, it is estimated that the cumulative recurrence rate after one year is 12.9% after two years 16.6% after five years as 22.8% and after 10 years as 30.4%.[14]
- 15-25% of thromboembolic events in pregnancy are recurrent events.[10]
- Symptomatic DVTs have a 30% recurrence rate.[15]

Prevalence & Cost.

Australian Commission on Safety and Quality in Health Care.

The Australian Commission on Safety and Quality in Health Care and Independent Hospital Pricing Authority established a Joint Working Party in 2012 to consider potential approaches to pricing for safety and quality in public hospital services in Australia. This led to the development of the Hospital Acquired Complications (HACs) list.

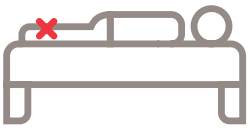
The HACs list below details 16 agreed, high-priority complications which clinicians, managers and others can work together to address and drive improvements in healthcare safety and quality.

	Hospital-Acquired Complication	Rate[a]
1	Pressure injury	10
2	Falls resulting in fracture or intracranial injury	4
3	Healthcare-associated infections	135
4	Surgical complications requiring unplanned return to theatre	20
5	Unplanned intensive care unit admission	NA[b]
6	Respiratory complications	24
7	**Venous thromboembolism**	**8**
8	Renal failure	2
9	Gastrointestinal bleeding	14
10	Medication complication	30
11	Delirium	51
12	Persistent incontinence	8
13	Malnutrition	12
14	Cardiac complications	69
15	Third and fourth degree perineal laceration during delivery (per 10 000 births)	358
16	Neonatal birth trauma (per 10 000 births)	49

a per 10,000 hospitalisations except where indicated.
b na = national data not available.

30,000

Around 30,000 hospital-acquired episodes of VTE occur each year in Australian Hospitals.



+21.4

Patients with this HAC require **21.4 extra days** in hospital compared to those who don't.

+44,384

Each episodes of care for this HAC could cost the hospital an **additional $44,384.**

Incidence of VTE in Different Patient Groups without Prophylaxsis.[7]

Patient Group			
Stroke	56%	Myocardial infarction	22%
Elective hip replacement	51%	Abdominal vascular surgery	19%
Multiple trauma	50%	Isolated lower limb injuries	17%
Total knee replacement	47%	Peripheral vascular surgery	15%
Hip fracture	44%	Elective spinal surgery	15%
Spinal cord Injury	35%	Gynaecological surgery for benign disease	14%
Retro pubic prostatectomy	32%	Burns	12%
ICU patients	25%	Transurethral prostatectomy	9%
General surgery	25%	Geriatric patients >65	9%
Neurosurgery	22%	General medicine	8%
Gynaecological surgery for malignancy	22%	Knee arthroscopy	8%

What Causes VTE.

Causal Factors for Venous Thromboembolism.

Nineteenth century German pathologist Rudolf Ludwig Karl Virchow established a three-pronged formula to explain the cause of thrombosis. This formula, commonly known today as **Virchow's Triad** (see *Figure 1.*), remains the prevailing theory of how DVT forms.

DVT risk factors have their basis in at least one of the triad categories:

1. Stasis.

Stasis is a primary causal factor associated with hospitalised patients. All hospital patients will be immobile for a period of time. Prolonged immobility will slow the circulation of blood and contributes to clot formation. There are additional patient related factors which also cause stasis, such as obesity, pregnancy and prior DVT.

2. Vessel Wall Damage.

Vessel wall damage is thought to result from surgical limb manipulation producing vessel kinks intra-operatively in procedures such as knee or hip surgery. Pooling of venous blood following administration of smooth muscle relaxants and saline administered intra-operatively causes venous distension and consequently damages the endothelial lining of the vein walls.

3. Coagulation Changes.

Coagulation factors are circulating blood proteins that are necessary for clot formation, dissolving old blood clots and preventing unwanted blood clots. Over 30 substances are involved with coagulation. The delicate balance between pro-coagulant (coagulant factors that promote clotting) and anti-coagulants (coagulation factors that prevent clotting) determines whether or not the blood will clot. A list of some coagulation factors are presented in *Table 1.*

Hyper-coagulability increases the risk of thrombus. This may result from deficiencies of factors in the blood that prevent clotting, increase in the factors that promote clotting or alterations in the viscosity and coagulation of blood itself.

Table 1: Coagulation Factors

Pro-coagulants	Anti-coagulants
Platelets	Protein C
Von willebrand factor	Protein S
Tissue factor	Antithrombin
Clotting factors I-XII	Heparin cofactor II

The Clotting Process.

Coagulation and fibrinolysis are normal processes in the body. The coagulation cascade is a step by step process that results in the formation of a thrombus. Conversely, the fibrinolysis cascade outlines the process of thrombus breakdown. (see *Figure 2.*)

Figure 1: Virchow's Triad

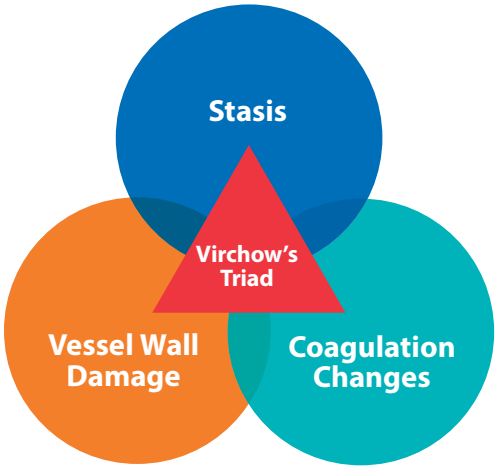
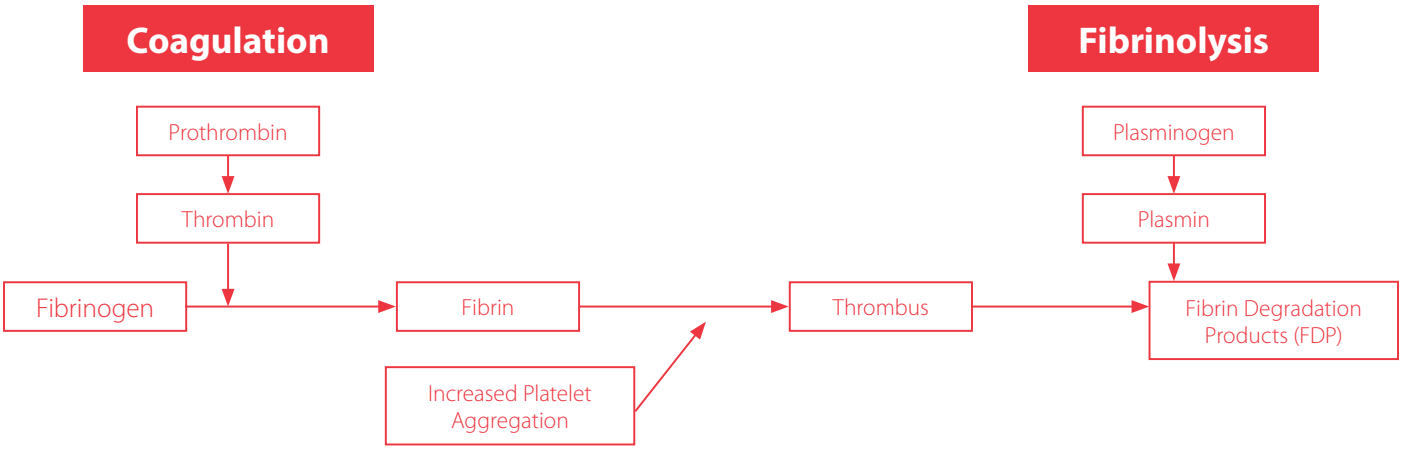


Figure 2: Coagulation & Fibrinolysis Cascade



THE CLOTTING PROCESS: COAGULATION AND FIBRINOLYSIS ARE NORMAL PROCESSES IN THE BODY. THE COAGULATION CASCADE IS A STEP BY STEP PROCESS THAT RESULTS IN THE FORMATION OF A THROMBUS. CONVERSELY, THE FIBRINOLYSIS CASCADE OUTLINES THE PROCESS OF THROMBUS BREAKDOWN.

Virchow's Triad.

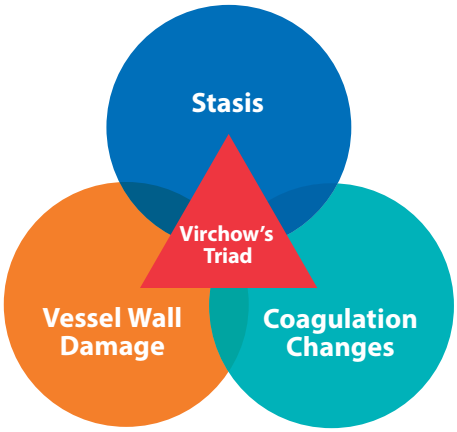
Causal Factors for Venous Thromboembolism.

Please Note:

GCS – Graduated Compression Stockings (e.g. T.E.D.) increases blood flow velocity, minimise venous distension and reduce likelihood of vessel wall damage by limiting micro-tears from venous dilation.

IPC – Intermittent Pneumatic Compression (e.g. SCDs) enhances venous return and increases fibrinolytic activity whilst clearing blood behind valve cusps.

FIT – Foot Impulse Technology (e.g. A-V Impulse) increases venous return and stimulates release of Endothelial Derived Relaxing Factor (ERDF) which inhibits platelet aggregation. FIT has been shown to enhance circulation to reduce lower limb pain and oedema after surgery.



Stasis: Abnormalties of Flow

Intervention Related	Patient Related

• Immobilisation
  - External fixation
  - Paralysis (stroke, spinal cord injury)
  - Partial weight bearing
• Dehydration or blood loss
• Intraoperative patient positioning
• Laparoscopic procedures
• Major surgery or trauma
• Assisted delivery or C-section
	• Previous DVT/PE
	• Increasing age
	• Obesity (BMI>30kg/m^2)
	• Malignancy
	• Varicose veins / chronic venous stasis
	• Long distance travel
	• Pregnancy and postpartum
	• Acute medical illness (e.g. myocardial infarction, heart or respiratory failure)

Mechanism of Action (IPC, FIT and GCS)
IPC, FIT and GCS increase blood flow velocity
IPC maximises blood flow by mimicking muscle contractions
FIT maximises blood flow by mimicking the processes which occur during weight bearing ambulation
IPC prevents distal trapping and ensures clearance of blood from behind valve cusps and soleal sinuses

Hypercoagulability

Intervention Related	Patient Related
• Trauma, injury, surgery • Dehydration • Excessive blood loss • Blood transfusion • Hormone therapy • Oral contraceptives • Assisted Reproduction	• Increasing age • Disseminated Intravascular Coagulation • Heparin-Induced Thrombocytopenia • Hyperfibrinogenemia • Thrombophilia (inherited or acquired) • Obesity (BMI>30kg/m2) • Malignancy or cancer related treatments • Autoimmune disorders • Acute infection • Pregnancy and postpartum • Inflammatory conditions (e.g. inflammatory bowel disease)

Mechanism of Action (IPC, FIT & Anticoagulants)
FIT stimulates the release of endothelial derived relaxing factor (ERDF) which inhibits platelet aggregation
IPC increases fibrinolytic activity
Anticoagulants inhibit various phases of the coagulation pathway

Vessel Wall Damage

Intervention Related	Patient Related

• Venous distension
  - Extra circulating volume
  - Effect of anaesthetic
• Trauma, injury, surgery
• IV injection of irritants
• Pacemaker wires
• Central and peripheral venous access
	• Venous distension
	  - Hormone mediated (preeclampsia)
	  - Sepsis
	  - Spinal cord injury
	• Previous DVT/PE
	• Varicose veins
	• Smoking

Mechanism of Action (GCS)
GCS reduce micro-tears secondary to venous distension
GCS reduce venous distension resulting from various intervention and patient related factors such as those mentioned above

Who is at Risk?

Risk Identification & Management.

Risk factors are accumulative, the more risk factors in place, the greater the risk of VTE. To effectively provide prophylaxis to surgical and medical patients, it is essential to look beyond the presenting diagnosis. Every patient must be risk assessed according to their individual level of VTE risk to ascertain the most appropriate measure to prevent VTE in the individual patient.

Today's hospital population may be at higher risk for VTE due to the following factors: advanced age, increased number of co-morbidities; longer stays in critical care units, increased incidence of cancer with more intensive cancer therapy and extensive surgical procedures.

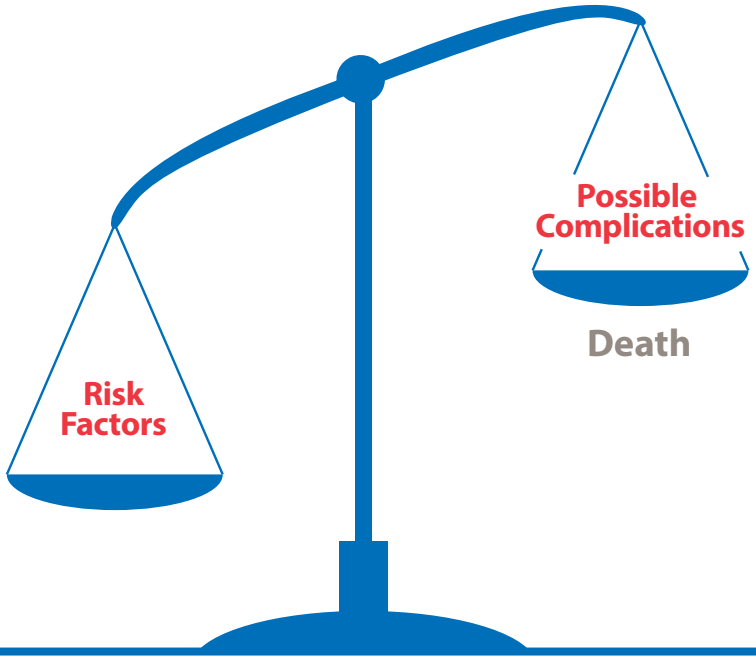
There are numerous local and international VTE Guidelines published to assist with the identification and treatment of patients at risk of VTE. Unfortunately despite the extensive evidence available these are often poorly adhered to.

The final decision to provide thromboprophylaxis is a clinical decision based on the number and type of risk factors balanced against risk of bleeding and any contradictions to mechanical or chemical prophylaxis

The illustration below highlights some of the risk factors for VTE as well as some of the possible complications.

Risk Factors

- **Stroke**
- **Increased Blood Thickness**
- **Obesity**
- **Aged Over 40**
- **Malignancy**
- **Surgical Procedure**
- **History of DVT or PE**
- **Being confined to bed for more than 72 hours**
- **Heart Conditions**
- **Pregnancy**
- **Oral Contraceptive**
- **Immobility**



Possible Complications

- **Persistent Swelling**
- **Bacterial Infection**
- **Increased Pigmentation**
- **Pruritus (Itchiness)**
- **Pain**
- **Eczematoid Dermatitis**
- **Ulceration**

*GREATER THAN 4 HOURS

Risk Assessment.

Being hospitalised is a major risk factor for the development of Venous Thromboembolism (VTE). Patients with decreased mobility - due to bedrest or recovery - or who experience blood vessel trauma - due to surgery or other serious injury - are more likely to develop blood clots.

- Risk factors are cumulative: increased risk factors = increased risk of VTE.[17]
- American College of Chest Physicians recommends that every hospital develop a formal written, institution wide VTE prophylaxis policy.[11]
- Combined modalities are more effective in reducing the incidence of VTE than single modalities.[18]
- About 50%–75% of people admitted to hospital have at least one risk factor for VTE, while 40% have three or more.[5]
- Patients with cancer are four to seven times more likely to develop VTE than are patients without cancer.[19]
- Cancer-associated thrombosis is the second leading cause of death in cancer patients after disease progression.[19]
- The risk for development of VTE in cancer patients undergoing operations is about twice that for patients without cancer.[20]
- Thrombophilia is found in approximately 50% of women with a VTE during pregnancy.[20]
- There is 4 to 5-fold increased risk of developing a VTE in pregnancy.[21]
- VTE was the leading cause of direct maternal death in Australia 2006–2016.[21]
- The greatest risk is in the weeks immediately after birth.[21]
- When compared to control subjects, obese individuals had an odds ratio of 2.33 for developing VTE.[13]
- Obesity, is associated with increased thrombin formation and decreased fibrinolysis.[22]

All admitted patients should have a VTE risk assessment as part of their hospital admission, and they should receive optimal VTE prophylaxis according to their level of risk, and existing contraindications to prophylaxis.

Risk Assessment Tool.

Prophylaxis Rates in Hospitals.

Work is needed to improve prevention of VTE in hospitalised patients.

Data show that, globally, a large proportion of hospitalised individuals—both surgical and medical—are at risk for VTE, and that recommended VTE prophylaxis is underused.

Endorse Study.[23]

A multinational, cross sectional study designed to assess the prevalence of VTE risk in the acute hospital care setting, and to determine the proportion of at-risk patients who receive effective prophylaxis.

	Surgical	Medical
Patient Separation	30 827 (45%)	37 356 (55%)
High Risk of VTE	19 842 (64.4%)	15 487 (41.5%)
Prophylaxis to Guidelines	11 613 **(58.5%)**	6 119 **(39.5%)**

Key Point: The under prophylaxis of patients remains prevalent. Patients remain at high risk.

358

Hospitals

32

Countries

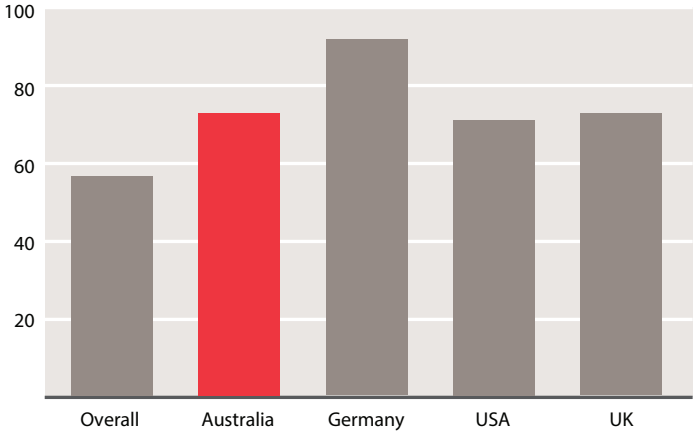
68 183

Patients

How Australia Compares?

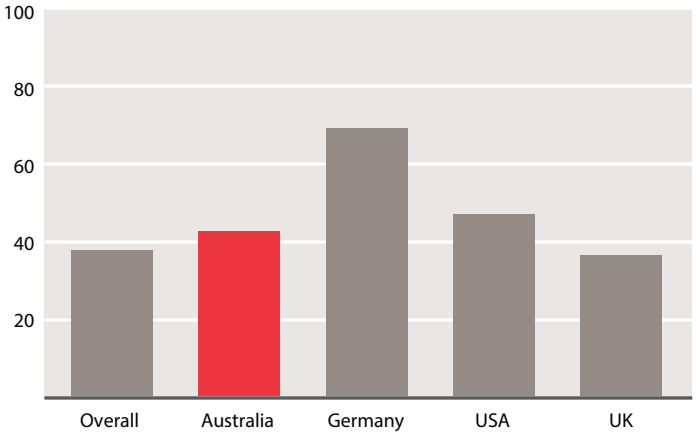
Surgical.

% of at risk surgical patients receiving ACCP recommended prophylaxis.



Medical.

% of at risk medical patients receiving ACCP recommended prophylaxis.



When Do Clots Form?

45%
within 24hrs

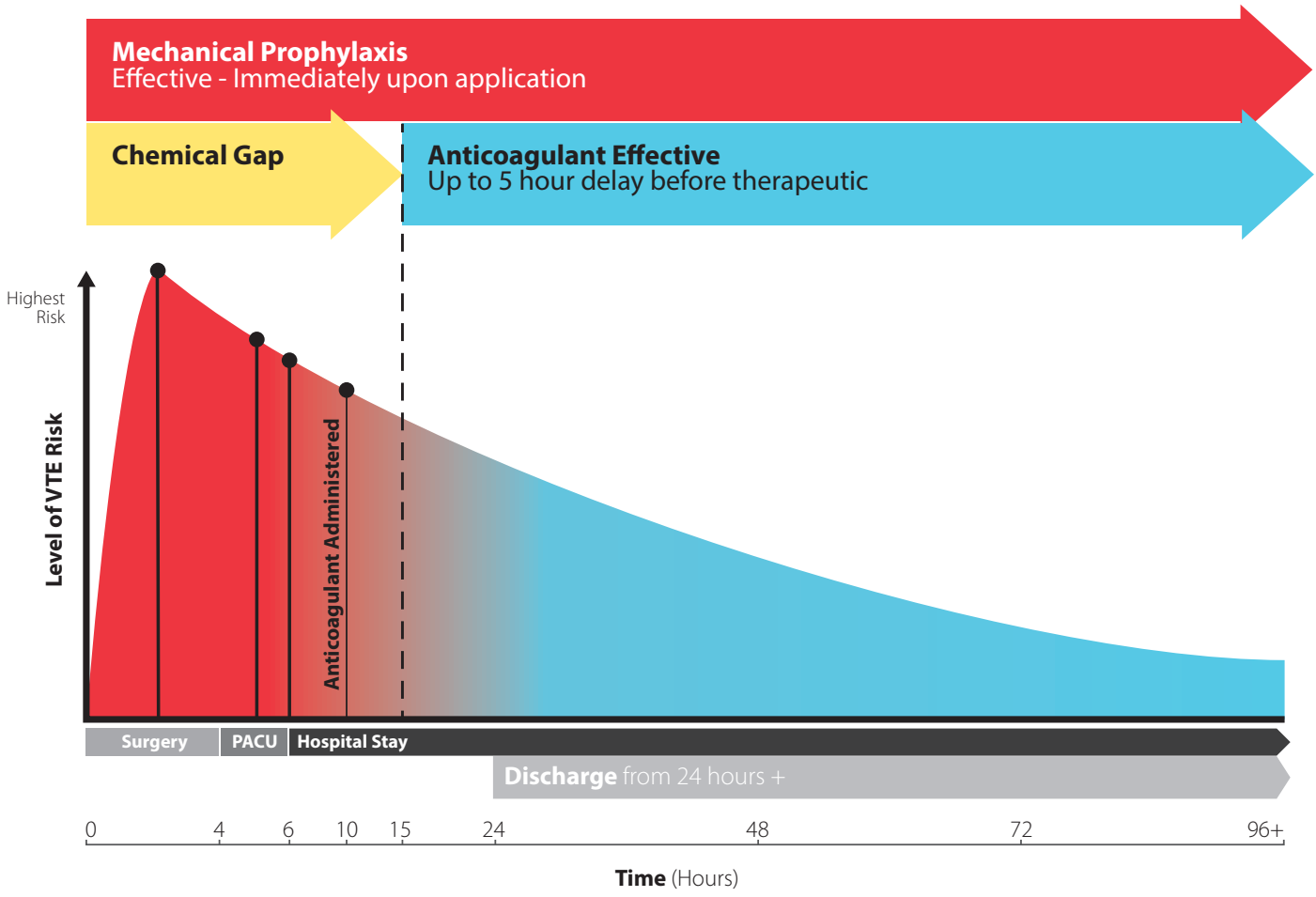
75%
within 48hrs

24hrs 48hrs

- According to Nicolaides et al 45% of DVTs occur on the day of surgery.[24]
- O'Meara et al suggest that 75% of DVTs have occurred by day two but only 25% of patients that develop DVT display clinical symptoms,[2] therefore highlighting the importance of commencing DVT prophylaxis during the operative period and continuing into the post-op period.

Achieving a balance between bleeding risk during surgery and VTE prevention can be challenging and expose the patient to a gap in chemical prophylaxis during the operative period.

Gap in VTE Prophylaxis.



Signs, Symptoms, Diagnosis & Management.

VTE can occur without any warning signs or symptoms and can go unrecognised and undiagnosed by a healthcare professional. Symptoms that do appear may be associated with either DVT or PE.

Deep Vein Thrombosis (DVT).

- Pain or tenderness, often starting in the calf
- Swelling, including the ankle or foot
- Redness or noticeable discoloration
- Increased warmth of the leg

Diagnosis of DVT.

In addition to using the risk factor assessment and taking clinical observation into account, physicians rely on diagnostic test methods to diagnose DVT. Some options include the Wells clinical prediction rule, D dimer blood test, Doppler Ultrasound and Venography.

Treatment of DVT.

Depending on patient risk factors and the severity of the DVT a patient will most likely go home on oral anticoagulants or low molecular weight heparin (LMWH) for a period of 3-6 months.

During this time patients should be encouraged to ambulate and exercise as well as wearing treatment grade compression stockings if directed by their clinician. If the clot is significant the treating doctor may elect to do a thrombectomy or use catheter directed thrombolysis. Patients should also be educated on the symptoms of PE and what to do if they experience any of these symptoms.

Pulmonary Embolism (PE).

- Unexplained shortness of breath
- Rapid breathing
- Chest pain (may be worse upon deep breath)
- Rapid heart rate

Diagnosis of PE.

In addition to clinical observation, some of the diagnostic options for PE include D-dimer testing, Arterial Blood Gases (ABG), Ventilation Perfusion (V/Q) Scan, Pulmonary angiogram and CT Pulmonary angiogram (CTPA).

Treatment of Pulmonary Embolism.

Large clots or repeated small clots may increase the patient's risk of death, therefore to increase the chances of patient survival and recovery, a physician must diagnose and treat the pulmonary embolism quickly. Treatment of PE typically includes anticoagulant medication such as heparin, LMWH or oral anticoagulants. Depending on the severity of the PE, surgical embolectomy or catheter directed thrombolysis may need to be performed.

Despite heparin prophylaxis, asymptomatic DVT still occurs in 8–10% of general surgical patients and in 15–30% after hip or knee arthroplasty.[25]

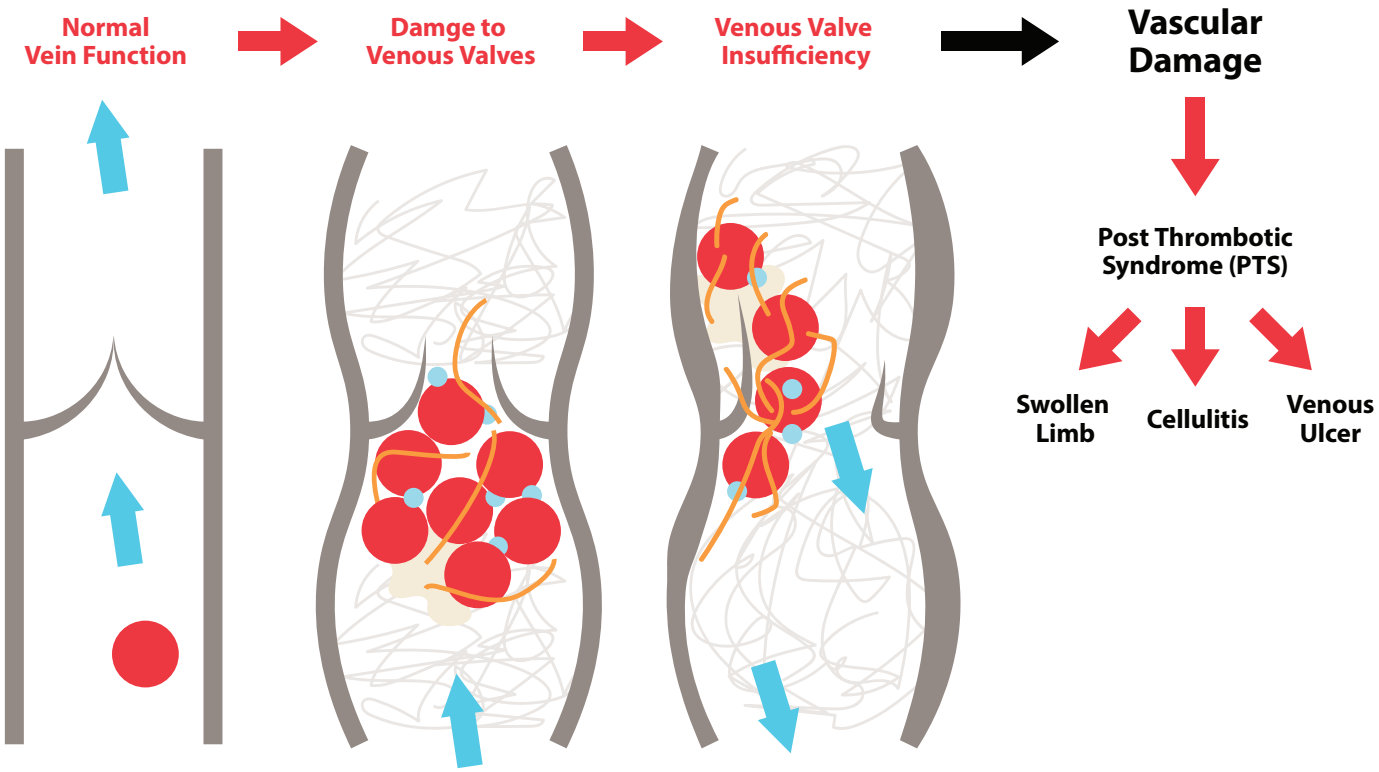
The majority of PE including fatal PE occur in patients with asymptomatic DVT.[26]

In almost 25% of people affected, sudden death is the first clinical sign of PE.[5]

Patient Impact.

The main cost of VTE is the loss of healthy life it entails.

Vascular Damage Related to DVT.



VTE has Short- and Long-Term Impact on Patient Lives.

Pain, erythema and Shortness of breath. Symptoms can last up to 2 months.[27]

Patient distress.

- 58% of patients on anticoagulants had a fear of bleeding.
- 27% reported high levels of general psychological distress.[28,29]

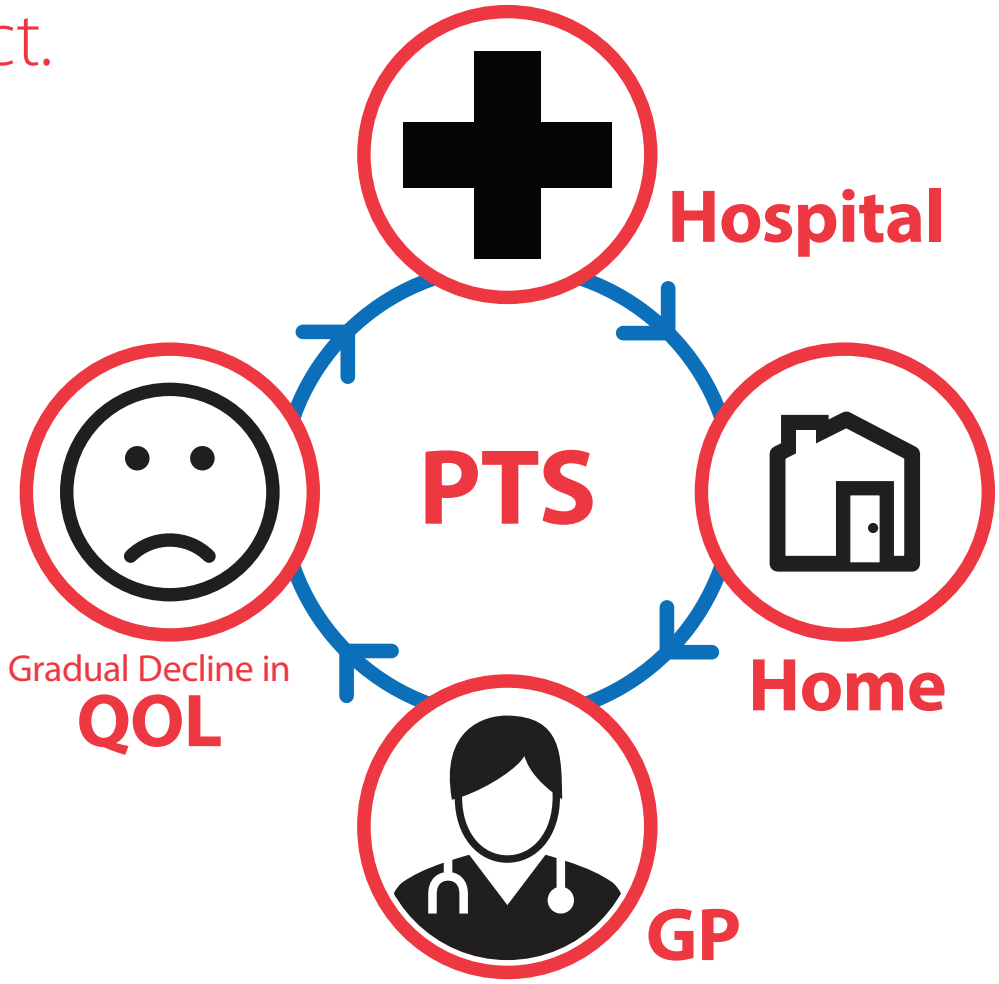
Post-Thrombotic Syndrome.[16]

- Pain aching swelling of the limb.
- Leg tingling, itchy or cramping.
- Leg ulcers
- Almost 50% of patients with VTE can be affected, one third of cases being severe.

30% of patients have recurrence of VTE within 10 years.[16]

Patient Impact.

Reduced Quality of Life.[30]



47% (155 of 334)
of patients surveyed developed Post-Thrombotic Syndrome (PTS) following a DVT diagnosis.

- Self-reported physical QOL in patients with PTS is poor, to a degree that is comparable to that of patients with serious chronic diseases such as diabetes, obstructive lung disease, and congestive heart failure.
- The principal factor that influences long term QOL after DVT is whether or not a patient develops PTS.
- Patients with DVT who do not develop PTS can expect that at 2 years, their QOL will improve to a level similar to that of the general population.
- In a study by Pengo et al, 3.8% of 314 consecutive patients who presented with acute pulmonary emboli developed symptomatic pulmonary hypertension within 2 years.[31]
- Pulmonary hypertension is a progressive disease and symptoms include dyspnea, fatigue, fainting, chest pain, ankle and leg swelling and for many patients can lead to significant heart failure.

VTE Prevention.

Pharmaceutical.

The Body's Natural Mechanisms

Natural Anticoagulants

- Protein C, Protein S.
- Protein Z-Dependent Protease Inhibitor/Protein Z.
- Antithrombin.
- Tissue Factor Pathway Inhibitor.

Slow down the process of blood coagulation.

Natural Platelet Aggregation Inhibitors.

- Nitric Oxide/EDRF, Prostacyclin.

Natural Fibrinolytic Enzyme.

- Plasmin.

Breaks down fibrin within blood clots.

Medications

Anticoagulants.

- Low Molecular Weight Heparin (enoxaparin, dalteparin)
- Low Dose Unfractioned Heparin (heparin sodium)
- Direct Thrombin Inhibitor (dabigatran)
- Factor Xa Inhibitors (rivaroxaban, apixaban, fondaparinux)
- Vitamin K Antagonist (warfarin)

Antiplatelets.

- Aspirin

Fibrinolytic Agents.

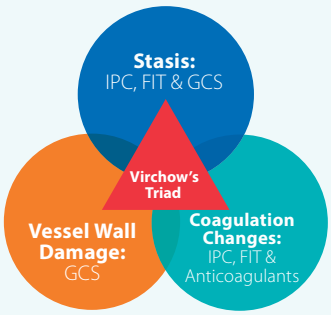
- Alteplase, Tenecteplase, Urokinase

Pharmacological Prophylaxis of VTE.

A. What pharmacological agents are currently used to prevent VTE in Australia and/or New Zealand?

- Low Dose Unfractionated Heparin (LDUH).
- Low Molecular Weight Heparin (LMWH).
  - enoxaparin.
  - dalteparin.
- Fondaparinux.
- Warfarin.
- Rivaroxaban.
- Dabigatran Etexilate.
- Apixaban

Virchow's Triad and Prophylaxis.



B. Are there any contraindications for PHARMACOLOGICAL prophylaxis?

The Australia & New Zealand Working Party on the Management and Prevention of Venous Thromboemolism has recommended that anticoagulants are contraindicated in the presence of:

- Active bleeding or high risk of bleeding e.g. Haemophillia, thrombocytopenia (platelet count <50 x 109/L).
- History of GI bleeding.
- Severe hepatic disease (INR > 1.3).
- Adverse reaction to heparin.
- Patients on current anticoagulation.
- Very high risk of falls and palliative management.
- Renal impairment (see manufacturer's product information for LMWH).

Please refer to manufacturers instructions for use/data sheets for more information.

VTE Prevention.

Pharmaceutical.

The differences between these agents?[32-38]

Examples	heparin sodium/ DBL™	enoxaparin/ Clexane™, dalteparin/ Fragmin™.	fondaparinux/ Arixtra™	rivaroxaban/ Xarelto™	dabigatran etexilate/ Pradaxa™	apixabnan/ Eliquis(R)	Warfarin Coumadin™ Marevan™
Origin	Porcine or bovine origin	Porcine origin	No animal-source components	No animal-source components	No animal-source components	No animal-source components	No animal-source components
Absorption	Binds with plasma, platelet & endothelial proteins Variable dose effect response and decreased bioavailability	Rapidly taken up by endothelial cells with remainder bound to plasma proteins	100% absorbed from subcutaneous injections. Binds with single factor giving a predictable response	Rapidly absorbed via the gut	Stomach and Small Intestine	Throughout GI tract	Complete absorption in the GI tract
Bioavailability	Approximately 15%	> 85%	Approximately 100%	80-100%	65%	50%	Nearly 100%
Plasma half-life	1-2 hrs	4-6 hrs	17 hrs	5-9 hrs 11-13hrs (elderly)	7-9 hrs 12-14hrs (elderly)	12 hrs	5-7 days
Primary Mechanism(s) of action	Larger UFH molecules Bind with antithrombin which in turn inhibits thrombin (factor IIa) and factor Xa Smaller heparin molecules - Inactivate factor Xa	Primary anticoagulant activity is inhibition of factor Xa Inactivates thrombin (factor IIa) to lesser extent than UFH	Binds with antithrombin which inactivates factor Xa, this leads to inhibition of thrombin (factor IIa) and clot formation	Highly selective factor Xa inhibitor with oral bioavailability	Inhibition of thrombin (factor IIa)	Highly selective factor Xa inhibitor	Interferes with vitamin K metabolism in the liver, preventing synthesis of clotting factors II, VII, IX and X as well as protein C and protein S
Therapeutic Effect	Peak action 2-6hrs after subcutaneous injection	Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3-5hrs after post dose	Immediate onset of action; Peak plasma concentration 3hrs post dose	Within 30 min. Maximum inhibition of factor Xa in 2-4hrs	Within 30mins. Maximum inhibition of thrombin 0.5-2hrs post dose	3-4 hours	36 to 72hrs
Antidote/ Reversal Agents	Protamine Sulfate	Up to 60% with Protamine Sulfate	Recombinant activated factor VIIa may have some reversal effect	None	Praxbind® (idarucizumab) Rapid, specific reversal agent	None	Vitamin K or fresh frozen plasma. Prothrombin complex concentrate
Monitoring May monitor	No routine monitoring usually required	No routine monitoring	No routine monitoring	No routine monitoring	No routine monitoring	No routine monitoring	Prothrombin time (goal to maintain International Normalised Ratio (INR) between 2- 2.5
FBC platelet counts, stool occult blood tests and for symptoms of bleeding.	aPTT (indirect measurement) if necessary anti-Xa assays	May monitor anti-Factor Xa concentration in patients with renal dysfunction		May use prothrombin time or chromogenic anti-factor Xa assay	May use ecarin clotting time or aPTT (less sensitive) if required		
Metabolism Elimination	Metabolised mainly in the liver Renal clearance	Metabolised by liver Renal excretion	Majority of dose is eliminated unchanged in urine with normal renal function	2/3 metabolised in liver 1/3 eliminated unchanged	20% excreted via biliary system, 80% excreted by kidneys unchanged	Multiple routes	Metabolised by liver Renal excretion

VTE Prevention.

Mechanical.

A. What mechanical options are used to reduce the incidence of VTE?

Graduated Compression Stockings (GCS).

GCS are anti-embolism devices that improve venous circulation and prevent venous distension in leg veins by applying graduated compression.

Intermittent Pneumatic Compression (IPC).

IPC are air driven devices which deliver uniform or gradient compression to the leg to facilitate emptying of veins and reduce venous stasis.

Foot Impulse Technology (FIT).

FIT mimics the natural physiological process that occurs when walking. A rapidly inflating bladder is positioned under the plantar venous plexus located in the sole of the foot. Upon compression the plexus rapidly expels a turbulent bolus of blood into the deep veins of the legs.

FIT has three indications for use;

- reduce the risk of DVT
- reduce chronic and acute edema in the lower limbs and
- enhance peripheral arterial blood flow.

Inferior Vena Cava Filters.

Inferior vena cava filters are sometimes used to mechanically reduce the risk of PE in very high risk patients with recurrent VTE who are contraindicated for anti-coagulation. These are placed endovascularly in the inferior vena cava.

B. Are there any contraindications for use of mechanical prophylaxis?

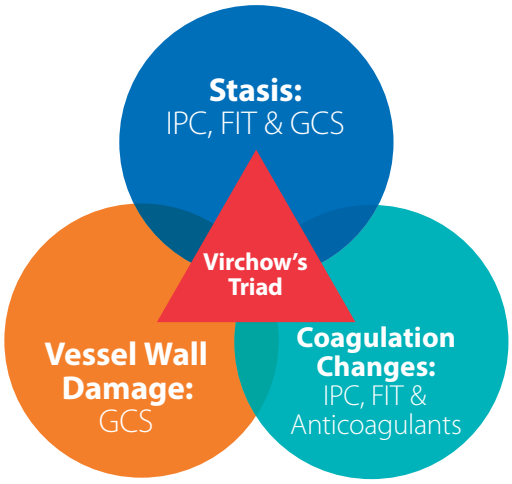
- GCS and IPC should be avoided if there are localised skin conditions, such as gangrene, immediate post-operative vein ligation, recent skin grafts, or leg deformity.
- GCS and IPC should be avoided if patient suffers severe arteriosclerosis or other ischemic vascular disease.
- IPC and FIT should not be used if a patient has a known or suspected acute DVT or PE; for these patients GCS are appropriate.
- No mechanical prophylaxis should be used in patients with massive oedema or pulmonary oedema caused by congestive heart failure.

C. What is the reason for using combined modalities of prophylaxis?

Combined modalities are more effective in reducing the incidence of VTE than single modalities[17]. Combined use of GCS with either IPC or FIT address all three factors in Virchow's Triad.

Using GCS as part of a patient's prophylactic regimen allows continual baseline prophylaxis when compression devices are interrupted, anticoagulants are withheld or patients are discharged from a facility.

Virchow's Triad and Prophylaxis.



Graduated Compression Stockings (GCS).

Mechanism of Action.

GCS provide graduated pressure pattern to the legs, delivering 18mmHg at the ankle which decreases to 8mmHg at the upper thigh (thigh length GCS), or decreases from 18mmHg at the ankle to 14mmHg at the popliteal vein (knee length GCS). This gradient pressure helps to increase blood flow back to the heart.

Research has shown that when GCS are used on moderate risk surgical patients they reduce the risk of a DVT by 68%.[39]

T.E.D.™ Anti-Embolism Stocking is a trademarked brand of graduated compression stocking and is the only GCS proven to reduce venous distension which can lead to vessel wall damage and can occur as a result of surgery and hospitalisation.[40]

Mechanism of Action
Stasis
Prevents distal trapping and ensures clearance behind valve cusps/soleal sinuses
Increases blood flow velocity
Reduces venous stasis
Maximises blood flow
Vessel Wall Damage
Reduces venous distension
Prevents vessel wall damage by reducing risk of micro-tears from venous dilatation following smooth muscle relaxants e.g. General anaesthesia

The T.E.D.™ Addresses Two Components of Virchow's Triad

T.E.D.™ increases femoral vein blood flow velocity by 138% over baseline.[41]

T.E.D.™ reduces venous distention by 48%.[40]

Fitting should always follow the manufacturer's instructions. To ensure correct fit, correct measurement is essential.

Intermittent Pneumatic Compression (IPC).

Mechanism of Action.

Intermittent Pneumatic Compression (IPC) refers to compressing a patient's leg intermittently by using a controller (pump) to pneumatically inflate a garment wrapped around the patient's limbs. The SCD™ is an IPC device that uses sequential, gradient circumferential compression.

1. Sequential.

The leg sleeve is sequential in that there are three separate chambers of inflation that squeeze the leg in a 'milking action' The most distal area (lower calf) inflates/compresses first, and the subsequent chambers follow moving up the leg in the same manner.

2. Gradient.

The SCD™ leg sleeve is gradient in that each of the three chambers inflates at a different compression pattern. The distal at 45mmHg, middle at 40mmHg and proximal at 30mmHg.

3. Circumferential.

The SCD™ leg sleeve is circumferential in that it compresses the entire circumference of the leg—front, back and sides.

Vascular Refill Detection (VRD).

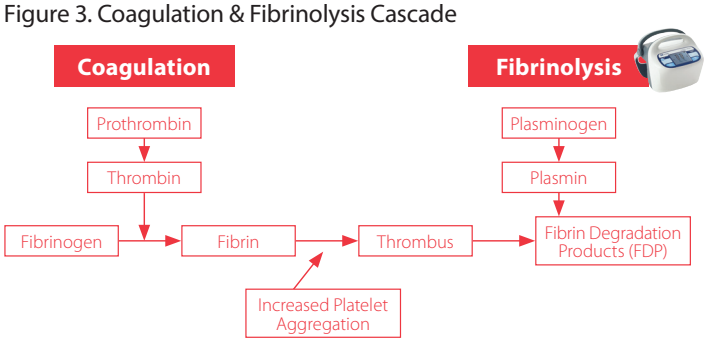
Vascular Refill Detection (VRD) is a proprietary non-invasive method of measuring venous refill time—the time it takes for a vein in a patient's leg or foot to refill with blood after being compressed. Without VRD, compressions take place on a fixed 60 second cycle time. The SCD with VRD moves more blood over time compared with other IPCs. VRD Technology has been proven to move 76% more blood over time compared with IPC devices without VRD.[42]

The Kendall SCD™ system is clinically proven to reduce the risk of both DVT and PE, and to improve survival in stroke patients.[43]

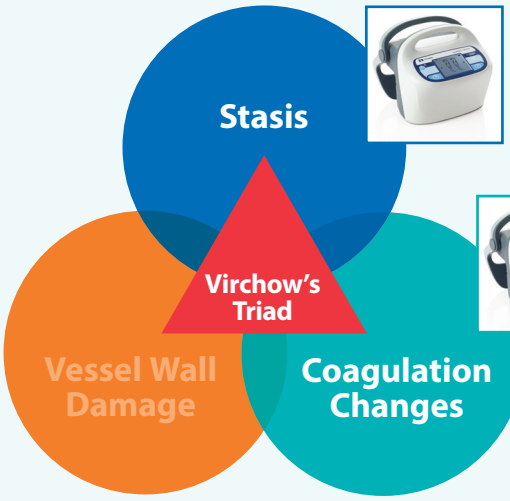
Mechanism of Action
Stasis
Prevents distal trapping and ensures clearance behind valve cusps/ soleal sinuses
Increases blood flow velocity
Reduces venous stasis
Maximises blood flow
Coagulation Changes
Increases fibrinolytic activity

Figures 3. identifies the stages where the SCD's™ mechanism of action plays a role in the coagulation cascade.

Figure 3. Coagulation & Fibrinolysis Cascade



The SCD™ Addresses Two Components of Virchow's Triad



SCD™ increases femoral vein velocity by 240% over baseline[44]

Stimulates endogenous fibrinolytic activity[45]

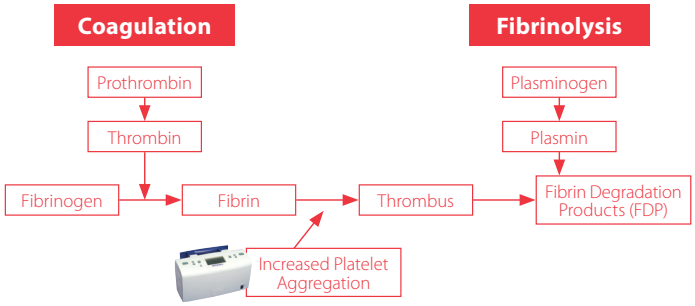
Foot Impulse Technology (FIT).

Mechanism of Action.

The A-V Impulse™ foot compression system is a DVT prophylaxis technology that mimics the natural haemodynamic process of the foot's ambulatory weight-bearing heel-to-toe strike (walking). When walking, upon every step, the plantar venous plexus (arch of the foot) is flattened, causing an immediate evacuation of blood from the plexus of veins in the bottom of the foot. This action sends a column of blood up the leg and back to the heart.

Numerous peer-reviewed clinical studies have documented the A-V Impulse™ foot compression system's efficacy in helping to prevent VTE as well as post-operative swelling and pain.

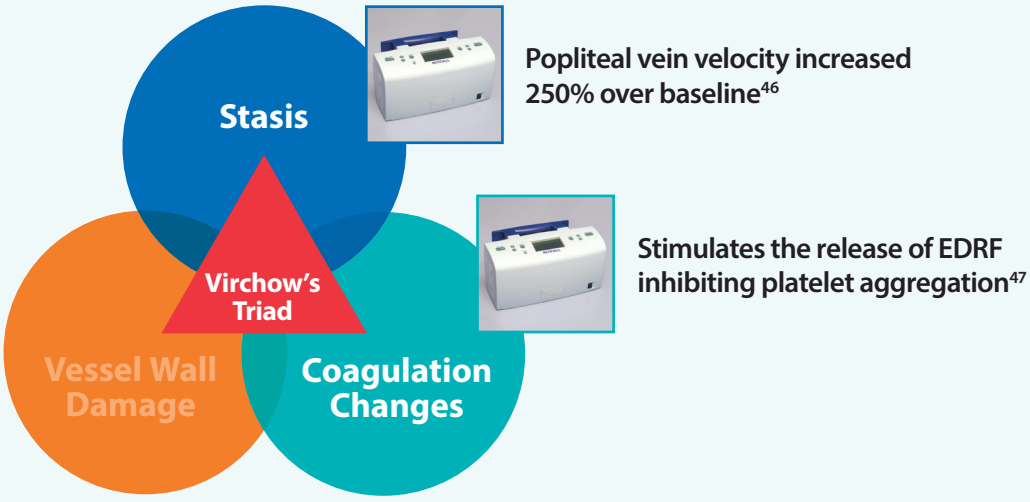
Figure 4. Coagulation & Fibrinolysis Cascade



Mechanism of Action
Stasis
Prevents distal trapping and ensures clearance behind valve cusps/ soleal sinuses
Increases blood flow velocity
Reduces venous stasis
Maximises blood flow
Coagulation Changes
Stimulates release of Endothelial Derived Relaxing Factor (EDRF) which inhibits platelet aggregation

Figures 4. identifies the stages where the A-V Impulse's™ mechanism of action plays a role in the coagulation cascade.

The A-V Impulse™ Addresses Two Components of Virchow's Triad



Popliteal vein velocity increased 250% over baseline[46]

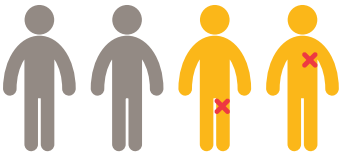
Stimulates the release of EDRF inhibiting platelet aggregation[47]

Summary.

VTE is the Most Preventable Cause of Death in Hospitalised Patients.

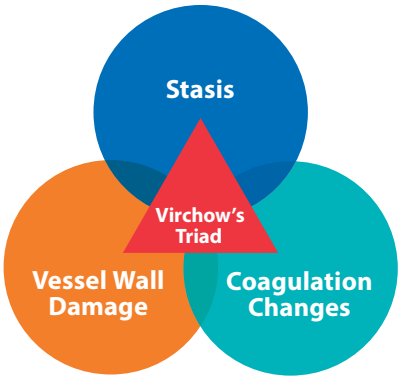
All admitted patients should have a VTE risk assessment as part of their hospital admission, and they should receive optimal VTE prophylaxis according to their level of risk, and existing contraindications to prophylaxis.

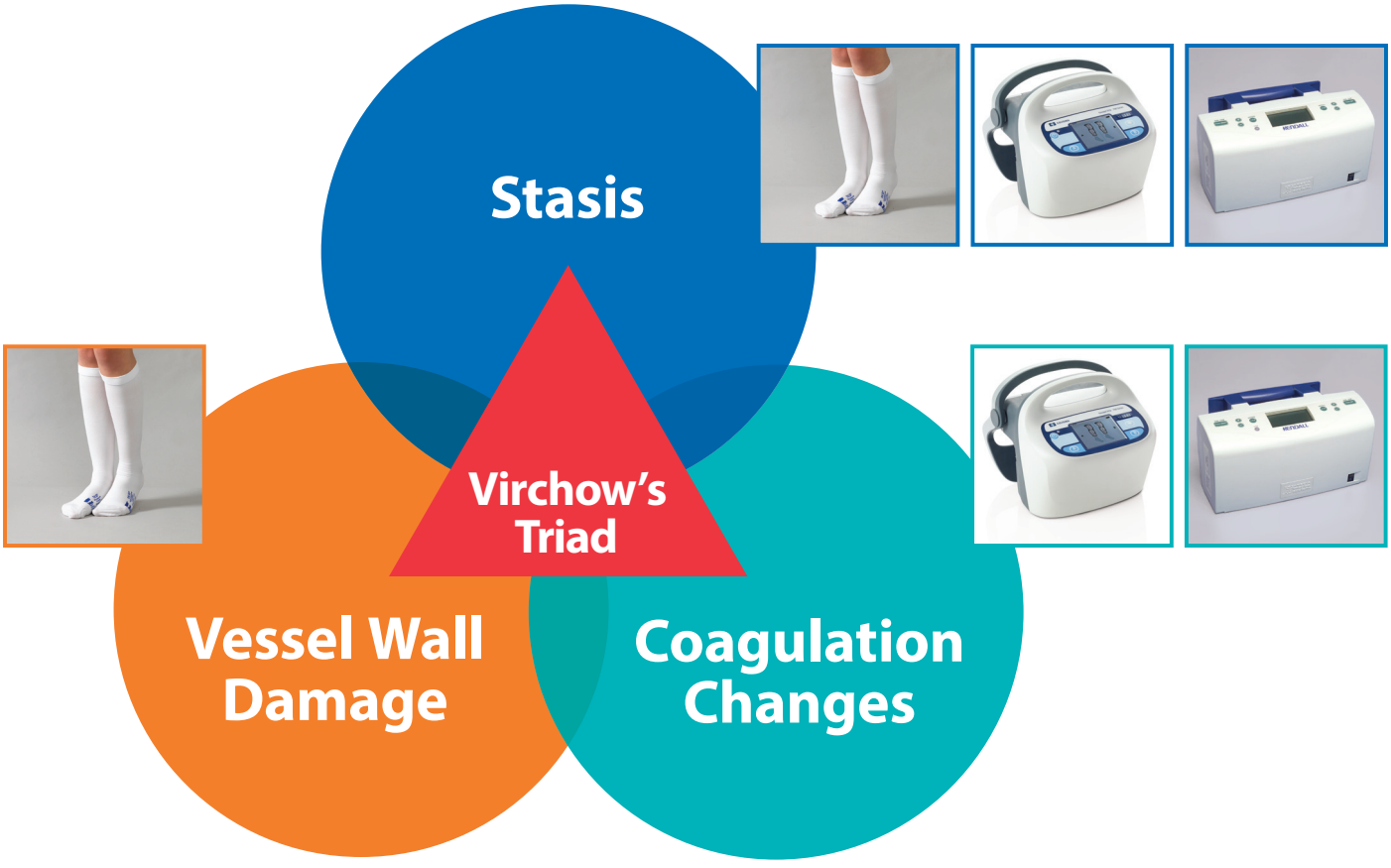
The choice of thromboprophylaxis should aim to address the 3 causal factors of VTE in Virchow's Triad. The long term complications of VTE can have significant effects on patients quality of life. Prevention is key.



50%

of DVTs are **sympomatic**





VTE Quiz

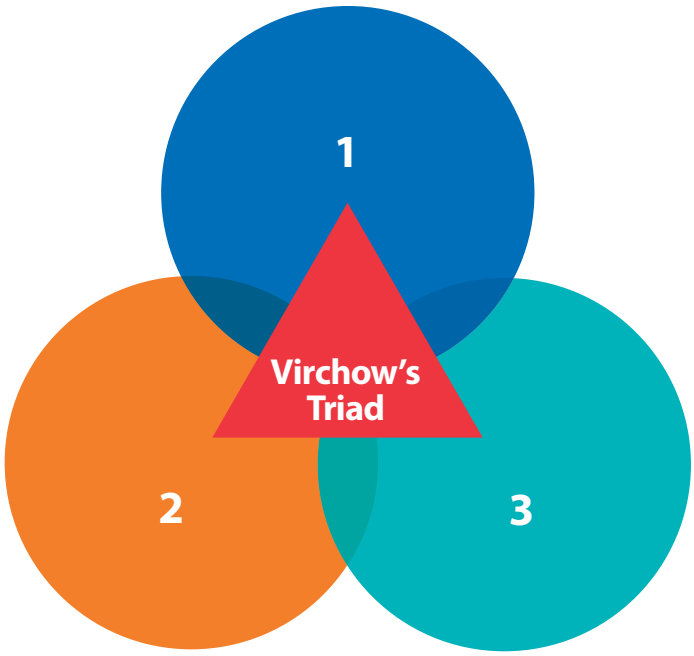
True or False: **Mark your answer with an X**	**True**	**False**
1. DVT and PE can always be easily diagnosed by observing clinical signs and symptoms.		
2. Calf clots are clinically insignificant because they do not embolise (break loose and travel) and do not cause any long term problems.		
3. Fatal PE is the most common, preventable cause of hospital deaths.		
4. Long-term effects from DVT include post-phlebitic (thrombotic) syndrome and recurrent DVT.		
5. Most hospitalised patients have multiple risk factors for VTE.		
6. Coagulation abnormalities may result from malignancy, surgical intervention/procedures and dehydration.		
7. VTE risk assessment should start at admission and repeated throughout their length of stay.		
8. Medical patients are at lower risk for developing DVT and PE.		
9. Obesity, immobility and central venous catheters increase a patient's risk of developing DVT and PE.		

10. Please list the three VTE Causal Factors known as Virchow's Triad:

1:

2:

3:



Further Information

VTE Guidelines.

ANZ. Australia and New Zealand Working Party Guidelines:

- Prevention of VTE

NHMRC. National Health and Medical Research Council:

- Clinical Practice Guidelines for the prevention of venous thromboembolism in patients admitted to Australian hospitals.

ACCP. American College of Chest Physicians:

- Prevention of venous thromboembolism.

ICS. International Consensus Statement:

- Prevention and treatment of venous thromboembolism: Guidelines according to scientific evidence.

NICE. National Institute of Clinical Excellence:

- Venous thromboembolism – Reducing the risk (CG92)

Arthroplasty Society of Australia:

- VTE guidelines for hip and knee arthroplasty

National VTE initiatives.

WHO. World Health Organisation:

- Surgical safety checklist for Australia and New Zealand.

Australian Commission on Safety and Quality in Health Care:

- National in patient medication chart (NIMC) with dedicated VTE prophylaxis prescribing box.
- Patient information
- HACs (Hospital Acquired Complications)

NHMRC. National Health and Medical Research Council:

- National inpatient medication chart with dedicated VTE prophylaxis section.
- "Blood Clots Reducing Your Risk" patient information brochure.
- Clinical Practice Guidlines for the Prevention of Venous Thromboembolism and guidlines summary for clinicians.

Educational web sites.

www.preventdvt.org/

www.thrombosisjournal.com/

www.kingsthrombosiscentre.org.uk

https://clotconnect.wpcomstaging.com/

www.stoptheclot.org/

www.worldthrombosisday.org/

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35. Rivaroxaban Product Information
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