An E-Learning Approach to the Prevention of Venous Thromboembolism: An Educational and Human Factors Study

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A thesis submitted in fulfillment of the requirements for the Degree of Doctor of Philosophy

On

12th July 2019

THE UNIVERSITY of ADELAIDE

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

_____ 12th July 2019

Dr Eamon Patrick Raith MBBS, MACCP

Acknowledgements

It is important to acknowledge the financial support provided in early career research, and I wish to thank the Covidien VTE Management and Prevention Scholarship Program for their support of this project. Although since acquired by Medtronic, and now no longer a separate entity, the support of this scholarship was invaluable in allowing me to perform the research that has culminated in this thesis.

Completing a Doctorate is no small task, particularly when also completing a clinical specialty training program, and would be impossible without the support of supervisors, other academics, colleagues, friends and family.

First, I would like to thank Associate Professor Peter Devitt for his unwavering support, encouragement, mentorship, kindness and friendship since I was a third-year medical student. Associate Professor Devitt's surgical excellence, clinical acumen, and dedication to research have been a continued inspiration. He encouraged me to ask questions and investigate them, to develop a sense of the importance of medical research, and to understand the *absolute requirement* that research begins and ends at the bedside. Above all, I thank Prof for passing on a love of teaching. Professor Devitt embodies the finest examples of Oslerian medicine in his lectures to pre-clinical students, his bedside teaching and on Grand Rounds. His development of the eMedici website brought examples of patients and clinical medicine to students across multiple universities, allowing all of us to "go to sea" in

charted waters. I will continue to value his friendship, wisdom and guidance long after the completion of this research.

Associate Professor Michael Wan has provided singular support and expertise in the conduct of our research together, and in the preparation of the publications arising from this work. I am indebted to him for taking on a PhD student living and working in a different State, and for his encouragement and expertise in the development of educational studies. Without his insight and input, this work would not have approached the standard it has.

I would like to thank Ms. Suzanne Edwards, who has provided invaluable statistical support during the development of this project and the writing of this thesis. She provided much helpful advice and encouragement in formulating the statistical plan for this work.

Completing a PhD part-time while also completing a clinical specialty-training program is, perhaps, a non-standard approach to an academic medical career in Australia. As a result, however, I have been fortunate to work with a number of clinical academics that have provided me with encouragement, inspiration and opportunities to grow as both a trainee-Intensivist and an academic. Professor David Pilcher and Professor Andrew Udy both deserve my thanks for taking an interested, yet junior, registrar and researcher and giving me the opportunity to develop new

research questions beyond my thesis, and for teaching me how to lead research projects and present them in national and international forums. I am grateful for their continued mentorship and support. Similarly, Professor Marianne Chapman and Dr. Ben Reddi have provided wonderful encouragement and professional development since I returned to Adelaide in 2017, and have shown me the possibilities that lie ahead in a career as a clinical academic. I value our frequent and thought-provoking discussions greatly, and continue to leave each one with a renewed sense of purpose, enthusiasm and optimism.

Shakespeare wrote, "Words are easy, like the wind; Faithful friends are hard to find." I am fortunate to have a faithful friend in Dr. Matthew O'Connor. Firm in friendship, kind in words, and giving of soul and time, one could not ask for a better, closer friend than Matthew. He has been a sound companion through the greatest highs and the deepest, darkest, lows. I owe him a debt of friendship that can never be repaid, and am constantly grateful for his wisdom, insight and compassion.

I would be remiss if I did not acknowledge the support of my family. I thank my parents, Ann and Duncan Raith for encouraging a love of reading and learning from a young age, and for teaching me to strive for any goal I chose to set my mind to. I also thank my grandparents, Patricia and Seamus Mulvihill, for their unwavering support, encouragement and love. From them I learned much about kindness, compassion and duty; lessons that I take with me into my practice each day.

Finally, I must thank my extraordinary wife, Dr. Claire Frauenfelder. She is a Surgeon of exceptional skill, a physician of unparalleled competence, and a Doctor of inimitable dedication to her patients and her craft. She embodies both the science and art of medicine. Beyond this, Claire is a superb listener, a generous and wonderful friend, and the person to whom I turn in my darkest hours and at the peak of my greatest achievements. Without Claire, her guidance, and her constant, unwavering love, this research and this thesis would not have been possible.

To my darling wife, I say, without reservation or hesitation, thank you.

Hahndorf,
South Australia
June 2019

Publications And Presentations Arising From This Thesis

Publication Submissions

Online Learning In Venous thromboembolism Education: A Randomised Controlled Trial

Factors Associated With Test Performance In Venous Thromboembolism E-Learning: A Subgroup Analysis of the OLIVE Trial.

Computers in Medical Education: Evaluation of Instructional Ergonomics in the Online Learning in Venous thromboembolism Education Study

Presentations

Online Learning In Venous thromboembolism Education: The OLIVE Trial.

Royal Australasian College of Surgeons 86th Annual Scientific Congress, Adelaide, May 2017

Online Learning In Venous thromboembolism Education: The OLIVE Trial.

Australian and New Zealand Intensive Care Society 10th Annual Tub Worthley Traveling Scholarship Presentations, Adelaide, May 2017

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Thesis Summary

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The research contained within this thesis submitted for the degree of Doctor of Philosophy in Medicine investigates the role of e-learning in improving knowledge mastery around venous thromboemolism prophylaxis among medical students. Following an exhaustive literature review of venous thromboembolism epidemiology, pathology and prevention, educational theory, e-learning techniques and the delivery of education about venous thromoboembolism to medical students, the key deficiencies in our understanding of this disease were identified. We found multiple small cohort studies about the use of e-learning in medical education, but a paucity of randomised controlled trial data surrounding the use of e-learning platforms, and limited information regarding the role of instructional erongomics in e-learning delivery for medical education.

Conducting a randomised controlled educational trial may determine the utility of e-learning for improving student's knowledge of venous thromboembolism prophylaxis.

This investigation commenced with the development of e-learning modules in surgery, medicine, oncology, obstetrics & gynaecology and orthopaedic surgery. Two further assessment modules were also developed; one to measure baseline knowledge about venous thromboembolism prophylaxis, and one to measure post-intervention effect.

A randomised controlled trial was conducted to measure the effect of e-learning at improving knowledge of thromboprophyaxis guidelines. Students randomised to use

the e-learning module did not demonstrate any improvement in knowledge surrounding VTE prophylaxis, either in comparison to the control group, or in comparison to their own baseline scores. Interestingly, however, students demonstrated a statistically significant improvement in knowledge when they were re-tested six months after finishing the e-learning program.

This result may demonstrate that e-learning is a useful tool in a blended learning model of teaching, however, there is a possibility that confounding factors had played a role. We conducted a subgroup analysis to determine whether performance in certain cases within the e-learning module were predictive of final outcome, and whether time spent on each case was associated with final performance. We demonstrated that performance in the eMedici VTE Prophylaxis Module appeared to be associated with performance in areas of medicine in which students had prior experience, or were currently rotating.

Finally, we were interested in examining ergononic factors related to the use of e-learning material, particularly as one member of the group had published similar research examining the use of computer-aided learning when material was presented on CD-ROM. There is limited reporting on ergonomic data in the medical education literature, and we felt that this study may also help explore the possible causes of the results of the randomised controlled trial. This study demonstrated the importance of usability testing in designing online medical education resources, and suggests the importance of supporting online learning through the provision of physical learning spaces and infrastructure within the clinical setting.

Section 1. Review Of The Literature

Chapter 1. Epidemiology of Venous Thromboembolic Disease

Venous thromboembolism (VTE) is a syndrome composed of deep vein thrombosis (DVT) and, to a lesser extent, Pulmonary Embolism (PE); the terms "thrombosis" and "embolism" were coined by Rudolf Virchow[1] in order to demonstrate a mechanistic link between DVT and PE.[2,3]

Global Impact of Venous Thromboembolism

Venous thromboembolism is the third most common cardiovascular cause of death in the world, resulting in more than 500,000 deaths per year in both the European Union and the United States of America.[2,4] The annual incidence of VTE ranges from 0.75 to 2.69 per 1000 population, and is a common condition across low-, middle- and high-income countries.[4] Importantly, increasing age is strongly associated with increasing incidence of VTE; annual incidence ranges from 0.2 to 5.3 per 1000 population between the ages of 40-69, increasing to 2 to 7 per 1000 population among those aged ≥70 years, and 3 to 12 per 1000 population among those aged ≥80 years.[4]

The burden of disease generated by VTE is also globally significant, responsible for 7,681 Disability-Adjusted Life Years (DALY) based on World Health Organisation-commissioned epidemiological studies, and an extensive literature review; VTE was the leading cause of DALYs in low- and middle-income countries, and the second-leading cause in high-income countries.[4,5] Non-fatal consequences of VTE, and resulting disability, were responsible for 34% of DALYs associated with VTE,

resulting in significant years lived with disability (YLD) and years of life lost (YLL) due to premature mortality.[4]

Re-analysis of the Framingham Heart Study

A retrospective analysis of the original, offspring, third generation and omni cohorts of the Framingham Heart Study (n=9,754) for the period 1995-2014 has provided further information on the incidence, associated mortality and predisposing factors for VTE.[6] The overall unadjusted incident rate of VTE was 26.8 per 10,000 person-years (PYs), with unadjusted incident rates of 7.8 per 10,000 PYs for unprovoked VTE, 10.8 per 10,000 PYs for provoked VTE (one predisposing factors other than cancer – surgery, fracture, hospitalization, immobilization, Hormone Replacement Therapy/Oral Contraceptive use, travel >4 hours or pregnancy/puerperium), and 8.3 per 10,000 PYs for cancer-related VTE. The overall age-adjusted incident rate was 20.3 per 10,000 PYs, and was higher in men (23.5 per 10,000 PYs) than women (17.5 per 10,000 PYs).[6]

Analysis of the Framingham Heart Study dataset demonstrated that the median number of predisposing factors for provoked VTE was 2 (range 1-4), and 1 (range 0-4) in cancer-associated VTE.[6]

Crude all-cause mortality in patients with any VTE was 145 per 1000 PYs, compared with a mortality rate of 20 per 1000 PYs for patients without VTE. The hazard ratio was four-fold higher in patients with VTE compared to those without (HR=4.02; 95% CI 3.40-4.74), and was higher in patients with pulmonary embolism vs. deep vein thrombosis (HR=2.55; 95% CI 2.08-3.13 vs. HR=1.45; 95% CI 1.11-1.89; $p<0.05$). There was no significant difference in hazard ratios between unprovoked and

provoked VTE (HR=2.38; 95% CI 1.62-3.49 vs. 2.37; 95% CI 1.78-3.16). Cancer-associated VTE had a very high hazard ratio for mortality (HR=16.43; 95% CI 12.88-20.94). There was no significant difference between hazard ratios for mortality between genders (p=0.40).[6]

All-cause mortality amongst patients with VTE was 11.8% at thirty days, 29.6% at 1 year and 43.1% at 5 years.[6]

Venous Thromboembolism in Australia

Numerous studies into the epidemiology of venous thromboembolic disease have been performed in Australia.[7-9] A community-based study in 2008 demonstrated an annual VTE event rate of 0.85 per 1,000 residents in metropolitan Perth, Western Australia, with a crude annual incidence of 0.83 per 1,000 residents.[7] The crude annual incidence for DVT was 0.52 per 1,000 residents, and 0.31 per 1,000 residents for PE.[7] 74.5% (102 cases) were for first-ever thrombotic event, with a VTE incidence of 0.62 per 1,000 population.

A 2018 paper reviewed this incidence by combining inpatient data with Emergency Department (ED) presentations across New South Wales to provide a more accurate estimate of VTE incidence, and factors associated with increased post-discharge diagnosis of VTE.[8]

This study, by Stubbs et al, reported an incidence rate of 9.7 per 1,000 admissions, with a median length of stay of 8 days. DVT was the more common presentation (62.6%) than PE. Most hospital-acquired VTEs were diagnosed post-discharge

(70.6%); in-hospital diagnoses had a longer median length of stay (18 days) than VTE diagnosed post-discharge (6 days). The median length of time between discharge from original admission and a diagnosis of VTE requiring admission was 17 days.[8]

Stubbs et al demonstrated a 9% lower risk of VTE in men than in women (Incident rate ratio = 0.91), and an increasing risk of VTE for both genders with increasing age. Factors protective against VTE were identified as Asian-born parentage, non-emergency admission to hospital, and admission for medical or obstetric complaints. Risk associated with surgical admission was determined by using VTE risk for patients undergoing cholecystectomy as a baseline for comparison, with orthopaedic surgical patients experiencing a 1.79 to 3.6-fold increase in risk of hospital-acquired VTE. Increased rates of co-morbidity (as measured by the Charlson Comorbidity Index) and longer in-hospital length of stay were both associated with increased risk of hospital-acquired VTE. The authors reported a case fatality rate of 4.3%, with the majority of deaths (53.3%) caused by pulmonary embolism, and occurring during the index admission (57.7%).[8]

There has been a trend towards increasing rates of venous thromboembolism since 2010, with the incidence rate of hospital-acquired VTE increasing from 9.2 per 1,000 patients in 2010, to 10.2 per 1,000 population in 2012; adjusted rates for in-hospital VTE also increased by 44% during the study period, while conversely, the adjusted incidence rate of post-discharge VTE declined by 9% to 6.1 per 1,000 population.[8] Factors associated with increased risk of post-discharge VTE were increasing age, being a medical patient, undergoing coronary artery bypass grafting, undergoing total knee replacement[10] and total hip replacement surgery[8,10] having a diagnosis of cancer

or chronic pulmonary disease or admission to smaller hospitals including district general hospitals or rural and regional hospitals.[8]

Chapter 2. Pathophysiology of Venous Thromboembolism

In a recent review of the pathogenesis of venous thrombosis, Budnik and Brill describe the development of venous thrombi as a three stage process; blood flow stasis and hypoxia, endothelial activation, and blood cell recruitment.[11] In this section we consider first the anatomical considerations in the pathogenesis of venous thrombosis, and then the pathogenesis of deep vein thrombosis in the manner described by Budnik and Brill.[11,12]

Anatomical Considerations in the Pathogenesis of Venous Thrombosis

The deep veins of the lower limbs are divided into two systems; the thigh veins and the calf veins, with the calf veins representing the greatest source of embolic venous thrombi.[12]

While the thigh veins (iliac vein and femoral vein) are thick-walled and carry few venous valves, the calf veins (crural veins – posterior tibial vein, anterior tibial vein, peroneal vein – and intramuscular veins – soleal vein and gastrocnemius vein) are paired to arteries and have multiple branches and inter-venous anastomoses. The calf veins also contain multiple venous valves to allow unidirectional blood flow (Figure 2.1[13]).

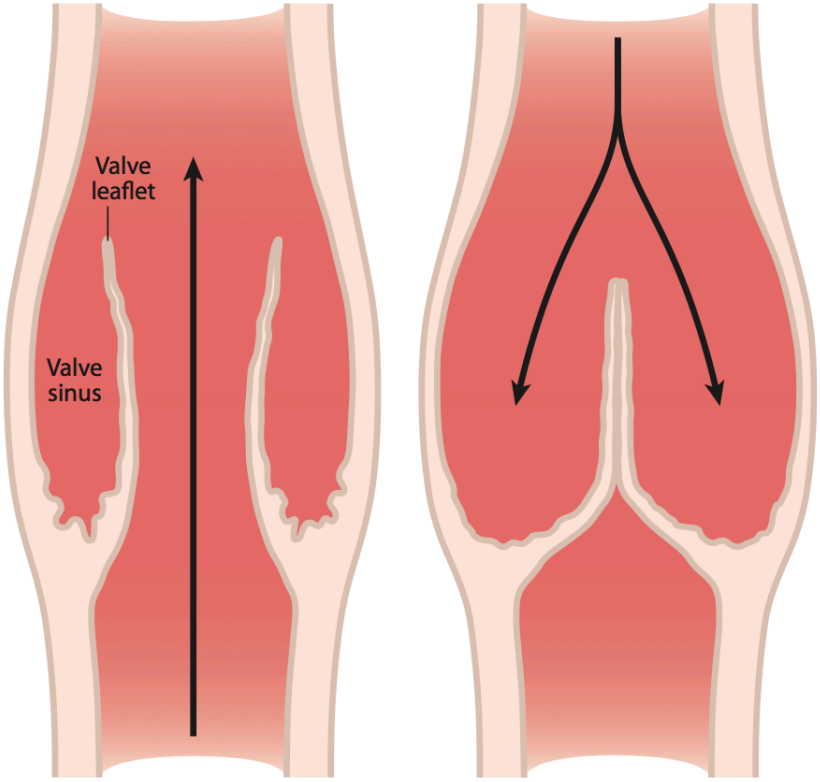

Figure 2.1 Normal function of venous valves.

In the image on the left, the valve is open and blood flows towards toward the right heart through a combination of transmitted pulsatility from adjacent arteries and muscular contraction. In the image on the right, valve closure maintains unidirectional blood flow. (From Bovill et al[13])

Consequently, thrombosis is more likely to occur in intramuscular veins that require active pumping and adequate valve function when there is limited calf movement (e.g. bed rest, prolonged air travel). Within the intramuscular veins, thrombosis is more likely to occur in the soleal veins rather than the gastrocnemius veins due to the lower frequency of venous valves (which tend to be incomplete), the location of venous valves at the gathering sites of thin veins, the presence of multiple anastamoses, and the need for sustained muscular contraction for adequate venous drainage, in the soleal vein system.[12]

Haemostasis and Reduced Venous Oxygen Tension

In keeping with Virchow's triad for coagulation (blood stasis, endothelial injury and hypercoagulability),[1] venous stasis appears to be a significant factor in thrombogenesis. Of particular importance is the role of venous valves and valve pockets in providing a site of static blood flow, venous hypoxia, and relative endothelial injury.[2,11,13]

Venous valves and venous thrombogenesis

Aside from reduced blood flow as a result of reduced muscular contraction,[12] the presence of venous valves appears to play a significant role in the development of venous thrombi.[2,11,13]

Multiple venographic and post-mortem studies have demonstrated that valve pockets frequently demonstrate venous stasis and contain thrombi.[2,13-18] Histological examination of venous valves (Figure 2.2) demonstrates that thrombi appear to develop in areas of increased stasis and hypoxia, on the wall side of the vein sinus.[13,19] The thrombus develops in a progressive fashion, with increasing deposition of fibrin layers containing entrapped red cells.[19] These alternate with white layers, containing platelets, forming the lines of Zahn.[13,19] The presence of fibrin-rich red thrombus adjacent to the endothelial surface of venous thrombi suggests that tissue factor plays an important role in thrombus formation.[13]

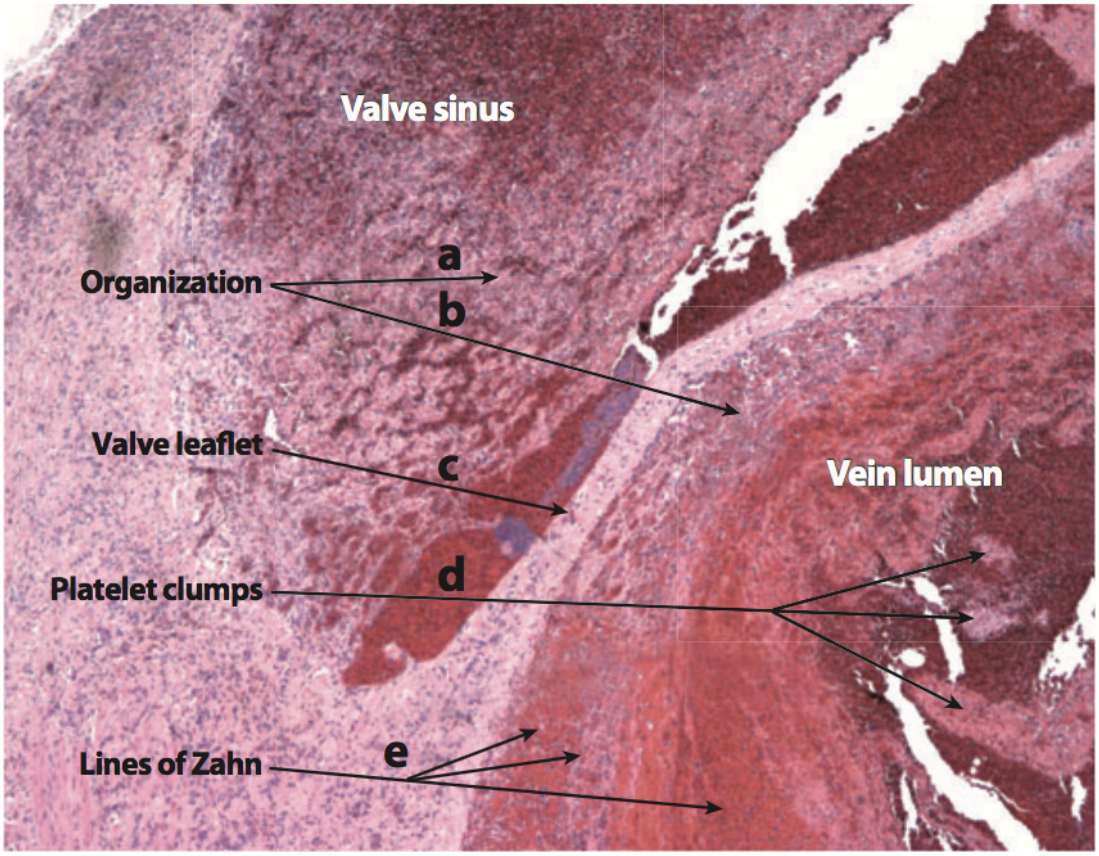

Figure 2.2 Histological section of a venous valve demonstrating valve thrombus involving both the valve sinus and the vessel lumen.

Arrow (a) demonstrates valve thrombus that is considerably more organized than thrombus present in the vein lumen (b), indicating that it is therefore older. This is consistent with findings described by Sevitt.[19] (d) demonstrates large platelet clumps distant from the vessel wall, a characteristic of venous thrombi. (e) indicates the lines of Zahn, alternating red cell and platelet clumps, indicating thrombus propagation. (Slide from the University of Alabama, Birmingham, Department of Pathology, PEIR collection, which is publicly available; Image reproduced from Bovill et al.[13])

Although stasis appears to be a key factor in venous thrombosis, valve sinus hypoxia has been documented in the same anatomical location as thrombus initiation.[13,20] In the only study of its kind, Hamer et al. demonstrated that the partial pressure of oxygen (PaO_2) decreased from approximately 5kPa to 0.1kPa (37.5mmHg to 0.75mmHg) at four successively deeper levels, from top to bottom, of the valvular sinuses in the veins of dogs, after 2 hours of venous stasis.[20] Hamer et al. also noted that the venous flow pattern in resting dog legs was streamlined, as compared to pulsatile when passive movement was performed.[20] An extension of the study in dogs was performed in three veins of two human patients undergoing elective

surgical procedures for removal of varicose veins; in this instance, measurement of valvular sinus PaO_2 again demonstrated decreasing oxygen tension, from approximately 7kPa (52.5mmHg) at the mid-vein level, to 4.3kPa (32.25mmHg) at the bottom of the valve pocket.[20]

The description of streamlined flow at muscular rest has implications for blood flow within the valve sinus.[13] As demonstrated in Figure 2.3, streamlined flow is demonstrated in valve sinuses during streamlined venous flow;[13,21,22] as blood flows out of the valve leaflet, a slower, counterrotating vortex is formed at the base of the sinus, which correlates with the location of sinus hypoxia. Red blood cells tend to remain trapped in this vortex, and begin clumping;[21,22] this combination of erythrocyte aggregation and local hypoxia then induces inflammation, endothelial cell activation, and activation of other pro-inflammatory cell types, including mast cells.[11,13] These events result in the cellular adhesion receptors (intercellular adhesion molecule 1) and the release of Weibel-Palade bodies, stimulating the initiation of coagulation and recruitment of lekocytes and platelets.[11,13]

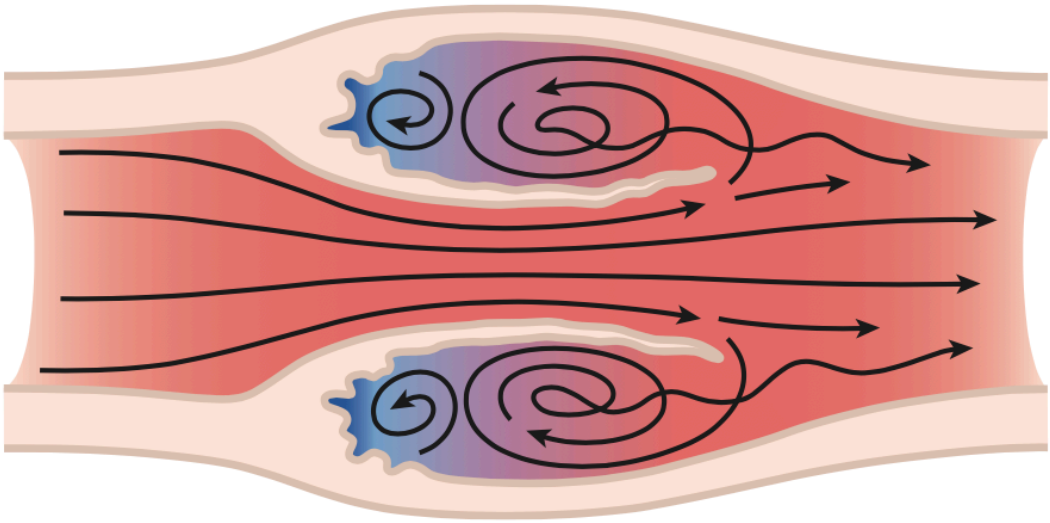

Figure 2.3 Venous flow and formation of basal vortices.

Streamlined venous flow is associated with the formation of basal vortices in venous valvular sinuses, in areas associated with the greatest degree of sinus hypoxia.[20] Small recesses at the base of the sinuses are evident on histological sections, and likely represent areas of maximal stasis and hypoxia, and consequently, the likely sites of early thrombogenesis.[13] Image reproduced from Bovill et al.[13]

Endothelial Activation

The effects of endothelial activation in venous thrombosis can be explained as cellular recruitment, plasma hypercoagualbility and the effect of mast cells as intermediaries of venous thrombosis.

Cellular Recruitment

In healthy vasculature, the endothelium expresses a master regulator, Krüppel-like factor 2 (KLF2), which positively regulates expression of thrombomodulin and maintains a vaso-protective state; the endothelium lining valve pockets has a greater expression of thrombomodulin and endothelial protein C receptor, and reduced levels of von Willebrand factor (vWF) than endothelium from non-valvular sites.[2] Endothelial injury, induced by hypoxia, inflammation or altered blood flow, results in reduced KLF2 expression and activation of nuclear factor- κB (NF-κB), which in turn

induces endothelial activation and gene expression, producing a pro-coagulant state.[2,11]

Activation of the endothelium and expression of NF-κB induces the expression of genes that promote endothelial adhesion and thrombosis, including vascular cell adhesion protein 1, E-selectin, the antifibrinolytic plasminogen activator inhibitor type 1 and procoagulant tissue factor. In addition, Weibel-Palade bodies (WPB) fuse with the endothelial cell plasma membrane and release von Willebrand factor (vWF) and P-selectin onto the cell surface membrane. P-selectin and vWF facilitate the binding of leucocytes and platelets, promoting thrombogenesis.[2,11]

Endothelial activation may also occur as a direct consequence of hypoxia, as synthesized reactive oxygen species (ROS) induce the expression of adhesion receptors and promote the extravasation of leucocytes.[11] In addition, ROS stimulate the complement system, and induce deposition of complement, particularly complement C3 and C5a, in vessel walls, indirectly activating the endothelium; high levels of C3 have been associated with increased risk of venous thrombosis in humans.[11,23]

Plasma Hypercoaguability

Given that the primary activator of coagulation is the tissue factor-factor VIIa complex, and the factor XIIa pathway, it has been theorized that plasma hypercoaguability may lead to increased thrombin generation; this has been supported by studies demonstrating an association between increased thrombin generation and primary and recurrent venous thrombosis.[2] Animal studies have

demonstrated that hyperprothrombinaemia (induced by infusion of prothrombin) is associated with increased thrombus size and accelerated fibrin deposition in venous injury models.[2,24] Activated endothelium enhances coagulation, and contributes to increased thrombosis, particularly through up-regulation of intercellular adhesion molecule 1 (ICAM-1).[11]

Mast Cells as Intermediaries in Venous Thrombosis

Mast cells are large, pro-inflammatory cells that form part of the innate immune system, and contain granules carrying multiple pro-inflammatory mediators and antithrombotic factors, including tissue plasminogen activator and heparin.[11] Mast cells have been demonstrated to accumulate at sites of venous thrombosis, however their relative contribution has been unclear. Recent studies have demonstrated that mast-cell deficient mice are protected against deep vein thrombosis, suggesting that it is the pro-inflammatory effects of mast cell degranulation that most contribute to venous thrombosis.[11,25] Similarly, reduced cell recruitment is demonstrated in mast cell deficient mice, suggesting that mast cells may have a role in endothelial cell activation, presumably via histamine release. The putative mechanism for this effect is mast cell activation by ROS, however a precise mechanistic relationship is yet to be elucidated.[11,25]

Blood Cell Recruitment

The recruitment of blood cells to the site of venous thrombosis is best described on the basis of recruited cell types, namely leucocytes, neutrophils, monocytes and platelets.

Leucocytes

Leucocyte recruitment and vessel wall adhesion appears to be stimulated by haemostasis, and to be primarily mediated by endothelial expression of P-selectin. In addition, increased plasma concentrations of low-density lipoproteins appear significant in leucocyte recruitment.[11]

Neutrophils

Neutrophils are important participants in venous thrombosis, and the absence of neutrophils has been demonstrated to inhibit venous thrombus formation. Neutrophil recruitment to the endothelium results in activation and release of nuclear material, stimulating the formation of neutrophil extracellular traps (NETs) that are composed of DNA, histones, secretory granule contents and other pro-inflammatory components. NET formation may be triggered by the presence of P-selectin, and activation of the P-selectin glycoprotein ligand-1, although under pathology-free (i.e. stasis) conditions, generation of NETs may occur via expression of high mobility group box 1 (HMGB1) on the surface of platelets adherent to the vascular wall. Neutrophil activation appears to play a more significant role in stenosed versus fully-closed vessels, suggesting that there is a requirement for residual blood flow in order for the inflammatory mechanism to operationalize; conversely, thrombogenesis in the setting of venous stasis may be more dependent on coagulation (i.e. tissue-factor related) mechanisms.[11]

Monocytes

Monocytes are a significant source of tissue factor, and therefore are major initiators of the extrinsic coagulation pathway, fibrin deposition and thrombosis.[11]

Toll-like receptor 9 (TLR-9) signaling is a major inhibitor of the prothrombotic function of leucocytes, as demonstrated in multiple studies involving mice with TLR-9 deficiency. In this setting, these animals demonstrated increased formation of NETs, increased markers of necrosis and of apoptosis in a stasis-based model of venous thrombosis.[11] Interestingly, it has been demonstrated that the lack of TLR-9 is associated with reduced monocyte recruitment to venous thrombi, although the complete clinical significance of this finding is not yet clear.[11,26]

Platelets

Platelets have been demonstrated to play an important role in venous thrombosis through the demonstration that platelet depletion results in reduced venous clot formation.[11,27] In venous thrombosis, platelets tend to be recruited as single cells adhering directly to the activated endothelium or adherent leucocytes, rather than forming aggregates consistent with arterial thrombosis.[11]

Recruitment to the thrombus is primarily mediated by the action of platelet receptor GP1bα and its interaction with surface endothelium vWF expression, however, interaction between platelet membrane CLEC-2 and podoplanin (a mucin-type transmembrane protein expressed in the tunica media and adventitia of murine inferior vena cavae) has also been implicated in platelet recruitment, particularly via hpoxia-mediated loosening of intercellular endothelial junctions, allowing increased platelet penetrance to subendothelial spaces.[11,28]

The indirect effect of platelets is as important as their direct thrombogenic actions. On recruitment, platelets provide pro-inflammatory stimuli via the release of Damage-Associated Molecular Patterns (DAMPs), namely HMGB1 and myeloid-

related protein-14 (MRP-14). HMGB1 promotes the formation of NETs by recruited neutrophils, and enhances the recruitment of monocytes and their subsequent tissue factor-mediated activation of the extrinsic pathway. Similarly, MRP-14 enhances NET formation, and assists in the propagation of venous thrombi.[11] It appears that there are factors that limit the role of platelets in venous thrombosis, including the interaction of apoA-1 (the major apolipoprotein in high-density lipoproteins) with SR-BI, an endothelial receptor scavenger. These mechanisms of limiting platelet activation may represent future targets for modulating the pathogenesis of venous thrombosis.[11]

The role of erythrocytes

Red blood cells have traditionally been thought of as passive participants in the formation of venous thrombi, however recent evidence suggests that this may not be the case; for example, red blood cell transfusion in patients with cancer is associated with increased rates of venous thrombosis.[2]

The mechanisms by which erythrocytes may contribute to venous thrombosis are not clearly delineated, but there are two prevailing theories. First, the aggregation of red blood cells in the low-shear environment may contribute to increased haemostasis, and retention of red blood cell aggregates in the basal hypoxic segments of venous pockets may occur via factor XIII-mediated mechanisms.[2,29] Secondly, red blood cells may express phophatidylserine (a procoagulant) that supports thrombin generation and may activate the contact (tissue factor) pathway of coagulation. In addition, erythrocyte-mediate release of adenosine diphosphate may trigger platelet activation, and red blood cells may decrease clot permeability and reduce fibrinolysis.[2]

Summary

The pathogenesis of venous thrombosis is a complicated process, involving anatomical, physical, and immune-mediated triggers for initiation. Targeting of immune-mediated and inflammatory pathways may represent new areas for potential inhibition of venous thrombosis. The mechanisms of thrombosis explain the utility of pharmacological and non-pharmacological interventions for VTE prophylaxis, however it is clear that our understanding of the pathogenesis of VTE is incomplete, and that multiple mechanisms interact to varying degrees depending on the cause of reduced venous flow (stasis versus stricture). An understanding of these processes is critical to understanding the methods used in the clinical setting to limit the rates of VTE and reduce morbidity and mortality from this important pathology.

Chapter 3. Venous Thromboembolism Prophylaxis

Introduction

Venous thromboembolism (VTE) is a potentially fatal condition that may result in a range of debilitating or disabling conditions.[30] It has a demonstrated incidence of 0.83 (95% CI 0.69-0.97) per 1000 population per year in the Australian setting[7], accounting for 7% of all in-hospital deaths in Australia.[31]

Aetiology & Pathophysiology

VTE pathogenesis is a result of alterations to haemostatic mechanisms and haemodynamics, including reduced or altered blood flow and stasis (e.g. gyrational flow and associated low oxygen tension around venous valve pockets),[32,33] hypercoaguability (with increased concentration of pro-coagulant proteins, decreased anti-coagulant proteins and decreased fibrinogen concentration[33,34]), endothelial activation with up-regulation and expression of tissue factor and endothelial adhesion molecules (leading to capture of leucocytes, platelets and microvesicles)[35] and inflammatory activation of Tissue Factor pathway and leucocyte-mediated endothelial activation mechanisms.[33,34,36]

Activation of these various mechanisms results in platelet adhesion to the vessel wall and aggregation of platelets though interactions between extracellular ligands and soluble proteins. Thrombin production and activation of multiple positive-feedback loops results in stabilisation of the thrombus.[30,35]

Options for VTE Prophylaxis

Following assessment of risk and need for VTE prophylaxis on admission,[7,37] an appropriate selection of pharmacological, non-pharmacological or combination prophylaxis should be made in the context of the patient's presenting complaint, past medical history, planned therapy and risk level.

Pharmacological VTE Prophylaxis

Pharmacological thromboprophylactic agents can be classified as parenteral anticoagulants, oral anticoagulants, antiplatelet drugs and new antithrombotic drugs.[38]

Parenteral Anticoagulants

Heparin is a highly-sulfated mucopolysaccharide, with a variable molecular weight (3000 – 30,000 KDa, Mean 15,000KDa). Only one third of heparin molecules contain the unique pentasaccharide sequence that confers anticoagulant action, and it is these that are responsible for heparin's anticoagulant effects.[39] Heparin functions by catalyzing the normally-slow reaction between antithrombin III (ATIII) and factors Xa, IXa, Xia, XIIa and thrombin. Binding of the high-affinity pentasaccharide chain present on active heparin molecules results in a conformational change in ATIII, changing it to a high-affinity, rapid inhibitor. Once the ATIII binds to an active clotting enzyme, heparin dissociates from the complex and can be re-used.[39] Heparin is administered as either a subcutaneous or intravenous injection, although higher initial doses should be used when administered via the subcutaneous route due to reduced bioavailability.

Unfractionated Heparin is eliminated in a rapid cellular saturatable phase (predominantly through endothelial cell receptor and macrophage binding with internalization and depolymerisation) and through slower, first order kinetics, predominantly through renal clearance.[40,41] Consequently, the anticoagulant response is non-linear, with the intensity and duration of anticoagulation increasing disproportionately as dose increases.[39] Given the importance of adequate initial heparin-dosing in patients with VTE (low-dosing being associated with increased risk of recurrence and higher rates of mortality),[39,42] initial intravenous dosing should ideally be weight-based (80units/kg bolus and 18units/kg/hr infusion)[39] or administered as a bolus of 5000units, with an ongoing infusion of at least 32,000 units per day.[39] Unfractionated heparin may be administered subcutaneously, either as an initial IV bolus of 5000units followed by 250units/kg subcutaneously, twice daily, or as an initial dose of 333units/kg subcutaneously, followed by ongoing therapy with 250units/kg twice daily.[39]

Use of UFH requires ongoing management of the patient's activated partial thromboplastin time, in order to ensure therapeutic concentrations are being reached, while avoiding increased risks of bleeding. Factors increasing the risk of bleeding while using UFH include recent surgical or interventional procedures, trauma, other haemostatic deficits, age >60 years, increased clotting times (greater than therapeutic range) and hepatic dysfunction.[39]

Low-molecular-weight heparin, derived from UFH by enzymatic or chemical depolymerization, is composed of low-molecular weight fragments (MW2000u – 9000u) of unfractionated heparin that exhibit reduced binding to proteins and cells

(including plasma proteins, macrophages and endothelium), and function through catalysis of the AT-mediated inhibition of coagulation factors.[39] Again, less than one third of LMWH chains carry the correct pentasaccharide sequence required for binding antithrombin, and as the molecules are smaller, only 25-50% are long enough to bridge antithrombin and thrombin.[39] Inactivation of Factor Xa by antithrombin is catalyzed by LMWH, however, as this reaction does not require bridging.[39]

LMWH has a more predictable anticoagulant effect and greater bioavailability (90%) than UFH.[39,43-45] LMWH has a dose-dependent half-life of 3-6 hours after subcutaneous injection, with peak anti-Factor Xa activity at 3-5 hours after administration.[39] It is important to note that LMWH is predominantly renally-cleared, and may have a longer half-life in patients with renal disease.[39]
LMWH should be administered once daily, as there is no evidence that twice-daily dosing demonstrates improved VTE prophylaxis.[46] A 2009 systematic review of 22 randomised controlled trials comparing fixed-dose subcutaneous LMWH with adjusted-dose intravenous or subcutaneous UFH in established VTE[47] demonstrated reduced rates of thrombotic complications (3.6% vs 5.4%, OR 0.68, 95% CI 0.55-0.84), major haemorrhage (1.2% vs 2.0%, OR 0.57, 95% CI 0.39-0.83), and overall mortality (4.5% vs 6.0%, OR 0.76, 95% CI 0.62-0.92) in groups treated with LMWH, compared to those treated with UFH. Similarly, the LMWH groups demonstrated improved reduction in thrombus size (reduction of 53% vs 45% OR 0.69, 95% CI 0.59-0.81).[47]

Four systematic reviews have compared the use of LMWH versus UFH and/or mechanical methods in surgical VTE thromboprophylaxis, and these are summarized

in table 3.1. At the time of writing, Cochrane Collaboration protocols were also in place for systematic reviews examining VTE prophylaxis in acute spinal cord injury, neurosurgery, cardiac or thoracic surgery, and total hip or knee replacement or hip fracture repair.[48,49]

Both UFH and LMWH have the potential to lead to heparin-induced thrombocytopaenia (HIT), and osteopaenia, although the risk of these complications is lower with LMWH.[39]

LMWH is recommended for pharmacological VTE prophylaxis in total hip replacement (Grade A), hip fracture surgery (Grade B), total knee replacement (Grade A), lower leg fractures or injuries with lower leg immobilization (Grade B), gynaecological surgery (Grade B), abdominal surgery (Grade B), cardiac, thoracic or vascular surgery (Grade B), neurosurgery (when not contraindicated) (Grade B), and trauma or spinal surgery (Grade C).[37] UFH is recommended for use in general surgery, gynaecological surgery, abdominal surgery, cardiothoracic or vascular surgery, or neurosurgery (Grade B).[37]

Type of Surgery/ Patient cohort	Outcome of LMWH vs UFH
Colorectal Surgery[28]	LMWH and UFH equally effective in preventing DVT and/or PE (OR 0.31, 95% CI 0.67-1.52)
Abdominal aortic surgery[50]	Insufficient evidence to make a recommendation regarding the use of anticoagulant drugs for DVT prophylaxis following abdominal aortic surgery.
Major gynaecological surgery[51]	LMWH and UFH are equally effective in preventing DVT (OR 1.03, 95% CI 0.33-3.20), PE ()R 1.82, 95% CI 0.57-5.80) or fatal PE (OR 3.33, 95% CI 0.13-83.24) in women undergoing major gynaecological surgery. *(Note: Review withdrawn from Cochrane Library in 2008 to be updated)*[32]
Trauma Patients[52]	LMWH reduced the risk of DVT compared to UFH (RR 0.68, 85% CI 0.50-0.94), however there was no statistically significant difference in the risk of PE (RR 3.16, 95% CI 0.13-76.91), or risk of bleeding (RR 1.62, 95% CI 0.63-4.22) between the two groups.

Table 3.1 Systematic Reviews comparing the use of LMWH versus UFH and/or mechanical methods in surgical VTE thromboprophylaxis

Fondaparinux is an artificial, modified analog of the antithrombin-binding pentasaccharide sequence of heparin. With a molecular weight of 1,728, fondaparinux has increased affinity for antithrombin and anti-Xa, improved specificity of action and a relatively longer half-life when compared with heparin.[39] It induces a conformational change at the active site of antithrombin, improving binding to factor Xa. Fondaparinux is then released from the AT-Xa complex, and goes on to catalyse other antithrombin-factor Xa interactions.[39,53]

Fondaparinux has a rapid, dose-dependent absorption profile due to its subcutaneous administration, with 100% bioavailability.[39,53] Peak plasma concentration occurs 2 hours after administration.[36]

Fondaparinux has a limited volume of distribution, close to that of plasma volume, and a half-life limited to 17-20 hours, allowing for once-daily dosing.[53] It does not appear to be metabolized, and is almost completely renally-excreted.[39,53] Due to this predominance of renal excretion, care should be taken with dose-adjustment in renally-impaired patients.[53]

Fondaparinux is recommended for thromboprophylaxis in orthopaedic surgery, following total hip replacement, hip fracture surgery, and total knee replacement in Australia.[37]

Four industry-sponsored phase III trials (PENTHIFRA, PENTAMAKS, PENTATHALON 2000 and EPHESUS) studied the efficacy of fondaparinux at a dose of 2.5mg in patients undergoing major lower limb surgery, and one RCT examined the role of extended thromboprophylaxis following hip fracture surgery (PENTHIFRA PLUS).[39] These studies reported clear superiority of fondaparinux to enoxaparin in DVT prophylaxis (Table 3.2).

	Fondaparinux 2.5mg daily	Placebo	Enoxaparin 40mg BD	Enoxaparin 30mg BD	Reported relative risk reduction	Calculated absolute risk reduction (based on reported data)
PENTHIFRA (Prophylaxis following hip fracture surgery)[54]	53/626 (8.3%, 95% CI 6.3-10.8) p<0.001	N/A	119/624 (19.1%, 95% CI 16.1- 22.4)	N/A	56.4%	10.8%
PENTHIFRA Plus (Extended prophylaxis following hip fracture surgery)[55]	3/208 (1.4%, 95% CI 0.3-4.2) p < 0.001	77/220 (35%, 95% CI 28.7-41.7)	N/A	N/A	95.9%	33.6%
PENTAMAKS (Prophylaxis after elective knee surgery)[56]	45/361 (12.5%, 85% CI 9.2-16.3) p < 0.001	N/A	N/A	101/363 (27.8%, 95% CI 23.3-32.7)	55.2%	15.4%
PENTATHLON 2000 (Prophylaxis after elective hip replacement)[57]	48/787 (6.1%, 95% CI 4.5-8.0) p = Not Significant	N/A	N/A	66/797 (8.3%, 95% CI 6.5-10.4)	26.3%	2.2%
EPHESUS (Prophylaxis after elective hip replacement)[58]	37/908 (4.1%, 95% CI 2.9-5.6) p < 0.0001	N/A	85/919 (9.2%, 95% CI 7.5-11.3)	N/A	55.9%	5.2%

Table 3.2 Incidence of VTE in patients receiving fondaparinux versus controls, for orthopaedic surgery

In Australia, Fondaparinux is recommended for use in total hip replacement (Grade B) for up to 35 days, hip fracture surgery (Grade B) fornup to 35 days and total knee replacement (Grade B) for up to 14 days.[37]

Danaparoid is a mixture of glycosaminoglycans (heparin sulphate, dermatan sulphate and chondroitin sulphate), derived from animal mucosa.[39,59,60] It is a low-molecular weight heparinoid, that primarily mediates coagulation through AT-III inhibition of factor Xa, with a lesser degree of associated factor IIa inactivation.[39,60]

Danaparoid has 100% bioavailability following subcutaneous injection, with peak plasma concentration at 4-5 hours post-administration, and a half-life of 25 hours.[39,44,59,60] It is administered twice daily, at a dose of 750 anti-Factor Xa units. Product recommendation recommends use for no longer than 10 days post-operatively.[59]

Although Danaparoid has been shown to be effective for the prevention of VTE in high-risk patients,[61-63] it has been withdrawn from marketing for this indication.[39] As of 2011, Danaparoid remains indicated for the prevention of venous thromboembolism in general and orthopaedic surgical patients,[59] however, the 2009 NHMRC clinical practice guideline for the prevention of venous thromboembolism only recommend the use of danaparoid in the treatment of patients suffering from heparin-induced thrombocytopaenia who require VTE prophylaxis.[37]

Oral anticoagulants

Dabigatran etixelate is a direct thrombin inhibitor, administered as an oral prodrug and metabolized by serine esterase enzymes following gut absorption. Dabigatran is a concentration-dependent molecule that binds to the active site of thrombin in both its free- and fibrin-bound states.[64]

Dabigatran etexilate reaches peak plasma concentrations within 0.5-2 hours of administration. Plasma concentrations drop by approximately 70%, within 4-6 hours, following initial dosing, however repeated dosing results in steady-state levels within 2-3 days, and a stable elimination half-life of 12-17 hours. Approximately 80% of Dabigatran etexilate is renally-excreted.[64]

The RE-MODEL, RE-NOVATE and RE-NOVATE II studies[65-67] have shown Dabigatran etexilate to be non-inferior to enoxaparin in total knee and total hip replacements,[62] and current guidelines support its second-line use in patients undergoing these procedures. LMWH remains the preferred means of anticoagulation in these cohorts, however dabigatran can be used in those unable to use LMWH (due to contraindications, high-risk of adverse events, or intolerant of repeated injection) and is particularly useful in the extended-prophylaxis setting.[63] In cases where dabigatran is used pre-operatively, special arrangements should be discussed between the surgical and anaesthetic teams due to the drug's extended half-life.[37,64]

Dabigatran etexilate interacts with a number of drugs during its absorption and metabolism. Dabigatran etexilate requires a low acidity environment to optimize absorption, and concomitant administration of pantoprazole therapy has been shown to reduce dabigatran absorption. Dabigatran plasma concentrations are also affected by changes in the function of the P-glycoprotein (P-gp)cell efflux transporter. Amiodarone, verapamil, ketoconazole, quinidine and clarithromycin all act to inhibit P-gp, and consequently increase plasma dabigatrin concentrations. Similarly, rifampicin and St. John's Wort induce P-gp function, and reduced plasma dabigatran concentrations.[64,68]

As of October 2015, Idarucizumab has been approved by the U.S. Food and Drug Administration as the only available agent for the emergency reversal of dabigatran's anticoagulant effects.[69]

Rivaroxaban is a selective, direct, reversible inhibitor of the active site of factor Xa. It inhibits free factor Xa and both prothrombinase complex- and clot-associated factor Xa.[64,68]

Rivaroxaban has been demonstrated have a similar efficacy in preventing VTE in patients undergoing total hip arthroplasty and total knee arthroplasty as LMWH in the RECORD trials[70], with relative risks of VTE of 0.38 and 0.77 when compared with 40mg daily and 30mg twice-daily subcutaneous enoxaparin dosing, respectively. It was found to be as safe as dabigatran and no significant increase in risk of bleeding was demonstrated in the studies.[68,70]

Again, although rivaroxaban may be used (Grade 1c), LMWH remains the preferred means of anticoagulation in patients undergoing total hip or knee arthroplasties (Grade 2B). Rivaroxaban can be used, however, in those unable to use LMWH (due to contraindications, high-risk of adverse events, or intolerant of repeated injection).[64,68]

Rivaroxaban reaches peak effect within 1-4 hours of administration. Rivaroxaban is predominantly cleared by the hepatobiliary system, however up to one-third of the drug is cleared renally. Consequently, its half life varies from 5-9 hours in young healthy patients,[71] to 11-13 hours in elderly subjects.[64,68,72] Rivaroxoban is partially metabolized by the cytochrome P450 3A4 system, and interactions have been noted when used in combination with strong CYP450 inducers and inhibitors.[68]

Apixaban is a direct factor Xa inhibitor, administered orally and actively inhibits free and clot-bound factor Xa, binding directly the active site and inhibiting the conversion of prothrombin to thrombin.[68]

Apixaban has an oral bioavailability of 50%[68] and reaches peak plasma concentrations within 1-4 hours of administration.[68] It has a half-life of 8-15 hours.[68] Apixaban is a highly protein-bound molecule (87%) and is predominantly excreted via hepatobiliary/faecal clearance and the cytochrome P450 CYP3A4/5 pathways (73%) with the remaining 27% being excreted renally.[68]

In Australia, Apixaban is indicated for VTE prophylaxis in patients that have undergone elective total hip and total knee arthroplasties (Grade 1C); LMWH remains the preferred means of anticoagulation in these cohorts, however Apixaban can be used in those unable, or unwilling, to use LMWH (Grade 2B).
The ADVANCE-2 and ADVANCE-3 trials[73,74] demonstrated that Apixaban is non-inferior (and in the ADVANCE-3 trial was, in fact, superior) to enoxaparin for VTE prophylaxis in total knee and total hip replacements, with no greater risk profile that enoxaparin.[68,73,74]

The AMPLIFY-EXT study recently demonstrated that Apixaban was safe for extended VTE prophylaxis in patients that had undergone earlier treatment for DVT or PE and in whom the decision whether to cease or continue anticoagulant therapy was clinically ambiguous.[75] The study revealed a statistically significant reduction in risk of VTE in either treatment group (2.5mg and 5mg twice daily) compared with placebo, with the 2.5mg group demonstrating a relative risk of recurrent VTE or

VTE-related death of 0.19 (95% CI 0.22 - 0.48) compared with placebo, and the 5mg group showing a relative risk of 0.20 (95% CI 0.11 – 0.34), a difference of 7.2% (95% CI 5.0 – 9.3) and 7.0% (95% CI 4.9 – 9.1) respectively.[75] The study also demonstrated the safety of Apixaban in extended VTE prophylaxis; although clinically relevant non-major bleeding rates increased with dose (placebo = 2.3%, 2.5mg Apixaban group = 3.0%, 5mg Apixaban group = 4.2%), the rate of death from any cause was highest in the placebo group (1.7%) and lowest in the 5mg Apixaban group (0.5%).[75]

Betrixiban is a novel selective Factor Xa inhibitor that is efficacious in providing extended-duration VTE prophylaxis in acute medical patients when commenced in-hospital, and continued in the community for up to 35-42 days, aged >75 years or with ≥2 risk factors for VTE.[76,77]

Recent reviews have suggested that the Novel Oral Anticoagulants (NOACs) may be considered as first-line agents for both the treatment and prophylaxis of VTE, although data in sub-groups of patients is limited.[78].

Overall NOACs are non-inferior to other anticoagulation regimens, with similar associated rates of bleeding, and it is reasonable to consider their use as first-line agents for VTE treatment and prophlyaxis, particularly as reversal agents become available to practitioners (e.g. idarucizumab,[79] and andexanet alfa[80]). These agents are contraindicated in patients with severe renal insufficiency (creatine clearance <30ml/min) and hepatic impairment, however, due to an increased risk of coagulopathy.[78]

Antiplatelet Agents

Aspirin is the best-known and most widely-studied antiplatelet drug, and primarily acts to prevent platelet activation. Aspirin acts through dose-dependent blockade of the thromboxane-A_2 (TXA_2) pathway, with low-dose therapy preventing only the production of TXA_2 (a promoter of platelet aggregation), and not of Prostaglandin I_2 (PGI_2 – a strong platelet aggregation inhibitor). Aspirin prevents TXA_2 production through the permanent inhibition of prostaglandin H-synthase-1 and -2 (COX-1 and COX-2) cyclo-oxygenase activity, thus preventing the conversion of Arachidonic acid to Prostaglandin H_2, the immediate precursor of TXA_2 and PGI_2.[81]

Aspirin is rapidly absorbed in the upper gastrointestinal tract, specifically the stomach and upper intestine, and platelet inhibition begins within an hour of ingestion. Enteric-coated aspirin has a longer rise to peak plasma concentration of between 3 and 4 hours.[81] The half-life of aspirin is between 15 and 20 minutes, although the effect lasts the lifetime of the platelets due to aspirin's permanent COX-1 inhibitory function in both circulating platelets and megakaryocytes, thus preventing platelet activation in both circulating and newly-produced platelets. Approximately 10-12% of platelets are replaced daily, however the non-linear relationship between COX-1 inhibition and TXA_2 synthesis and the ability of residual thromboxane produced by platelets unaffected by aspirin to continue platelet aggregation, means that recovery of platelet function is faster than anticipated based on platelet production.[81]

Aspirin has been shown to be effective in preventing VTE after major orthopaedic surgery,[81,82] and the current American College of Chest Physicians guidelines

recommend its use for VTE prophylaxis in patients undergoing general, abdominal or pelvic surgery at high risk of adverse events from, or with contraindications to the use of, Low-molecular-weight heparin or unfractionated heparin (Grade 2c), those undergoing total-hip or total-knee arthroplasty (Grade 1c), patients undergoing hip fracture surgery (Grade 1c).[64] In all cases, however, aspirin should not be considered a first-line agent for VTE prophylaxis.

To date ***clopidogrel*** has not been recommended for the prevention or treatment or VTE, and recent guidelines support not using this drug for this indication[81,83].

New Anti-thrombotic Agents

A range of new anti-thrombotic agents are being trialled that may have a future role in surgical VTE prophylaxis, including NAPc2, Idraparinux, Idrabiotaparinux and recomodulin.[84] None are currently licensed for use in Australia.

Summary

A broad range of pharmacological thromboprophylactic agents is available, with new drugs currently undergoing trials. VTE prophylaxis will always remain an important aspect of peri-operative care, and correct selection of therapeutic agents in the context of the patient's presenting complaint, past medical history, planned therapy and risk level is vital. It is important for surgeons and surgical trainees to have an understanding of the range of thromboprophylactic agents available, and their pharmacological activity.

Chapter 4. Theoretical Basis of Learning and E-Learning

Learning theory underpins our understanding of how student learn, and how best to deliver opportunities and material for learning to students. The theories of learning are, however, subject to social and psychological pressures and contexts that mean they have evolved over time, depending on the prevailing societal constructs of the day. This chapter will briefly review the key learning theories of the 20th and 21st centuries.

Learning theories can be divided into two epistemological groups; objectivist epistemology and constructivist epistemology.

Objectivist epistemology is a predominantly 20th Century approach that includes the theories of behavioural, cognitive and constructivist learning. It underlies the didactic approach to teaching. The objectivist approach relies on the belief in an objective truth that is discovered over the course of time, existing outside the human mind, or, alternatively, outside of what an individual may or may not believe. 20th Century learning is categorised as behavioural, cognitist and constructivist theories. Conversely, constructivist epistemology (confusingly, separate from constructivist theory) is a 21st century approach to learning that includes the theories of connectivism and collaboratism.[85] Although a 21st century theory, few, if any components of constructivist epistemology are yet practiced in medical education, and as such will not be discussed in this review.

This section will consider each of these theories in turn, and explore recent developments in the theoretical basis of e-learning.

Behaviourist Learning Theory

Behaviourist learning theory focuses on the observable characteristics of learning; developed in the late 19th century, it espouses an empirical, observable and measureable theory of learning. It is a learning theory that rigorously applies the scientific method, and only measures observable findings; that is to say, behaviourist learning theory considers the learner's mind, and it's workings, to be an irrelevant "black box", instead emphasizing the study of environmental stimulus and observed response.[85]

The theory emphasizes classical conditioning and operant conditioning as responses to environmental stimuli, embodied in the quintessential works of Pavlov[86] (behaviour becomes a reflex response to a stimulus) and Skinner[87] (behaviour is reinforced by reward or punishment). While this holds some appeal, in terms of restricting the study of learning to measurable factors, amenable to randomized studies and clear input-output models of education, the model has limitations, limiting the process to learning and education to a narrow, mechanised process that ignores the impact of environment and social constructs. As a result, it is most successfully applied in the context of unambiguous learning objectives, and achievement of specific, agreed criteria for task-oriented performance.[85]

Behaviourist Pedagogy

Behaviourist pedagogy relies on the underlying principle of learning as a behaviour that demonstrates acquisition of knowledge or skill. Reward and punishment techniques are designed to promote desirable behaviour in students via positive or negative reinforcement. This is manifested in common classroom practices such as

teacher-student learning contracts, immediate consequences after a particular behaviour occurs, the use of positive and negative reinforcement, and the use of positive and negative punishment. This approach relies on the assumption that there is a predictable link between stimulus and response, and that such responses are consistent, automatic and replicable.[85]

The earliest forms of e-learning relied upon a behaviourist pedagogy, with computer-assisted instruction (CAI) being designed to rely upon encouragement and repetition to promote positive learning outcomes.[85,88] In this model of e-learning, control sits with the program designer and not the learner, with an instructional emphasis on behavioural control.[85]

Cognitivist Learning Theory

Cognitivist learning theory emerged in the 1920s as an extension and reaction to behaviourist learning theory, in recognition of the importance of social inputs and internal mental processes to learning. Three schools of thought developed around cognitivist learning theory, although all subscribe to the concept of the "Mind as Computer".[85]

The Cognitive Information Processing school was the first to hold, and most strongly imbued with, the concept of the human mind as a computer-like information processor. The school saw information processing in a precise, mechanical way, following a formal structured pathway through storing, retrieving, transforming and using information, with the formation of associations as a component of learning.

This computer-science approach to learning, later had strong influence on the developers of early e-learning techniques.[85]

The Schema Theory school argued that learning occurs when new information is compared to existing knowledge, and held in a representation or structure for retrieval. As a result, learners must develop symbolic systems to help develop new skills or retain new information; how these schema are developed is variable, however, with schema potentially existing as memory structures, abstract schema, networks, dynamic structures or contextual overlays.[85]

The final cognitivist school is that of Gagné's instructional design, based on his experience studying instructional techniques in the military, which presented the view of instruction as the transmission of information, with the role of the student as willing recipient, and the instructor as designer and presenter of stimuli to elicit appropriate student behaviour.[85]

It is in Gagné's work that the similarities between behaviourist and cognitivist theories of learning become most apparent, given that both theories subscribed to the concept of taxonomies of learning. The classic behaviourist example of taxonomies of learning is Bloom's Taxonomy of Educational Objectives Handbook,[89] a taxonomy that related learning to the development of intellectual skills, with problem-solving as a higher-order skill.[88] Bloom's taxonomy ranked six key elements of learning, from lowest to highest order, and each element being based on the ones below it, namely, remembering (recognizing and retrieving information), understanding (constructing meaning from information), applying (executing or

implementing knowledge), analysing (breaking new material down into parts, and relating them to each other and outside structures), evaluating (judging and critiquing information, and using that process to evaluate decisions) and creating (putting the learned elements together to form a coherent whole meaning, or constructing a new pattern or structure).[88,89]

Gagné built upon Bloom's structure, and developed a new theory of instruction that would form the basis for cognitivist instructional design, and formed a process for the delviery of information to students by instructors.[85,88] Gagné's theory was composed of a taxonomy of learning outcomes, a list of specific conditions for each learning outcome, and nine events of instruction that were effectively methods and procedures to enable learning processes (Table 4.1).[85]

Learning Outcomes	Specific Conditions for Learning	Events of Instruction
Verbal Information	Verbal Information	Gaining Attention
Intellectual Skills	Intellectual Skills	Informing Learner of Objective
Cognitive Strategies	Cognitive Strategies	Presenting Stimulus
Attitudes	Attitudes	Presenting Material
Motor Skills	Motor Skills	Providing Guidance
		Eliciting Performance
		Providing Feedback
		Assessing Performance
		Enhancing Retention and Transfer

Table 4.1 Gagné's Theory of Instruction

Cognitivist Pedagogy

Cognitivist pedagogy is closely associated with behaviourist pedagogy, and can be viewed as an extension of the latter rather than a completely new theoretical foundation.

Cognitivism holds that human behaviour is predictable, and therefore subscribes to the behaviourist theory that instruction should be prescriptive, and that learning

outcomes are predictable based on repeated responses to the same stimulus. This resulted in the pedagogy of cognitivist instructional design, wherein the instructor attempts to determine which stimuli result in the desired response from the learner, and applies them in order to achieve the required outcome.[85]

When combined with Gagné's taxonomy (which empowered the required instructive approach) and the concept of learning schemata, the field of educational technology emerged as a key component of cognitive pedagogy, with computers taking on roles in intelligent tutoring systems (an extension of the earlier computer assisted learning approach). The intelligent tutoring system works through determining the student's baseline understanding of the material, and then decides *what the student needs to know*, delivering that information through a problem-solving exercise.[85]

Intelligent tutoring systems are limited by the inherent limitations of the baseline student learning model, and by the concept of 'machine intelligence', insofar as the machine is, in fact, following defined algorithms, rather than truly adapting to learner requirements. This has generated an interest in the possibility of artificial intelligence as an educational tool, however current technology has neither the capacity nor capability for the meaningful use of artificial intelligence in learning at this time.[85]

Constructivist Learning Theory

Constructivist learning theory emerged in the 1970s, and was a significant departure from the preceding theories of learning. According to constructivist learning theory, learned construct their knowledge and understanding through experiences and

reflection on their experiences. Although there are many perspectives on constructivist learning theory, there does appear to be general agreement that learning is a constructive rather than acquisitive process, with instruction having a supportive role in knowledge development.[85,88]

Vygotsky has described a social constructivist theory of learning as a problem solving exercise, based on a social construction of solutions that occurs in a "zone of proximal development", with the teacher providing the social environment in which learning occurs. This is similar to the theories of Dewey, who described learning as a series of social experiences, consisting of learning by doing, collaborating and reflecting with others.[88]

Conversely, Piaget developed a cognitive constructivist theory of learning,[90] focused on the individual, and based on four stages of cognitive development; the sensorimotor stage (reflex-based learning, occurring from birth to 2 years old), the preoperational stage (learning based on words and thoughts, and acting on objects. A self-oriented phase from ages 2-7 years), the concrete operational phase (a phase of problem solving-based learning, from age 7-11 years), and the formal operational phase (from age 12+ years, characterized by abstract thinking and theoretical reasoning). In this model, the instructor challenges the student's pre-existing ideas with the aim of creating cognitive disequilibrium, the problem that the student then has to solve to restore a sense of cognitive balance. Thus, Piaget's theory relied on the premise that knowledge is constructed in the learner's mind, and forms a fit with reality, as opposed to the objectivist view that knowledge must match with reality.[85]

Constructivist Pedagogies

Constructivist pedagogies focus on the learner and the needs of the learner, in the belief that instruction should facilitate the development of meaning and understanding as the learner actively constructs knowledge; this has resulted in a number of approaches, based around the concepts of active learning, learning-by-doing, scaffolded learning and collaborative learning.[85]

Active learning is a requires instructors to encourage students to participate and act in their learning (e.g. examining a patient, conducting an experiment); it is a student-centred approach that requires the student to engage in an activity, reflect upon it, and then discuss how their understanding is changing, while the teacher uses their understanding of the student's pre-existing understanding to guide the activity toward improving that understanding.[85]

A constructivist approach to education requires the teacher to encourage and assist students in developing their knowledge of a subject, rather than transmitting information to be memorized. Instructors must use problem-solving and inquiry-based activities to engage the learner as an active participant in the learning process, and play an active role through identifying a knowledge problem for trainees to assess, providing guidance in how to understand it, and guiding students toward appropriate resources to solve the problem.[85] That problem should be an authentic, complex and ill-defined, and therefore reflect the real-world problems that the trainee will face on completion of their studies. In this model, instructors facilitate learning and teach by negotiation, rather than imposition.[85,91]

'Learning by doing' is an approach advanced in many educational institutions. The classical example of this methodology is that of engaging children in the use of the Logo programming language developed by Papert and others at the Massachusetts Institute of Technology; combined with a device called the "turtle", a programmable robot holding a pen, students learn the logo language in order to make the turtle draw geometric shapes. The key tenet in this process is that students learn to do something, rather than about something.[85] This approach extends into other constructivist pedagogical approaches, including problem-based learning (students are presented with a scenario to resolve, with aspects of the problem presented from different perspectives), distributed problem-based learning (a group of students working on a problem-based scenario), case-based learning (in which students discuss specific, typically real-world, examples of a problem, engaging them in knowledge-building and analysis as a group of learners. In this instance, there may be no correct answer), inquiry-based learning (a form of self-directed learning in which students take a greater responsibility for directing what they need to know) and role-play simulation (including game-based learning, in which students act out roles in order to understand various perspectives around the problem to be solved).[85]

Scaffolding is an alternative term used to refer to Vygotsky's Zone of Proximal Development (ZPD); in this method, an instructor or teacher assists the learner in constructing knowledge until the need for support has passed. The 'scaffold' refers to specialized techniques designed to support learning at the introduction of a new subject.[85]

Finally, collaborative learning is a key principle of social constructivism. This pedagogy emphasises collaboration, particularly among learners, in order that participation and interaction produces a finished result owned by more than one person. This most commonly refers to small-group learning.[85]

Constructivist pedagogies are likely to be those most commonly associated with our current understanding of e-learning in medicine, insofar as the technologies used are often referred to as learning environments. While construction worlds and microworlds exist in other specialty teaching areas, by far the most common use of constructivist learning environments in medicine is through online learning and course delivery platforms (e.g. Blackboard, Moodle, etc.).[85] These platforms utilise constructivist theory in that they facilitate user-generated content and can be altered by the user to facilitate discussion. This describes the potential utility of these platforms, however, and many educators use these platforms as mechanisms for disseminating knowledge (in a behaviourist or cognitivist approach), rather than exploring the social opportunities that such platforms present; that is to say, constructivist designers cannot ensure that educators will use constructivist pedagogy in education delivery.[85]

Summary

Educational theory has evolved over time, from a mechanistic perspective to one of collaborative, constructivist learning opportunities. While new theories based around Massive Open Online Courses have evolved in the early part of the 21st Century, much of current online medical education is based on a constructivist

theorem. The next chapter will analyse the role of e-learning in medical education, and provide the justification for the studies undertaken as part of this thesis.

Chapter 5. E-Learning in Medical Education

E-learning is defined as the use of the internet for education, and may also be described as web-based learning, online learning, distributed learning, computer-assisted instruction, or internet-based learning, and aims for a flexible, engaging, interactive, collaborative and learner-centred approach to education.[92-95] Two modes of e-learning, distance learning and computer-assisted instruction, are commonly used to deliver teaching through the use of tutorials, online discussion groups and virtual patients.[92,94] In this context, students may be situated in a variety of environments either at a distance, or in traditional learning settings via computer laboratories, operating theatres, hospitals, or any site with internet access.[93] This provides the opportunity for the delivery of classical online teaching (i.e. the delivery of facts and information in stand-alone online modules or presentations), however in recent years this approach has broadened to include combinations of online educational delivery and direct contact between students and students and instructors, resulting in an approach described as 'blended learning'.[95,96]

In this context, the e-learner is any individual that mediates some learning activities online,[93] and uses content and activities presented by instructors and material created by the learner or other learners.[93] As a result, e-learning offers a number of advantages to learners over traditional approaches.[92,95]

E-learning may occur independent of time and place, conferring flexibility in opportunities for learning that benefit adult learners. Similarly, the pedagogical process can occur over vast distances, and allows for educational opportunities for distant (even international) learners, and those in remote areas who may otherwise

lack educational opportunities. There is a significant degree of social engagement involved in e-learning, and the medium may permit an improvement in skills in online communication, including the ability to produce concise, coherent writings. This aspect also confers a need for a greater degree of academic and persona reflection than might occur in traditional academic settings, resulting in improved learning and competence development.[94,95] Online education also permits the generation of perpetual resources that are easily updated (particularly important as new medical evidence is generated), the opportunity for novel instructional methods facilitating deliberate and distributed practice, and the opportunity for assessment and documentation of educational objectives, thus permitting immediate, customizable, feedback.[94]

Online education is not without disadvantages, however, and many of these relate to the perceived advantages of web-based instructional delivery.

Despite the potential for improved social interactions as part of e-learning, learners may suffer a relative increase in social isolation, often studying alone, and engaging in online discussion that follows a distinct social organizational structure that is different from in-person interactions. In addition, the anticipated benefits of perceived individualised learning may not be apparent, and learners may experience significantly *less* individualised instruction if the web-based learning program is not designed to measure and respond to learner needs.[94,95]

E-learning is attractive to many educational institutions as a cost-saving method of delivering instruction, however the initial development of effective online learning

material can be expensive and time-consuming, and ongoing online discussions and student interactions require moderation by faculty members. In addition, there is an opportunity cost to the learner, as online study must occur in time that may have been devoted to other purposes, and potentially carries a significant workload that may not have been totally appreciated by instructors designing the learning program.[94] This also speaks to the quality of instructional design, which may be highly variable in the e-learning environment; instruction in the online setting requires precise and dedicated preparation and implementation, and research demonstrates that many online learning environments do not meet these standards.[94,97]

A key tenet of e-learning is the dependence on technology, and as a result the e-learning environment will suffer from some form of technical problem at some point in time; unlike traditional pedagogical approaches, however, the dependence on technology in e-learning increases the impact of problems when they do occur. While catastrophic problems are relatively uncommon, and easily identified (e.g. the crashing of a server), technical problems include minor, but disruptive, issues (e.g. slow responses to user input) that can result in decreased learner satisfaction and increased cognitive load, thus impeding learning.[94]

E-learning has been enthusiastically taken up in medical education, and many forms of e-learning are in use, from simple text-based websites, to case-based learning platforms (of which eMedici is one example) and online, virtual simulations of patient encounters.[85,92,94,95] It is a now a component of undergraduate, graduate, paediatric, surgical and general medical education.[98-103]

Web-based learning takes on multiple modalities, and is perhaps most widely used in the instruction of medical students. Tang et al[99] conducted a scoping review of the use of online lectures in undergraduate medical education in 2018. They found that online lectures have been extensively integrated into undergraduate medical education, across multiple subjects and levels of training. The authors demonstrated that medical education has been poor at incorporating principles of multimedia design into online lectures, despite evidence of the importance of such principles existing for approximately ten years. The authors attribute this lag in uptake to a combination of time constraints, existing standards of practice, and the likelihood that clinician-teachers have not received training in multimedia design principles, or may not have fully integrated these principles into their practice.[99] Tang et al. found that most studies demonstrated that the use of online lectures was non-inferior to traditional pedagogies, with all studies reporting high student satisfaction with online learning and improved knowledge following its use. Interestingly, multiple studies reported superior learning outcomes in medical students using online lectures as part of their education; however, these results should be treated with caution, as it may not be that online learning is a superior medium, but that the conditions associated with e-learning (including extra learning time, ability to re-review material, access to resources, etc) lead to improved student learning outcomes.[99]

Jwayyed et al conducted a review of the literature concerning the use of technology-assisted education in graduate medical education in 2011.[100] They demonstrated that the most commonly used modalities of online learning in graduate medical education were computer and internet-based methods, followed by simulation and virtual reality techniques. Studies were most commonly conducted in medical students,

followed by residents, and sought to measure knowledge gains, satisfaction and attitudes to educational interventions. Of the studies conducted that directly compared technology-assisted learning with traditional teaching methods, the majority found technology-assisted learning to be equal or superior to traditional methods, although the authors could not identify a 'best-method' for delivering technology-assisted education. Similarly, the indications and timing for using technology-assisted education over traditional methods could not be identified from the literature.[100]

In 2018, O'Doherty et al. conducted a review of the literature with a view to identifying the barriers and solutions to the development and implementation of e-learning in medical education. They identified four core themes as areas impacting on the production of e-learning; skills, resources, institutional strategies and support, and attitude.[104]

The only identified skills-based barrier to the use of e-learning was the presence of a skill deficit; that is, a lack of technical skills in computing and typing, associated with poor infrastructure, leading to reduced engagement with online learning. The author's proposed engagement as a solution to this barrier, both directly (i.e. the educator must make a conscious decision to try to use e-learning modalities) and through training via online material and the use of faculty workshops.[104]

Time and infrastructure were identified as the principle resources barriers to the use of e-learning by medical educators. Educators, who already have teaching, clinical, research and personal commitments, have limited opportunities to spend time on

mastering the tools of online learning, and appear to have few incentives to engage with e-learning. The review demonstrated that the use of digital tools for teaching can, overall, increase available free time and permit increased opportunities for instructors to learn e-learning concepts and reflect on their practice; however the reviewers note the importance of developing formal mechanisms for acknowledging efforts and rewarding time spent by faculty on developing e-learning material. Conversely, access to technology and infrastructure may be significant barriers to the introduction of e-learning, particularly in low- to middle-income countries, including poor wireless internet connectivity, access to physical infrastructure, and access to computers. In this respect, the authors identified the use of 'break-even analysis' as a tool for determining the cost of introducing e-learning programs, and found that online education was more cost effective than traditional learning, permitting fewer enrolments for a program to reach its break-even point that traditional teaching methods. As a result, initial investment in e-learning technologies may prove to be a more cost-effective approach to education delivery in the low-resource setting.[104]

Institutional support for the introduction of e-learning is vital, and a component of this process is communication between faculty members both in the set-up and use phase of e-learning development. Poor institutional support and limited direction in the use of e-learning for Faculty may result in listless project development and poor communication between team members, resulting in a reduction in the active exchange of ideas and shared knowledge within teams, and across institutions.[104] Collaboration is a key component of the development and introduction of e-learning, and must be an imperative and active process, including the use mechanisms to

ensure dedicated human and financial resources are in place to support the project, and to ensure the support of all stakeholders in the project. O'Doherty et al recommend the use of institutional strategies to facilitate the implementation of key skills and methodologies when staff are working toward the introduction of web-based learning.[104]

The final barrier to e-learning implementation identified by O'Doherty et al. was culture. The use of online learning technologies imposes a learning curve on faculty members as they attempt to master new e-learning tools and technologies, and instructors may become frustrated with minor technical issues or overwhelmed by the development process, inducing negative attitudes towards e-learning. In this setting, it is critical to assist teachers in maintaining a positive attitude towards e-learning through the development of a positive learning culture, fostering a change of norms and attitudes, and providing support for faculty members.[104]

What is the efficacy of e-learning?

There has been significant educational and research interest in the use of e-learning in medical education in the past 20 years, and multiple studies have been conducted, using various methodologies, into the efficacy of e-learning.

In an attempt to answer the question of whether e-learning is more effective than traditional learning in licensed healthcare professionals for improving patient outcomes or health professionals' skills, behaviour and knowledge, Vaona et al. published a Cochrane systematic review of the literature in 2018.[105]

The authors identified 16 studies from 10 countries, providing data on 5,679 participants (4759 mixed healthcare professionals, 587 nurses, 300 doctors and 33 childcare health consultants). All trials compared e-learning with traditional face-to-face learning, except for two studies that compared e-learning to guideline dissemination or availability. 11 trials administered e-learning as a sole intervention; in the five remaining trials, e-learning was identified as a core facet of a multifactorial educational intervention. Outcomes used in the 16 studies included health professionals' behaviours, patient outcomes, and knowledge, assessed through the analysis of administrative and patient record data, and the administration of testing, simulation and objective structured clinical examinations (OSCEs).[105]

The systematic review revealed that the use of e-learning may make little to no difference in terms of patient outcomes when compared with traditional learning, and was not associated with changes positive (i.e. desired) changes in healthcare professionals' behaviours, with two studies that addressed behavioural outcomes revealing no improvement in rates of screening or patient treatment for dyslipidaemia (the target pathology in the two studies) (Figure 5.1).[105]

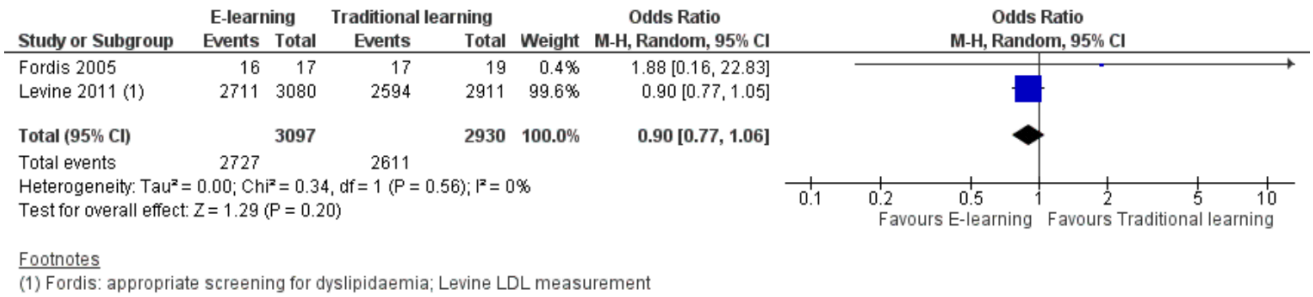

Figure 5.1 Forest plot of comparison between e-learning and traditional learning for healthcare professional behavioural outcomes.

Although there is a small trend toward improved outcomes from e-learning, the effect is not statistically significant, and the meta-analysed measured effect crosses the line of no effect (From Vaona et al[105])

The certainty of evidence surrounding the effect of e-learning on healthcare workers skills was assessed as low in the meta-analysis, but appeared to show no difference between e-learning and traditional teaching groups. One study assessed performance of students in cardiac arrest simulation; while the initial analysis appeared to demonstrate no difference between the two groups, analysis of unpublished data excluding students and participants with missing health professional status from the analysis demonstrated that the proportion of healthcare professionals passing the test simulation was higher in the traditional learning group than the e-learning group (OR 1.46, 95% CI 1.22-1.76).[105]

Eleven studies assess the effect of e-learning on healthcare professionals' knowledge, although only eight studies reported the data adequately enough to permit pooling. There was moderate heterogeneity between the studies, with an I^2 value of 47%, so the authors conducted the analysis using both a fixed-effect and random-effects model. The meta-analysis demonstrated that e-learning made little to no difference to health professionals' knowledge when compared with traditional teaching techniques (Figures 5.2 and 5.3).[105]

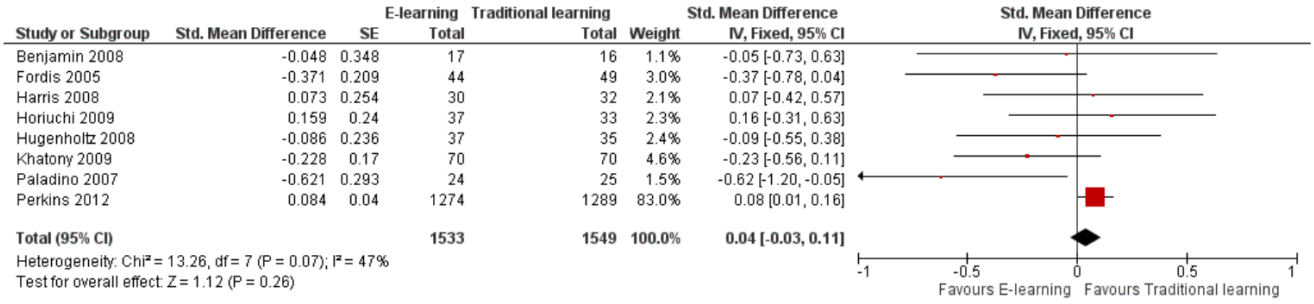

Figure 5.2 Forest plot of comparison between e-learning and traditional learning for healthcare professional knowledge using a fixed-effect model.

The analysis demonstrates a small trend in favour of traditional learning, however the marker of measured effect crosses the line of no effect (From Vaona et al.[105])

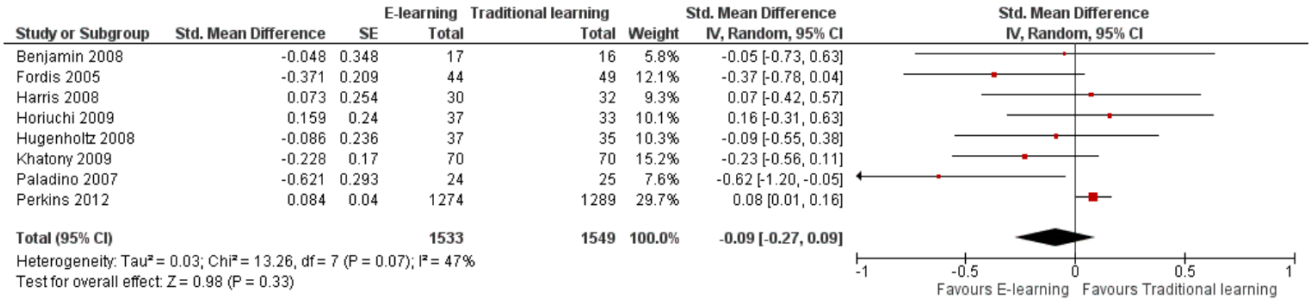

Figure 5.3 Forest plot of comparison between e-learning and traditional learning for healthcare professional knowledge using a random-effects model.

The analysis demonstrates a small trend in favour of e-learning, however the marker of measured effect crosses the line of no effect (From Vaona et al.[105])

The overall conclusion of Vaona et al. was that e-learning may lead to little or no difference in patient outcomes, health professionals' behaviours and knowledge, and have little to no effect on healthcare professionals' skills, when compared with traditional learning, although they recognise that the evidence for effect on outcomes, behaviours and knowledge is low-certainty evidence, while the evidence for effect on skills is very low-certainty. The authors conclude that e-learning was associated with no important benefits compared with traditional learning, and that the only large trial included in their study favoured traditional learning for skills.[105]

Conversely, Jayakumar et al. conducted a systematic review of the role of e-learning in surgical education, published in 2015, and identified e-learning as an effective mode of teaching, with relevance for surgical education, although they concluded that further research comparing e-learning with traditional learning in surgical education needs to be performed.[103]

Jayakumar et al. identified 38 studies for inclusion in their analysis, across three themes of e-learning; Case-based teaching (18/38 studies), e-learning to teach

theoretical knowledge (18/38 studies) and e-learning to teach surgical skills (2/38 studies). [103]

Study quality was variable across the entire analysis. In the case-based e-learning theme 9/18 studies (50%) did not use a control or comparison group in analysis, and 4 used historical controls. In the 5 studies that had concurrent control groups, participants were randomized to case-based teaching or traditional teaching. The largest study[106] of the effect of e-learning in urological teaching to medical students demonstrated significantly higher test scores following web-based education compared with traditional teaching both immediately post-intervention and at 5 months' follow-up. In this study, students acted as their own controls, however, interpretation of the results is limited by variable participation rates between medical schools, and the effect of participants accessing online modules that they were not allocated to.[103,106]

The use of e-learning for teaching theoretical knowledge in surgery was demonstrated to result in a statistically-significant increase in knowledge on post-intervention testing, however the majority of studies reviewed (11/18) did not use control groups for comparison, nor include a pre-intervention test to determine baseline knowledge. Similarly, the use of e-learning to teach surgical skills in 2 studies (intraoperative surgical manoeuvres for thoracic and abdominal surgery,[107] and microsurgery skills[108]), demonstrated improved knowledge and skills in the e-learning cohorts. The studies had important limitations however, with both being small studies (15 and 17 residents respectively), and the thoraco-abdominal surgical skills

program failing to use a control group for comparisons, with a pre- and post-test study design.[103,107,108]

The literature appears to demonstrate little to no-efficacy of e-learning over traditional learning in medical education, however a number of clinical and research implications of these findings have been identified.[105]

While e-learning alone may not result in improved patient or health professional outcomes, it is recognised that blended learning may play an important role in merging the benefits of e-learning with face-to-face teaching. It is possible that e-learning and traditional learning have very similar effect sizes, and as such demonstrating statistically-significant superiority of one modality over another may require unachievably large sample sizes;[105] despite this, many studies addressing e-learning use small sample sizes,[103,105] and as a result, positive findings for e-learning in specialty areas may represent a Type I statistical error.

Importantly, trial design and outcomes were frequently poorly considered in e-learning research. Vaona et al. suggest that future trials should focus on content, frequency of delivery, duration and intensity of e-learning and cost-effectiveness. They also suggest that studies should use randomised controlled trial designs, and should focus on the effect of e-learning on healthcare professionals' behaviours and patient outcomes rather than knowledge or skills, while also using multiple time points during study follow-up to determine the persistence of e-learning effects. Importantly, future study designs should include pre-defined data scales and reporting rules in order to improve research accountability.[105]

Vaona et al. identified the need for more studies into the role of e-learning in specific medical areas and rare conditions, and specifically identify surgical education as a target area of research;[105] indeed, heterogeneity in skills, educational needs, motivation and taught material may represent a cause for the apparent lack of e-learning effect in pooled data analysis.

E-Learning in Venous Thromboembolism Education

This thesis focuses on the use of e-learning to deliver education regarding venous thromboembolism prophylaxis to undergraduate medical students. We conducted a literature search through PubMed and Scopus, using the terms "e-learning", "online learning", "web-based learning", "e-training", "online training", "web-based training", "venous thromboembolism" and "venous thrombosis". The initial search returned 10 results, which were then reviewed and papers that did not relate to education of healthcare professionals were excluded. This resulted in three papers available for review. The design, conclusions and limitations of these studies are included in Table 5.1. No papers related to the use of online learning for the delivery of VTE education to undergraduate medical students. One paper[109] addressed the use of e-learning to teach physician assistants about venous thromboembolism, one paper[110] addressed the effect of blended learning on pharmacy student performance in a cardiovascular pharmacotherapy course, and one paper evaluated the use of online training for VTE education among surgical residents.[111] The study by Soukoulis et al[109] was excluded from review, as it used an e-learning module that included both prophylaxis and treatment options for VTE management, focused on healthcare

professionals only working in the oncology setting, and was targeted at Physicians Assistants, a clinical role that is not present in Australia.

McLaughlin et al used an online module to didactically deliver 57 slides to students, including a pre- and post-test, prior to attending classes related to VTE prophylaxis, where active learning exercises were used. They demonstrated that students that accessed less of the module performed more poorly in the end of unit examination for questions mapped to content covered by the online module. There was no significant difference in results for questions that were not specifically mapped to the module, as may be expected. Students accessing all of the online module score significantly higher in the post-test, compared with the pre-test (60.9% vs 53.8%, p=0.015), however module post-test scores were not significantly correlated with final examination performance. The majority of students (62%) found the use of pre-class material useful.[110] The study is limited, however, insofar as it does not contain any control groups, and students were not randomised to receive the new online module or baseline instruction.

Wolpin et al[111] published a paper in 2011 describing a test-retest study of the efficacy of an online training module for VTE prophylaxis, provided to 69 residents and fellows from two medical centers.[111] The participants were provided access to an online learning module regarding VTE prevention, and the authors tested two hypotheses; first, that use of an online learning module would improve knowledge mastery, and secondly, that use of question/response case studies after review of static slides containing VTE prevention information would result in improved post-test scores compared with participants that were only exposed to static slides.

A pre- and post-test study design was used to evaluate the first hypothesis, with individual participants serving as their own controls. There was no separately defined control group used for comparison. The mean pre-test score for participants was 79.28%. Participants then accessed the online module (with randomisation at that time to either the enhanced learning or usual learning groups) and completed a post-test at the end of the module. The mean post-test score was 82.32%. Analysis of these results using a two-tailed paired t test (alpha set to 0.05) revealed no significant difference in pre- and post-test scores (t=-1.655, p=0.102), with a small standardized mean difference effect size of 0.23. [111]

The authors reported that they then re-analysed this data using non-parametric methods (which may have been more appropriate, given a sample size of n=69, although specific methods were not described). Rates of knowledge mastery (score ≥80%) were measured for the study cohort at pre-test (47%) and post-test (57%), representing a 14.5% improvement in knowledge mastery (p=0.05).[111]

The second hypothesis was tested by randomizing participants to either an enhanced learning (use of question/response case studies after review of static slides containing VTE prevention information) group or a usual learning (review of static slides containing VTE prevention information only), and comparing post-test scores between groups. The enhanced learning group had a mean post-test score of 79.39%, while the usual learning group had a mean post-test score of 85%. Analysis of covariance was performed to control for baseline knowledge in each group, and demonstrated no statistically significant difference in scores between the groups.[111]

Wolpin et al. acknowledge the limitations of their study in their article, including the small sample size and small effect size, however they raise important questions regarding the use of venous thromboembolism e-learning. They demonstrated an increase in rates of knowledge mastery among their participants, although the length of time this improvement persisted was not established. Although their study suggests that there is no improvement in knowledge following the use of the module, the study is underpowered to detect this change, and this may represent a type II statistical error; the authors call for further research into this area to be performed.[111]

Study	Design	Conclusion	Limitations
Soukoulis V, Sullivan A. An interactive web-based module to teach physician assistants about venous thromboembolism. *Acta Cardiol*. 2015;70(2):163-168. doi:10.2143/AC.70.2.3073507.[109]	Open, Retrospective Cohort study.	• A brief, interactive web-based module increased knowledge and comfort level with VTE management among Physicians Assistants	• Did not target Physicians (Physcians Assistants only)> • Targeted a subset of a specific PA specialty at one hospital. • Possible that the survey selected for PAs with an inherent interest in web-based learning and/or VTE. • Did not assess long-term outcomes. • Did not have the capability or power to track long-term retention of knowledge or change in clinical behaviour.
McLaughlin JE, Gharkholonarehe N, Khanova J, Deyo ZM, Rodgers JE. The impact of blended learning on student performance in a cardiovascular pharmacotherapy course. *Am J Pharm Educ*. 2015;79(2):24. doi:10.5688/ajpe79224.[110]	Open, Retrospective Cohort study.	• Student engagement with online foundational VTE content provided prior to class is positively related to academic performance and in-class engagement.	• Unblinded, non-randomised design. • Retrospective cohort study; demonstrates correlation but not able to demonstrate causal associations. • Did not measure long-term outcomes. • Did not target Physicians (only Pharmacy Students)
Wolpin S, Lee J-A, Glenny RW, Wittkowsky AK, Wolf FM, Zierler BK. Evaluation of online training on the prevention of venous thromboembolism. *Vasc Endovascular Surg*. 2011;45(2):146-156. doi:10.1177/1538574410391281.[111]	Prospective, Non-blinded, Test-retest, Randomised Controlled study.	• Potential for increasing mastery of VTE prophylaxis concepts. • No additional knowledge gain with the use of additional "question/ response" case studies. • Findings differ from earlier literature demonstrating increased knowledge gains in case-based versus text-based interventions.	• Non-blinded design. • Study limited to Residents and Fellows. • Findings reflect learning at only one point in time. • Paper does not assess long-term outcomes. • Patient outcomes not assessed. • Practice outcomes not assessed. • Pre- and post-test question validity not established.

Table 5.1 Previous Studies of E-Learning in Venous Thromboembolism Education

Summary

E-learning has been readily absorbed into medical education, and is now a key component of many courses, at both the undergraduate and graduate level. While the evidence appears to suggest that e-learning is no better than traditional learning methodologies (although a true non-inferiority study has not been conducted), e-learning brings multiple non-learning based benefits, including flexibility, cost savings and the opportunity for deliberate and distributed practice, that traditional learning cannot provide. To date, there have been few high-quality studies into the role of e-learning in specialty medical areas, and no randomised controlled trials have been conducted assessing the role of e-learning in educating health professionals about VTE prophylaxis.

Chapter 6. Summary of the Literature Review

Venous thromboembolism (VTE) is a multi-factorial disease primarily manifesting as deep venous thrombosis (DVT), and less-frequently as pulmonary embolism (PE). The majority of deep vein thrombosis occurs in the legs, with a smaller percentage occurring in the arms; when it occurs most frequently in patients with cancer or in the presence of a central venous access device.[2]

VTE is common and its annual incidence is consistent across Western Europe, North America, Australia and Argentina, with rates between 0.75 to 2.69 per 1,000 of population. The impact of VTE is felt across the globe, with 3.5 cases hospital associated VTE per 1,000 of population, per annum, in high-income countries, and 1.1 cases per 1,000 of population, per annum, in low- and middle-income countries.[112] VTE is the third most common cardiovascular cause of death, after coronary artery disease and stroke.[2] Hospital-associated VTE remains the leading cause of disability-adjusted life years lost in low- and middle-income countries, and is responsible for more years lost than hospital-acquired pneumonia, central-line associated blood stream infections and adverse drug events.[112]

Venous thromboembolic disease represents a significant economic burden on healthcare systems.[113] Cohoon et al demonstrated that adjusted mean predicted costs are 2.5-times higher for patients with VTE associated with admission for acute illness, and 1.5-times higher for patients admitted for major surgery, than for matched patients, controlled for type of surgery or cancer status, with costs greatest in the first three months after the VTE event date.[113-115] Predicted costs were 1.9-times higher over five years for patients with VTE and active cancer compared to

those with cancer, but no VTE.[113,116] Perversely, adherence to global thromboprophylaxis guideline has decreased over time, primarily due to poor implementation of guidelines post-discharge,[117] and educational interventions to improve thromboprophylaxis management on the ward have had variable and limited success.[111,118]

'E-learning' is a term used to refer to a variety of learning and teaching modalities, including any computer-based delivery of learning material, internet-based delivery of learning materials and the use of virtual learning environments or digital social networks for the purposes of education.[96] Environmental, social, pedagogical and clinical factors have encouraged the acceptance and use of e-learning in medical education as changes in educational venues, distribution of students and residents across healthcare networks, and changes in learning models towards learner-centered, competency-based curricula drive changes in teaching delivery.[92] e-Learning has been demonstrated to promote self-directed learning, provide flexible learning opportunities, and engage learners in collaborative learning communities.[119] While there are many potential benefits to the use of e-learning in medical education, the development of online educational resources can be resource- and time-intensive, costly, and demand a high level of expertise for the initial design of delivery modalities and content.[120] Maertens et al[120] conducted a systematic review of the literature in 2016 demonstrating significant heterogeneity between learning platforms used in surgical e-learning. 87 randomized controlled trials were included in their analysis, with most (71) tools designed to teach cognitive skills, including knowledge or pattern-recognition, or psychomotor skills (36).[120] Other studies focussed on the use of e-learning in non-technical skill acquisition.[120] The authors

demonstrated that most e-learning platforms are effective teaching tools, particularly for cognitive processes, but online learning platforms did not demonstrate superiority over other educational interventions. Only two studies demonstrated transfer of skills to the clinical environment, and there was no evidence that the use of e-learning improved patient outcomes in surgery.[120]

Wolpin et al published a paper in 2011 describing a test-retest study of the efficacy of an online training module for VTE prophylaxis, provided to 69 residents and fellows from two medical centers.[111] They identified a trend for knowledge gains related to VTE guidelines on post-test for clinicians with a 14.5% increase in content mastery ($p=0.05$, 2-tailed). Although effect size was small (0.23), the authors noted an overall improvement in knowledge mastery relating to VTE prophylaxis between pre- and post-tests, but no additional knowledge gain through the use of question/response case studies.[111]

In the late 1990s, an e-learning medical education program, "Medici" was developed at The University of Adelaide.[121] Originally designed for delivery using a CD-ROM, the learning tool translated to the online learning environment in the early 2000s, and was re-branded "eMedici". eMedici is a website providing an open-ended series of case-studies across medical and surgical specialties, primarily aimed at medical students.[122]

The aim of this study was to assess the educational benefit of using an online, case-based learning system to deliver educational material relating to VTE prophylaxis

across medical, surgical and critical care specialties using eMedici, and to attempt to validate the findings described by Wolpin et al.[111]

Section 2. Study Design

Chapter 7. Study Design & Technology

Aims of the studies performed

1. Assess the educational benefit of using an online, case-based learning system to deliver educational material relating to VTE prophylaxis across medical, surgical and critical care specialties using eMedici.

2. Describe the Factors Associated With Test Performance In Venous Thromboembolism E-Learning.

3. Attempt to validate the findings described by Wolpin et al, suggesting that the use e-learning systems may improve knowledge of venous thromboembolism prophylaxis among healthcare professionals.[111]

4. Describe the dynamics involved in the use and apparent benefits of e-learning.

5. Identify and describe the interaction of students with an e-learning system, and the human factors involved during student participation in a structured online learning exercise.

The EMedici Learning System

eMedici is the online iteration of a software package developed in the Department of Medical Education, and now maintained in the Discipline of Surgery, at The University of Adelaide.[123] It is an open-ended series of case studies covering various medical specialties, and presents material to students in the form of case scenarios,

in which the student is then encouraged to manage the case in a realistic way.[122,123] As students progress through the case, feedback is provided on the veracity of the student's choices, encouraging in-situ reflection on clinical decision-making.[122-124]

Students select a case, and is presented with clinical findings, clinical data and pathological specimens in the form of text, photographs, or video images. Students are then asked to choose from a selection of diagnostic, investigation or management options, or are invited to provide a free-text answer to the scenario. After submitting an answer, students are then presented with real-time responses to their answers, and further clinical information, prior to answering a new set of questions. At the completion of the case, a summarising explanation and critique of the problem is provided, and students receive an overall score, matched to criteria for competency in addressing that clinical scenario.[122-124]

Student, instructor and author access to eMedici is via a web portal (http://www.eMedici.com/). Access is controlled via individual or institutional registration.[122]

Cases are created by volunteer authors, who design, write and submit a case to the website. Once prepared, material is assessed in a peer-review process, prior to review at a large group session (including multiple authors and content area specialists). Once final editing occurs, the case is reviewed by the editorial board, and the case is loaded to the website for use in its intended module. As of 2018, there is a range of surgical modules, addressing breast/endocrine surgery, digestive disease, urology, vascular surgery. There are also modules containing case studies in

cardiology, obstetrics & gynaecology, ophthalmology, psychiatry and venous thromboembolism prophylaxis.[122]

Study Methodology

The study was designed as a randomized controlled trial, with an indwelling assessment of human factors affecting the utility of e-learning processes.

Randomized Controlled Trial Methodology

A randomized controlled educational trial was designed and conducted based on methodologies described by Wolpin et al and Farah et al.[111,125] Medical Students in their penultimate year at The University of Adelaide were asked to participate in a randomized controlled educational trial. Students were eligible for participation if they were a fifth-year (penultimate-year) medical student at The University of Adelaide.

Students were excluded if they met any of the following criteria:

1. They refused consent to participate in the study (however, students still had access to the educational material).
2. They were currently enrolled in their obstetrics & gynaecology/paediatric medicine semester (due to the specific and high-volume workload of this semester, and associated end-of-rotation assessments).

The online module was made available across 4 semesters, over two years. Students had to complete the module within a single semester.

After consenting to participate in the study students were randomized to one of two groups (control vs. intervention) (Figures 7.1 & 7.2). A simple randomisation algorithm was incorporated into the eMedici program, and automatically allocated students to intervention or control groups, in a process that was blind to the investigators. 94 students were ineligible for inclusion in the study as they declined to participate. No other students were excluded from the study.

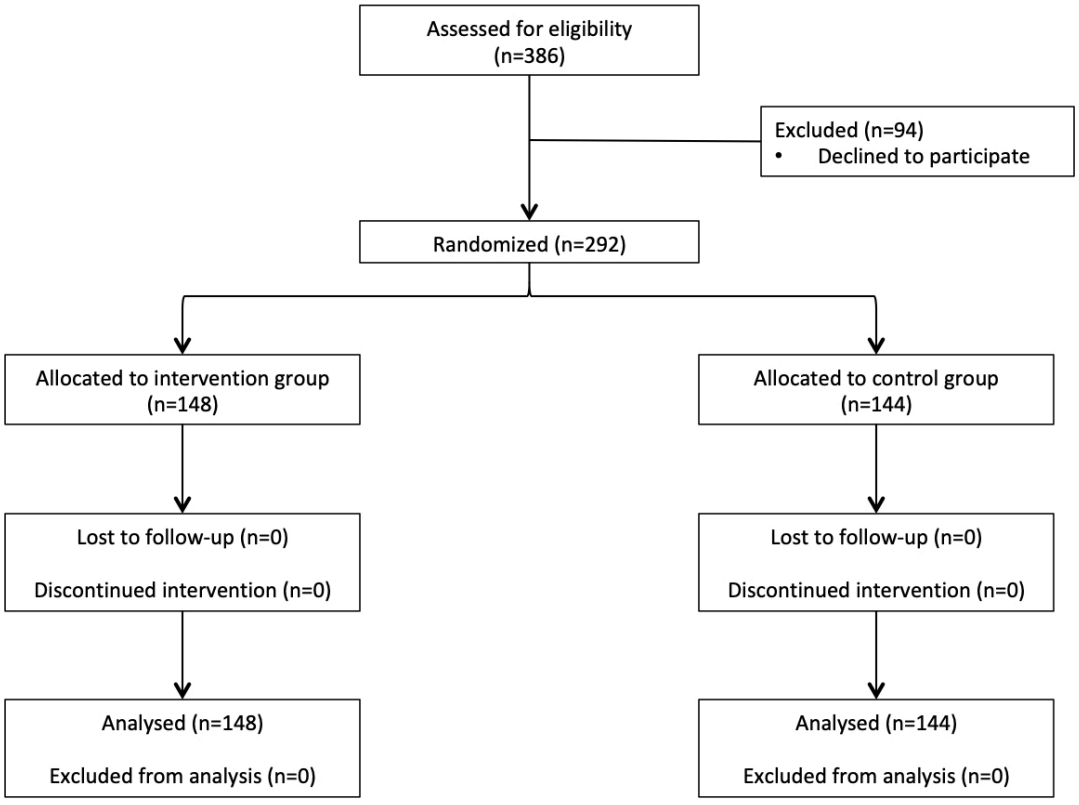

Figure 7.1 CONSORT Diagram.

Recruitment and allocation of subjects to control and intervention groups

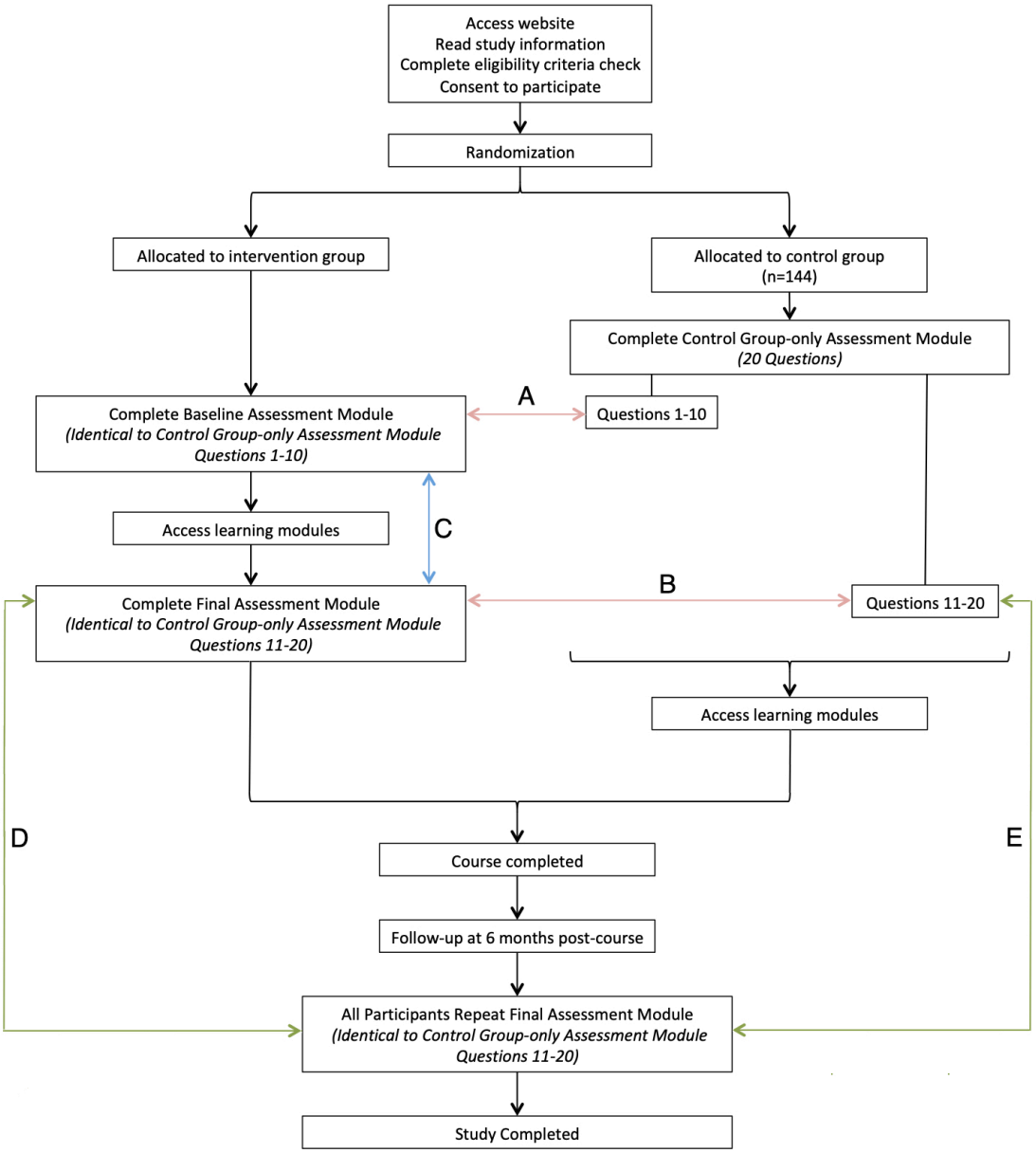

Figure 7.2 Graphic representation of trial process for students randomised to control and intervention groups.

A, Comparison of scores between groups (Control Group-only Assessment Module Questions 1-10 vs the ten-question Intervention Group Baseline Assessment Module. The questions used to establish baseline knowledge are identical between the two groups. B, Comparison of scores between groups (Control Grouponly Assessment Module Questions 11-20 vs the ten-question Intervention Group Final Assessment Module. The questions are identical between the two groups. C, Comparison of scores between Intervention Group Final Assessment Module and Intervention Group Baseline Assessment Module. D & E, Comparison of scores from six-month follow up with Intervention Group Final Assessment Module, to assess persistence of knowledge post-online learning program

The control group undertook an initial baseline-assessment case of twenty questions, assessing their knowledge surrounding VTE prophylaxis across the specialties of Oncology, Surgery, General Medicine, Obstetrics & Gynaecology, and Orthopaedics. They were then given access to the online educational modules.

The intervention group undertook a baseline assessment case composed of ten questions assessing their knowledge surrounding VTE prophylaxis across the specialties of Oncology, Surgery, General Medicine, Obstetrics & Gynaecology, and Orthopaedics. These were identical to Questions 1-10 completed by the control group. There was no difference in complexity or difficulty of questions between the groups. The questions across the assessment and teaching cases appeared to have good internal consistency, Cronbach's $\alpha = 0.74$.

The intervention group were then given access to six case-based modules teaching the fundamentals of VTE prophylaxis in Oncology, Surgery, General Medicine, Obstetrics & Gynaecology, and Orthopaedics, according to national[37] and international[38] guidelines. Following completion of these modules, students completed a 10 question post-test, matched to questions 11-20 completed as a baseline assessment by the control group.

Six months after completion of the course, all students were followed-up and asked to complete the 10 post-test questions/control group questions 11-20 again. The study was then completed.

'No Intervention'-Controlled Study Design

The choice of control condition for randomised controlled trials in educational research is a source of dispute in the medical education literature, with a number of concerns being raised regarding the use of placebo, or 'no intervention' controls, including concerns that this methodology may be unethical, impractical, unnecessary (in that it is better to compare interventions to usual practice), and may represent an attempt to generate invalid universal laws of cause and effect that do not hold true in the teaching setting. [126,127]

While it has been demonstrated that this methodology has a place in the educational research setting, [127-130] it is important to justify this choice of study design.

The choice of no-intervention for the control condition was partly guided by ethical restrictions on this study, and by logistical requirements. The ethical approval for this study required that all students ultimately have access to identical learning resources (see below). As a result, comparing the use of an e-learning module to 'usual practice' (e.g. a lecture or tutorial) would have required physical separation of the student cohort, and repeats of multiple teaching interventions, necessitating checks that students were not exposed to the incorrect intervention (e-learning module vs. tutorial) at the incorrect time. This would have necessitated either the recruitment and training of additional educators who were not part of the research team (which was prohibitively expensive), or breaking allocation blinding (which would have breached the ethics requirements for this study).

A no-intervention control condition was also felt to be appropriate as the control group would ultimately have access to the learning material, after completion of the final assessment questions. As a result, a placebo-controlled design would help minimise the potential for the Hawthorne Effect, as students would not know that they had been part of the control or intervention group until they had completed all of the assessment questions, and the associated module. [129]

Finally, the purpose of this study was to determine the efficacy of e-learning techniques in providing education relating to venous thromboembolism prophylaxis. Previous studies in this area were retrospective cohort studies[109,110] or a single, unblinded, randomized controlled trial that compared two methods of online teaching. [111] As a result there was no evidence to date that e-learning demonstrated any educational benefit in teaching venous thromboembolism prophylaxis.

Given this gap in the medical education literature, the ethical and logistical complexities associated with a study comparing e-learning to 'usual practice', and evidence that such studies could be safely and ethically conducted in medical education, this project was subsequently conducted using a 'no-intervention' control group design.

Human Factors Analysis Methodology

Descriptive data surrounding the usability of the eMedici module was collected on completion of the VTE module.

A questionnaire was developed based on a modification of the student reaction questionnaire proposed by Pike and Huddleston [131]. Students were asked to complete the questionnaire on completion of the eMedici module. The questionnaire covered the domains of administration and support, access, usage, technical performance, general usability, student expectations, content and instructional design and testing and assessment. At the end of the questionnaire students were asked to provide an overall rating for the course. Data was collected through a combination of Likert scales and drop-down options.

Five-point Likert scales were used for the majority of questions, with a score of one representing total disagreement with the questions, and a score of five representing strong agreement. Where no answer was provided a score of zero was allocated, and that result was excluded from analysis. Three questions relating to location of study, module completion and formal assessment of the information contained within the module used drop-down text options.

Ethics of Data Anonymization and Effect of Data Analysis

Students have special requirements for protection when participating in education research; Christakis noted "Students might be subject to inappropriate and undue pressure and might participate in studies in an attempt to garner better recommendations, better grades, or other favors (such as summer employment). The rules for medical students are more stringent … because a medical student is less free than a random adult to refuse the request of a faculty investigator to be a research subject." [132] Students are considered to be "People in dependent or unequal relationships" in the National Statement on Ethical Conduct in Human

Research, [133] and this document requires researchers to "…take special care to safeguard confidentiality of all information they receive, particularly in settings such as shared workplaces, hospital rooms or rooms in residential care." Medical students represent a special cohort as participants in education research, as they are prone to over-research and are exposed to increased risk of privacy breaches when involved in research projects. Protection of privacy is more important as medical students progress through their training as cohorts generally become smaller and professional stakes increase. Boileau et al note that extra care should be taken to protect medical student privacy when involved in educational research. They note that "an essential part of safeguarding participants' privacy relies on being very selective in determining what data will even be collected. The only personal information that should be gathered is that which is directly relevant to answering the research question." [134] Boileau et al recommend the anonymization or deidentification of data when conducting educational research, where anonymization (the irrevocable removal of all direct (e.g. name) and indirect (e.g. age) identifiers) is preferred, as it carries the least risk of re-identification. [134]

These factors were considered essential to the safe, ethical conduct of this research, and in preparing the ethics application multiple conversations were had with the University of Adelaide Office of Research Ethics regarding protection of medical student privacy.

In addition to the protection of student privacy, and protection against discrimination and coercion, the ethics committee required that all students ultimately had access to the same educational material regardless of allocation to

intervention or control group so as to prevent the intervention group receiving potentially-beneficial additional teaching compared to controls, which may have then conferred an additional advantage in later course examination requirements. As a result, the educational material would also have to be available to both groups in parallel, i.e. educational material could not be withheld from the control group until completion of the study, as this would disadvantage students in the first year of the two-year data collection window.

As a result of this study design, and the need for the use of anonymised data, students followed up at six months could not be identified by their previous allocation to intervention or control group.

Statistical Analysis Plan

All analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Statistical analysis was provided by a qualified statistician from The University of Adelaide, Adelaide Health Technology Assessment Data, Design and Statistics Service.

Randomized Controlled Trial Statistical Plan

Group comparisons were conducted using linear regression, linear mixed-effects models and Student's *t*-tests for normally distributed data. Descriptive results are reported as frequencies (%), means (standard deviations) or medians [interquartile ranges]. Inferential statistics are presented with estimates, 95% confidence intervals and P values. For linear mixed-effects models (used for comparison of scores

between baseline questions and final-assessment questions in the intervention group, or questions 1-10 vs 11-20 for the control group), assumptions of a linear model were upheld. A mixed effects model was used as scores within student would be more similar, more correlated, than scores between students, leading to erroneous standard errors and P values if not controlled for.

We also explored a novel variable, the improvement score (described by Khatib et al[135]), equivalent to the post-intervention score minus the pre-intervention score. For the control group this is reported as the score for questions 11-20 minus the score for questions 1-10, and for the intervention group the score for final-assessment questions minus the score for baseline questions.

Based on the study by Wolpin et al,[111] we calculated a requisite sample size of 200-270 participants, based on a minimum-anticipated score improvement of 14.5% (p=0.05).

A planned *a priori* subgroup analysis was undertaken on completion of the randomized controlled trial, in order to assess the effects of results from each case on the overall performance of the module.

Human Factors Analysis Statistical Plan

All forms assessing human factors relating to the module were de-identified and then reviewed by the lead author. Descriptive statistics were used for presentation and analysis of ordinal data [136]. Independent associations between categorical data were explored by the chi-square test, with statistical significance set at a p value of ≤ 0.05.

Funding for the Study

This research was funded by a $12,500 education grant from Covidien (now part of Medtronic). The company had no input into the design, conduct, analysis, presentation or publication of this research.

Chapter 8. Venous Thromboembolism e-Learning Cases

This chapter presents the case material for the eMedici module delivered to students. Case numbers relate to the index number for the cases in the eMedici learning system.

Case 28: Baseline Assessment Questions

Question 1:
Question Information:

This section provides 20 multiple-choice questions to assess your current knowledge of VTE prophylaxis in different situations. Prior to completing this VTE Prophylaxis Module, and the pre-test questions, we would like to ask you to consent to participate in a study on the use of an online learning system (eMedici) to deliver a module on venous thromboembolism (VTE) prophylaxis to medical, nursing and allied health professionals and trainees, with a view to improving outcomes in hospital-admitted patients and reducing the incidence and prevalence of VTE.

Data gathered from this study will allow us to determine the potential efficacy of using online educational software to improve knowledge of VTE prophylaxis methods in healthcare professionals, and potentially to improve application of this knowledge in the clinical environment. Results from this study will appear in Dr. Eamon Raith's Doctor of Philosophy (Surgery) thesis and in peer-reviewed medical journals.

This study has been approved by The University of Adelaide Human Research Ethics Committee and by The University of Notre Dame Australia Human Research Ethics Committee.

Participants may withdraw from the study at any time without prejudice to their future involvement in educational activities, or adverse impact on their medical education or training. Should participants wish, they may request the raw data, related to their cases, on completion of the study. All information provided by

participants (project enrolment information, survey results) will remain confidential and can only be accessed by the three investigators on this study.

Please note that once the Module is completed, withdrawal from the study component of the module is not possible, as results will have been de-identified.

Should any problems with the study arise, please do not hesitate to contact any member of the research team via the contact information below. Alternatively, you may contact the University of Adelaide using the independent complaints sheet (attached). Alternatively, if participants have any complaint regarding the manner in which a research project is conducted, it should be directed to the Executive Officer of the Human Research Ethics Committee, Research Office, The University of Notre Dame Australia, PO Box 1225 Freemantle WA 6959, phone (08) 9433 0943, research@nd.edu.au.

All investigators can be contacted through; Discipline of Surgery, School of Medicine, University of Adelaide [redacted] Prof P. Devitt - [redacted]

Dr. Eamon Raith - [redacted]

Question:
Consent to participate in the assessment of an online module on VTE Prophylaxis education.

Choice 1: I consent to involvement in the study Score : 1

Choice 2: I do not consent to involvement in the study Score : 0

Question 2:
Question Information:

As part of the research component of this module, we need to ascertain your level of training in 2013.

Question:
In 2013 I will be working at the level of...

Choice 1: A final year medical student in an undergraduate medical program
Score : 1

Choice 2: A final-year medical student in a graduate medical program
Score : 1

Choice 3: Intern
Score : 1

Choice 4: PGY-2 General Trainee
Score : 1

Choice 5: PGY-3 General Trainee
Score : 1

Choice 6: PGY-4 General Trainee
Score : 1

Choice 7: Service Registrar
Score : 1

Choice 8: Specialty-Training Scheme Registrar
Score : 1

Choice 9: Consultant
Score : 1

Question 3:
Question Information:

A 57-year-old woman has recently been diagnosed with a T2, N1, M0, oestrogen-receptor negative, carcinoma of her right breast and is being assessed for adjuvant therapy. Prior to her presentation with a lump in her breast three weeks ago she had been in good health. She noticed the lump shortly after returning from a holiday in Bali. Until her surgery for the breast lump she had been on hormone replacement therapy. She suffered a deep venous thrombosis after breaking a leg in an accident several years ago. She has two adult children. Her BMI is 29. Some thoughts are given to reducing the risk of venous thromboembolism during any subsequent treatment.

Question:
Which one of the following is the most important risk factor to take in account?

Choice 1: Her BMI
Score : 0
Choice Feedback: Incorrect

Choice 2: The recent long-distance travel
Score : 0
Choice Feedback: Incorrect

Choice 3: Planned radiotherapy
Score : 0
Choice Feedback: Incorrect

Choice 4: Her history of DVT
Score : 1
Choice Feedback: Correct

Choice 5: Her HRT
Score : 0
Choice Feedback: Incorrect

Question 4:
Question Information:

A 59-year-old man is admitted to hospital for chemotherapy of a locally advanced carcinoma of the stomach. Two weeks ago he recovered from an episode of left leg cellulitis for which he was bed-bound for three days. Three years ago he had a myocardial infarction from which he made a good recovery. His BMI is 29. He is considered for some form of prophylaxis against venous thromboembolism. It is anticipated he will be in hospital for about one week and go home with an intravenous infusion of cytotoxics.

Question:
Which one of the following would be the most appropriate form of prophylaxis against venous thromboembolism?

Choice 1: Graded compression stockings for the duration of the admission
Score : 0
Choice Feedback: Incorrect

Choice 2: Enoxaparin for the duration of the admission
Score : 0
Choice Feedback: Incorrect

Choice 3: Heparin infusion for the duration of the admission
Score : 0
Choice Feedback: Incorrect

Choice 4: Enoxaparin until cessation of the intravenous infusion
Score : 1
Choice Feedback: Correct

Choice 5: Warfarin until cessation of the intravenous infusion
Score : 0
Choice Feedback: Incorrect

Question 5:
Question Information:

A 20-year-old man is brought to the Emergency Department with an injured right leg. He was tackled heavily during a football match and was unable to get up because of the pain in his leg. An X-ray shows an uncomplicated fracture of the tibia. A backslab applied and the patient subsequently reviewed in the fracture clinic. A fibre-glass cast is applied and the patient is told that he will need to remain in the cast for up to six weeks.

Question:
Which one of the following is the most appropriate choice of VTE prophylaxis?

Choice 1: Low-molecular weight heparin for the duration of immobilisation
Score : 1
Choice Feedback: Correct

Choice 2: Dabigatran etexilate for the duration of immobilisation
Score : 0
Choice Feedback: Incorrect

Choice 3: Rivaroxaban for the duration of immobilisation
Score : 0
Choice Feedback: Incorrect

Choice 4: Fondaparinux for the duration of immobilisation
Score : 0
Choice Feedback: Incorrect

Choice 5: No pharmacological VTE prophylaxis is required
Score : 0
Choice Feedback: Incorrect

Question 6:
Question Information:

A 78-year-old man is brought to the Emergency Department following a farming accident. Examination reveals a patient in severe pain, with a below-knee traumatic amputation of the left leg. He is tachycardic, with a weak, thready carotid pulse and blood pressure of 70/40mmHg. His pressure improves to 90mmHg systolic following two 250ml boluses of 0.9% sodium chloride.

Question:
Which one of the following is the correct approach to VTE prophylaxis?

Choice 1: Commence Dabigatran etexilate once adequate haemostasis has been achieved.
Score : 0
Choice Feedback: Incorrect

Choice 2: Commence low-molecular weight heparin once adequate haemostasis has been achieved.
Score : 1
Choice Feedback: Correct

Choice 3: Commence fondaparinux once adequate haemostasis has been achieved
Score : 0
Choice Feedback: Incorrect

Choice 4: Commence use of calf-compression stockings only.
Score : 0
Choice Feedback: Incorrect

Choice 5: No VTE prophylaxis is required
Score : 0
Choice Feedback: Incorrect

Question 7:
Question Information:

Pregnancy and the puerperium increase the risk of venous thromboembolism.

Question:
During which one of the following stages is the risk greatest?

Choice 1: First Trimester
Score : 0
Choice Feedback: Incorrect

Choice 2: Second Trimester
Score : 0
Choice Feedback: Incorrect

Choice 3: Third Trimester
Score : 0
Choice Feedback: Incorrect

Choice 4: During Childbirth
Score : 0
Choice Feedback: Incorrect

Choice 5: The puerperium
Score : 1
Choice Feedback: Correct

Question 8:
Question Information:

A 62-year-old man is admitted to hospital for management of an acute lobar pneumonia. He saturates at 89% on room air and has a respiratory rate of 24/min. His temperature is 39.2oC, blood pressure 130/92 mmHg and a heart rate of 96/min. Despite some improvement with oxygen administered at 6L/min by Hudson mask and initiation of intravenous antibiotics, he is only able to mobilise from the bed to the toilet a couple of times per day. His biochemistry results shows a creatinine level of 50umol/L. He weighs 94kg.

Question:
Which one of the following is the most appropriate choice of VTE prophylaxis?

Choice 1: Enoxaparin 40mg BD
Score : 0
Choice Feedback: Incorrect

Choice 2: Enoxaparin 40mg Daily
Score : 1
Choice Feedback: Correct

Choice 3: Fondaparinux 2.5mg daily
Score : 0
Choice Feedback: Incorrect

Choice 4: Aspirin 100mg daily
Score : 0
Choice Feedback: Incorrect

Choice 5: Danaparoid 3000Units loading dose, followed by graduated infusion
Score : 0
Choice Feedback: Incorrect

Question 9:
Question Information:

An 82-year-old woman is admitted to hospital with 36 hours of left-sided weakness, slurred speech and left facial droop. A CT scan does not demonstrate any evidence of intracranial haemorrhage. She is admitted to the stroke unit for further management. Her blood pressure is stable at 136/87 mmHg, pulse is 78/min. She has a medical history of a DVT successfully treated with enoxaparin 12 years ago following a flight from Los Angeles. At a follow up appointment 3 weeks after the diagnosis of her DVT her general practitioner noted a mild anaemia and low platelets. She also has a history of asthma, and mild hypertension, adequately controlled with a beta-blocker. Her GFR is >60ml/kg/hr and her weight is 78kg.

Question:
Which one of the following is the most appropriate choice of VTE prophylaxis?

Choice 1: Graduated calf compression stockings
Score : 0
Choice Feedback: Incorrect

Choice 2: Enoxaparin, 80mg daily
Score : 0
Choice Feedback: Incorrect

Choice 3: Enoxaparin, 40mg BD
Score : 0
Choice Feedback: Incorrect

Choice 4: Danaparoid 3000Units loading dose, followed by graduated infusion
Score : 1
Choice Feedback: Correct

Choice 5: Fondaparinux, 2.5mg daily
Score : 0
Choice Feedback: Incorrect

Question 10:
Question Information:

An otherwise fit 45-year-old man is admitted for a laparoscopic fundoplication for chronic gastro-oesophageal reflux disease. Apart from a deep venous thrombosis after a leg injury in his teens, he is in good health. Mechanical calf compression devices will be used during surgery and other means of venous thromboprophylaxis must be considered.

Question:
Which one of the following is the most appropriate management?

Choice 1: No other prophylaxis required
Score : 0
Choice Feedback: Incorrect

Choice 2: Enoxaparin given immediately before surgery and continued until discharge
Score : 0
Choice Feedback: Incorrect

Choice 3: Enoxaparin given immediately after surgery and continued until discharge
Score : 0
Choice Feedback: Incorrect

Choice 4: Enoxaparin given immediately after surgery and continued for 10 days
Score : 1
Choice Feedback: Correct

Choice 5: Insertion of a caval filter
Score : 0
Choice Feedback: Incorrect

Question 11:
Question Information:

A 54-year-old man with severe dysphagia due to achalasia is booked for a laparoscopic cardiomyotomy. The patient is barely able to manage liquids and is rapidly losing weight. One month prior to the planned procedure he has a deep venous thrombosis in his right after a week in bed recovering from a chest infection brought on as the result of recurrent oesophageal regurgitation and aspiration. He has been started on warfarin.

Question:
Which one of the following is the most appropriate plan of management?

Choice 1: Continue warfarin and proceed to surgery
Score : 0
Choice Feedback: Incorrect

Choice 2: Continue warfarin and delay surgery for three months
Score : 0
Choice Feedback: Incorrect

Choice 3: Stop warfarin, start intravenous heparin and proceed to surgery
Score : 0
Choice Feedback: Incorrect

Choice 4: Stop warfarin, insert caval filter and proceed to surgery
Score : 1
Choice Feedback: Correct

Choice 5: Stop warfarin, give fresh frozen plasma and proceed to surgery
Score : 0
Choice Feedback: Incorrect

Question 12:
Question Information:

A 66-year-old man with type II diabetes is hospitalised for treatment of recently diagnosed acute myeloid leukaemia. Three years ago he had a myocardial infarction, with insertion of two stents. He is on dual antiplatelet therapy. Chemotherapy is started and five days later he collapses with severe chest pain. He is pale and sweating with a blood pressure of 80/60 mmHg. Myocardial infarction is excluded on the ECG and serum troponin. A CT pulmonary angiogram is performed, and demonstrates the presence of a pulmonary embolism. Treatment with a thrombolytic is considered.

Question:
Which one of the following would be the strongest indication for such an approach?

Choice 1: The radiological findings
Score : 0
Choice Feedback: Incorrect

Choice 2: The presence of diabetes
Score : 0
Choice Feedback: Incorrect

Choice 3: The blood pressure
Score : 1
Choice Feedback: Correct

Choice 4: The history of myocardial infarction
Score : 0
Choice Feedback: Incorrect

Choice 5: The dual antiplatelet therapy
Score : 0
Choice Feedback: Incorrect

Question 13:
Question Information:

A 59-year-old man is admitted to hospital for chemotherapy of a locally advanced carcinoma of the stomach. Two weeks ago he recovered from an episode of left leg cellulitis for which he was bed-bound for three days. Three years ago he had a myocardial infarction from which he made a good recovery. His BMI is 29. He is considered for some form of prophylaxis against venous thromboembolism.

Question:
Which one of the following would place him at greatest risk of such a complication.

Choice 1: The underlying malignancy
Score : 1
Choice Feedback: Correct

Choice 2: The myocardial infarction
Score : 0
Choice Feedback: Incorrect

Choice 3: His weight
Score : 0
Choice Feedback: Incorrect

Choice 4: The recent episode of cellulitis
Score : 0
Choice Feedback: Incorrect

Choice 5: The period of immobility
Score : 0
Choice Feedback: Incorrect

Question 14:
Question Information:

A 68-year-old woman is admitted to hospital with a three day history vomiting. She had recently been started on chemotherapy for inoperable carcinoma of the pancreas. Two weeks ago a biliary stent had been inserted to relieve her jaundice. This procedure had been complicated by a bleed from sphincterotomy site. She has been taking diclofenac for pain relief. The patient is cachectic and dehydrated. Her serum biochemistry demonstrates a markefly elevated creatinine and urea. Her LFTs are grossly deranged. The patient is given intravenous fluids to correct her dehydration. Some consideration is given to measures to be taken to reduce her risk of venous thromboembolism.

Question:
Which one of the following regimens would be most appropriate?

Choice 1: Warfarin
Score : 0
Choice Feedback: Incorrect

Choice 2: Enoxaparin
Score : 0
Choice Feedback: Incorrect

Choice 3: Dabigatran etexilate
Score : 0
Choice Feedback: Incorrect

Choice 4: Graduated calf compression stockings
Score : 1
Choice Feedback: Correct

Choice 5: Unfractionated heparin
Score : 0
Choice Feedback: Incorrect

Question 15:
Question Information:

A 28 year old man is brought to the Emergency Department following a motor vehicle accident at a low speed. He was the unrestrained passenger in the vehicle, striking his legs against the dashboard during the collision. Primary and secondary surveys reveal a stable patient with a shortened and externally rotated right leg. A FAST scan does not show any free intra-peritoneal or peri-cardial fluid. The chest X-ray does not show any evidence of a pneumothorax or rib fractures, and a CT of the brain shows no signs of acute intracranial pathology. The patient remains haemodynamically stable on transfer to the orthopaedic surgery unit.

Question:
Which of the following is the most appropriate choice of pharmacological prophylaxis?

Choice 1: Low molecular weight heparin
Score : 0
Choice Feedback: Incorrect

Choice 2: Fondaparinux
Score : 1
Choice Feedback: Correct

Choice 3: Rivaroxaban
Score : 0
Choice Feedback: Incorrect

Choice 4: Dabigatran etexilate
Score : 0
Choice Feedback: Incorrect

Choice 5: Aspirin
Score : 0
Choice Feedback: Incorrect

Question 16:
Question Information:

A 73-year-old man is retrieved from a rural property following an accident on his ride-on lawnmower. He was trapped, face-down, beneath the vehicle for 2 hours prior to extrication. He was stabilised at the scene and retrieved to the nearest major trauma centre. On examination he has a severe crush injury of the left hand, multiple rib fractures, and fluid in Morrison's pouch. The patient is supported in a pelvic brace. His blood pressure is 83/54 mmHg despite 2 litres of 0.9% NaCl. He is scheduled for emergency surgery.

Question:
Which one of the following is the most appropriate approach to post-operative VTE prophylaxis?

Choice 1: Commence fondaparinux once adequate haemostasis has been achieved
Score : 0
Choice Feedback: Incorrect

Choice 2: Commence use of calf-compression stockings only
Score : 0
Choice Feedback: Incorrect

Choice 3: No VTE prophylaxis is required
Score : 0
Choice Feedback: Incorrect

Choice 4: Commence low-molecular weight heparin once adequate haemostasis has been achieved.
Score : 1
Choice Feedback: Correct

Choice 5: Commence Dabigatran etexilate once adequate haemostasis has been achieved.
Score : 0
Choice Feedback: Incorrect

Question 17:
Question Information:

A 30-year-old woman who is G2P1 presents at 37 weeks gestation with a two day history of pain and swelling in her right calf. She has also noticed some breathless during this time. Her previous pregnancy was uneventful. There is some tenderness and redness of the calf and examination of the chest is unremarkable.

Question:
Which one of the following is the most appropriate initial investigation?

Choice 1: CT Pulmonary Angiogram
Score : 0
Choice Feedback: Incorrect

Choice 2: Ventilation-Perfusion Scan
Score : 1
Choice Feedback: Correct

Choice 3: Chest X-Ray
Score : 0
Choice Feedback: Incorrect

Choice 4: Duplex scan of the lower limbs
Score : 0
Choice Feedback: Incorrect

Choice 5: D-dimer
Score : 0
Choice Feedback: Incorrect

Question 18:
Question Information:

A 40-year-old man is admitted to the medical ward for intravenous antibiotics to manage an uncomplicated cellulitis of his left calf. An ultrasound scan shows no evidence of DVT. He is otherwise healthy and mobilises around the ward; he can often be found outside of the hospital talking to other patients. He is a non-smoker and drinks 1-2 standard drinks per week. He weighs 98kg.

Question:
Which one of the following is the most appropriate choice of VTE prophylaxis?

Choice 1: Graduated calf compression stockings
Score : 0
Choice Feedback: Incorrect

Choice 2: No VTE prophylaxis is required
Score : 1
Choice Feedback: Correct

Choice 3: Aspirin 100mg PO daily
Score : 0
Choice Feedback: Incorrect

Choice 4: Enoxaparin, 100mg daily, subcut
Score : 0
Choice Feedback: Incorrect

Choice 5: Low-dose unfractionated heparin
Score : 0
Choice Feedback: Incorrect

Question 19:
Question Information:

A 73-year-old man is hospitalised with an haemorrhagic stroke, proven on CT scan. As part of the rehabilitation program, consideration must be given to prophylaxis against venous thromboembolism. Immediately prior to the stroke the patient enjoyed an active life, although he had hurt his back recently and had been taking paracetamol immediately prior to his admission. Apart from some right-sided motor weakness in his arm, hand and leg, the physical examination is unremarkable. His serum biochemistry is shown: Haemoglobin 128 g/L (130 - 175) Platelets 130 x 10^9/L (150 - 450)

Question:
Which one of the following regimens would be most appropriate?

Choice 1: Calf compression stockings
Score : 1
Choice Feedback: Correct

Choice 2: Aspirin
Score : 0
Choice Feedback: Incorrect

Choice 3: Enoxaparin
Score : 0
Choice Feedback: Incorrect

Choice 4: Dabigatran
Score : 0
Choice Feedback: Incorrect

Choice 5: Warfarin
Score : 0
Choice Feedback: Incorrect

Question 20:
Question Information:

An otherwise fit 64-year-old man is about to undergo a partial gastrectomy for carcinoma. He will require some measures to minimise the risk of venous thromboembolic complications during his hospitalisation.

Question:
Which one of the following is the most appropriate intervention?

Choice 1: Pneumatic calf compression during surgery only
Score : 0
Choice Feedback: Incorrect

Choice 2: Sequential calf compression stockings until discharge
Score : 0
Choice Feedback: Incorrect

Choice 3: Enoxaparin starting at commencement of surgery until discharge
Score : 0
Choice Feedback: Incorrect

Choice 4: Enoxaparin starting immediately after surgery and given until discharge
Score : 0
Choice Feedback: Incorrect

Choice 5: Enoxaparin given immediately after surgery and continued for 14 days after discharge
Score : 1
Choice Feedback: Correct

Question 21:
Question Information:

A 35-year-old woman is admitted for an elective laparoscopic cholecystectomy, planned as a day case procedure. Apart from an episode of biliary colic two months earlier, she is in good health and there is nothing of note in the past medical history. She is on the oral contraceptive pill. With regard to minimising the risk of venous thrombo-embolic (VTE) complications, graded calf compression stockings will be applied before and during the operation. Measures need to be taken to reduce her risk of a venous thrombo-embolic event

Question:
Which one of the following is the most appropriate management?

Choice 1: Intraoperative pneumatic calf compression and perioperative enoxaparin until mobile
Score : 1
Choice Feedback: Correct

Choice 2: Intraoperative pneumatic calf compression and postoperative enoxaparin for two weeks
Score : 0
Choice Feedback: Incorrect

Choice 3: Intraoperative pneumatic calf compression and postoperative enoxaparin for four weeks
Score : 0
Choice Feedback: Incorrect

Choice 4: No additional measures are required
Score : 0
Choice Feedback: Incorrect

Choice 5: Pneumatic calf compression devices during surgery
Score : 0
Choice Feedback: Incorrect

Question 22:
Question Information:

A 72-year-old man is about to start a course of chemotherapy for a recently diagnosed small cell carcinoma of the lung. Consideration is being given to the most appropriate chemoprophylaxis to reduce his risk of VTE. Apart from his lung cancer the patient does not have any other apparent health issues and is still leading an active life. His pre-chemotherapy laboratory results are reviewed. His Hb was 98g/L, his leucocyte count 12.5x10^9/L and his platelet count was 450x10^9/L.

Question:
Which one of the following regimens would be most appropriate choice of anticoagulant drug?

Choice 1: Warfarin
Score : 0
Choice Feedback: Incorrect

Choice 2: Enoxaparin
Score : 1
Choice Feedback: Correct

Choice 3: Unfractionated heparin
Score : 0
Choice Feedback: Incorrect

Choice 4: Dabigatran
Score : 0
Choice Feedback: Incorrect

Choice 5: Aspirin
Score : 0
Choice Feedback: Incorrect

Synopsis

Thank you for completing the pre-test questions. Good luck with the rest of the module!

Case 441: VTE Prophylaxis in Oncology

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The University of AdelaideThis case study takes the user through some of the issues involved in the assessment and management of thromboprophylaxis in the medical patient. This includes hospital admission and outpatient setting and in particular, for problems associated with neoplastic disease.

Case Overview

Please note that, where available, staff should abide by local venous thromboembolism (VTE) prophylaxis and management policies, as these may take into account local clinical and economic factors that cannot be anticipated by the material in this module.

Learning Objectives

- Identify the patient suffering from neoplastic disease at risk of venous thromboembolic disease
- Assess the risk of venous thromboembolism in the patient suffering from neoplastic disease
- Assess the risk of bleeding in the patient suffering from neoplastic disease that is a candidate for VTE prophylaxis

- Correctly select an appropriate means of VTE prophylaxis for the patient suffering from thrombogenic neoplastic disease
- Understand the epidemiology and pathophysiology of VTE in neoplastic disease

Question 1:
Question Information:

Problems associated with venous thromboembolism are not confined to the surgical patient. Many patients whose primary problem is medical are at increased risk of a venous thromboembolic complication either during their illness, the treatment of the illness or during recovery. One group in which there is significant risk is the patient with cancer. There are some well recognised risks in this group.

Question:

Concerning the risk of VTE, which of the following statements are correct?

Choice 1: Cancer confers a four- to six-fold increased risk compared with age- and sex-matched control groups

Score : 1

Choice Feedback: Correct. Neoplastic disease markedly increases the risk of thrombosis through tumour-based activation of prothrombotic mechanisms, including; - procoagulant, fibrinolytic and proaggregating factors, - tumour-cell-derived pro-inflammatory and pro-angiogenic cytokines and, - direct cell-cell interactions between tumour cells and healthy cells (Refs: 4, 23, 24).

Choice 2: The incidence is the same in cancer and non-cancer patients undergoing similar surgical procedures

Score : -1

Choice Feedback: Incorrect. Patients undergoing surgery while suffering from neoplastic disease have approximately twice the incidence of VTE compared to patients without cancer undergoing the same procedure. This is likely due to the

increased pro-coagulant effects of tumorigenesis, and the physiological haemostatic response to surgical intervention.

Choice 3: Cancer patients with a history of VTE are likely to have recurrent episodes of thromboembolism

Score : 1

Choice Feedback: Correct. Patients suffering with cancer and a history of previous VTE have 2-3 times the rate of VTE recurrence compared with patients without cancer. Indeed there is evidence that the cumulative incidence of recurrent VTE in patients with cancer may be as high as 20.7%, and risk of recurrence appears to be related to cancer severity (Refs: 23, 24).

Choice 4: There is a high incidence of late thrombosis in surgical cancer patients

Score : 1

Choice Feedback: Correct. The @RISTOS study demonstrated that up to 40% of VTE events in cancer patients that had undergone surgery occurred more than 21 days post-operatively (Ref: 1).

Question 2:
Question Information:

Ingrid McCrystal is a 54-year-old woman who is brought to the Emergency Department by her family as she has been unable to cope at home after a recent course of chemotherapy. For the last three days she has had severe nausea and vomiting. She feels very weak and has barely been able to get out of bed and only then to the toilet, with the assistance of her husband. She has recently been diagnosed with Stage 2, oestrogen-receptor positive, adenocarcinoma of the breast. Two weeks ago she completed her initial course of chemotherapy. She has started tamoxifen and has been prescribed metoclopramide and paracetamol by her oncologist.

Unfortunately, these medications have not helped her over the last three days. Apart from her recent diagnosis of breast cancer, Mrs McCrystal does not have any other current medical problems, although she notes that she did need treatment for a deep venous thrombosis in her right leg after a long flight from an overseas holiday when she was in her 30s. She did use the oral contraceptive pill for about ten years. Mrs McCrystal a slender woman who is clearly dehydrated with reduced skin turgor, sunken eyes and dry oral mucosae. The rest of the physical examination is unremarkable. She requires admission for correction of her fluid loss and treatment of her nausea and vomiting. Consideration must also be given to any possible measures that might need to be taken to reduce her risk of venous thromboembolism (VTE).

Question:

Which of the following factors increase her baseline risk of VTE?

Choice 1: Age

Score : 1

Choice Feedback: Correct. The incidence of VTE in cancer patients increases with each decade over the age of 40 years (Ref: 18).

Choice 2: Active cancer

Score : 1

Choice Feedback: Correct. Active cancer increases the risk of VTE 4-6-fold, due to the procoagulant activities of tumour-mediated coagulation factors, cytokines and cell-cell interactions (Refs: 3, 7, 20, 23, 24).

Choice 3: Previous VTE

Score : 1

Choice Feedback: Correct. Cancer patients with a history of prior VTE have 6-7 times the risk of developing a VTE compared to those with no history of VTE (Refs: 3, 28).

Choice 4: Prolonged severe immobility

Score : 1

Choice Feedback: Correct. The patient has been bed-bound for three days, with minimal movement, suggesting that she has been immobile for a prolonged period of time (Ref: 28).

Choice 5: Pregnancy and the puerperium

Score : -1

Choice Feedback: Incorrect. Perhaps correct in other circumstances - but this patient is not pregnant.

Choice 6: Marked obesity

Score : -1

Choice Feedback: Incorrect. Whilst obesity in itself is a risk factor for VTE, the description of this patient being a "slender woman" would suggest her BMI is probably less than 20. There is no existing evidence that she is suffering from obesity.

Choice 7: Active treatment of her cancer

Score : 1

Choice Feedback: Correct. Systemic chemotherapy increases the risk of VTE by 6-7 times. Use of hormonal manipulation therapies significantly increases the risk of VTE, with tamoxifen specifically increasing risk of VTE by 2-5 times. This risk is even higher when selective oestrogen receptor modulators are combined with chemotherapy in post-meopausal women. The use of aromatase inhibitors has been associated with approximately half the risk of SERMs. Other agents, including angiogenesis inhibitors and thalidomide and lenalidomide, all increase risk of VTE, especially when combined with chemotherapy or high-dose dexamethasone (References: 7, 8, 10, 12, 15, 16, 20, 25, 28).

Choice 8: General anaesthesia

Score : -1

Choice Feedback: Incorrect. There is no evidence of the use of anaesthetic in her recent history.

Choice 9: A concurrent, pro-thrombogenic medical condition

Score : -1

Choice Feedback: Incorrect. There is no evidence of acute or acute-on-chronic chest infection, heart failure, AMI, ischaemic stroke or acute inflammatory bowel disease. These conditions, in themselves are risk factors for VTE - but none of them are present in Mrs McCrystal.

Choice 10: The type of malignancy

Score : 1

Choice Feedback: Correct. The type of malignancy is important in the assessment of VTE risk in patients with neoplastic disease. Risk of thromboembolic disease is highest in malignant brain tumours, adenocarcinomas of the lung, ovary, pancreas, colon, stomach, prostate, kidney and haematoligic malignancies (Refs: 6, 20).

Question 3:
Question Information:

Mrs McCrystal has several risk factors for VTE and these include:

- Her age
- The breast cancer
- History of dvt
- The current treatment of her breast cancer with chemotherapy
- Recent immobility

An intravenous line is inserted and an infusion of isotonic saline started. Blood samples are taken for laboratory analysis and Mrs McCrystal is admitted to the ward. Her haemoglobin on admission is 95g/L, with a platelet count of 200x10^9/L and a normal white cell count. Her pre-chemotherapy blood results are available for comparison and show: - Hb 120g/L - Plt 400x10^9/L - WCC: normal. Her biochemistry results correspond with moderate to severe dehydration. The risk that she will develop a thromboembolic complication need to be considered. It should be possible to calculate the risk of development of such a complication over the next six months.

Question:

Discuss how such a risk might be calculated. (*Free text answer option*)

Feedback:

A VTE risk score specific to cancer patients was developed in 2008 by Khorana et al, using 5 clinical and laboratory variables common to all cancer patients, to generate a score that correlates with cumulative risk of developing a VTE over the following 6 month period. Patient Characteristics Risk Score:

- Site of cancer - Very high risk (stomach, pancreas) 2
- High risk (lung, lymphoma, gynaecologic, testes, bladder) 1
- Prechemotherapy platelet count >/=350x10^9/L 1
- Haemoglobin level <100g/L or use of red cell growth factors 1
- Prechemotherapy leucocyte count >11x10^9/L 1 BMI >35 1

This scoring system has been validated twice, once by the original authors and a second time by an independent research team. The score is cumulative, and can be interpreted thus:

- High risk: Score >/= 3 (6.7-7.1% risk)
- Intermediate risk: Score 1-2 (1.8-2.0% risk)
- Low risk: Score 0 (0.3-0.8% risk)

References: 5, 15.

Question 4:
Question Information:

Apart from correction of her dehydration and treatment of the nausea, consideration must be given to risk reduction against venous thromboembolism. The use of VTE prophylaxis must be balanced against the risk of an haemorrhagic event. There are a number of factors which might increase the risk of bleeding in this patient with recently diagnosed carcinoma of the breast.

Question: (*Free text answer option*)

Discuss the factors which increase bleeding risk in patients with neoplastic disease.

Feedback:

Factors increasing bleeding risk that are of specific concern in patients with neoplastic disease include:

- Significant renal impairment (due to decreased clearance of renally-cleared anticoagulants e.g. Warfarin)
- Current active major bleeding (defined as requiring transfusion of at least two units of packed red cells or other blood products within a 24hr period)
- Current chronic, clinically significant, measurable bleeding over 48 hours
- Inherited or acquired bleeding disorders
- Severe platelet dysfunction or thrombocytopaenia (platelets <50,000/ul) (in neoplastic disease, often related to to uraemia or myelodysplasia secondary to disease process or medication effects)
- Recent central nervous system bleeding
- Intracranial or spinal lesion at high risk of bleeding
- Recent major surgical procedure of high bleeding risk

- Concomitant use of medications that may affect clotting
- Neuraxial block or recent lumbar puncture

Patients also remain at risk from the other factors increasing the likelihood of bleeding with pharmacological VTE prophylaxis, however these are not specifically increased in patients with neoplastic disease:

- Active peptic ulcer disease or ulcerative gastrointestinal disease
- Liver failure or prolonged obstructive jaundice
- High risk of falls

Question 5:
Question Information:

Once Mrs McCrystal has been re-hydrated she begins to feel better and her nausea subsides. Plans for VTE risk reduction are discussed with her. It might be practical to considered some form of mechanical prophylaxis.

Question:

Which of the following would contraindicate the use of mechanical prophylaxis?

Choice 1: Any factor preventing correct fitting of stockings

Score : 1

Choice Feedback: Correct. Any ill-fitting of thromboembolic deterrent stockings is likely to result in incorrect pressure graduation across the venous system of the lower leg and would not only be ineffective at preventing DVT, but would increase the risk of thrombosis. Therefore, any factor that prevents the correct fitting of mechanical prophylaxis is a contraindication to its use.

Choice 2: Inflammatory conditions of the leg

Score : 1

Choice Feedback: Correct. Caution must be used in patients with inflammatory conditions of the lower limb and rheumatoid arthritis as these patients may have small vessel disease, and application of graduated compression stockings may result in pressure necrosis.

Choice 3: Severe peripheral arterial disease

Score : 1

Choice Feedback: Correct. The use of graduated compression stockings or intermittent pneumatic compression devices is contraindicated in peripheral artery disease as compression should not be allowed to impede already-compromised arterial flow.

Choice 4: Severe lower limb oedema

Score : 1

Choice Feedback: Correct. The use of compression stockings in severe lower limb oedema is contraindicated as tight bands, particularly in poorly-fitting stockings, can induce ulceration. Similarly, the use of stockings in severe oedema can induce heart failure through rapid return of fluid to the central circulation, and consequent cardiac overload.

Choice 5: Lymphoedema

Score : -1

Choice Feedback: Incorrect. Lymphoedema is a result of either congenital or acquired deficiencies in lymphatic return-flow to the central venous circulation. The use of graduated compression stockings is indicated in the conservative management of lymphoedema.

Choice 6: Diabetic neuropathy

Score : 1

Choice Feedback: Correct. Caution must be used in patients with diabetes mellitus as these patients may have small vessel disease and application of graduated compression stockings may result in pressure necrosis.

Question 6:
Question Information:

Mrs McCrystal has some arthritic changes in her ankles and it is decided that mechanical measures might not be an appropriate form of VTE prophylaxis.

Question: (*Free text answer option*)

Discuss what forms of thromboprophylaxis would be appropriate

Feedback:

Ms McCrystal is a patient suffering from carcinoma of the breast, undergoing hormonal anti-neoplastic therapy. Based on her clinical history and current clinical status, she can be assessed as being at intermediate risk using the Khorana Risk Assessment tool for VTE in patients with cancer. The patient is relatively immobile and is recovering from dehydration and a recent acute illness. She is unlkely to mobilise rapidly and some form of chemoprophylaxis would be appropriate. She has contraindications to the use of pharmacological prophylaxis, although given her low platelet count, the use of pharmacological prophylaxis should be reviewed frequently throughout her admission. Current evidence supports the use of either low-molecular weight heparin or unfractionated heparin as appropriate pharmacological VTE prophylaxis, however there is currently no definitive evidence to support the use of one drug over the other. In the absence of definitive evidence supporting one pharmacological agent over another, it would be appropriate to use either the drug recommended by local policy guidelines and protocols, or in the absence of such guidelines, low-molecular weight heparin, due to its ease of dosing and administration. (References: 5, 13, 17, 19, 22.)

Question 7:
Question Information:

Whilst the indications for some form of mechanical or chemical prophylaxis have been reasonably well defined and validated for cancer patients with recognised risk factors, the place of VTE prophylaxis is not so clear for the ambulatory patient in a routine clinical setting.

Question:

With regard to the ambulatory patient receiving chemotherapy, which of the following statements are generally considered correct?

Choice 1: Pharmacoprophylaxis will not reduce the risk of central venous catheter-associated thrombosis

Score : 1

Choice Feedback: Correct. Whilst some form of VTE-related complication occurs in about 4% of cancer patients who have an indwelling venous access line, there is no good evidence that any form of pharmacoprophylaxis will prevent this complication (Ref 30). Current international guidelines do not recommend thromboprophylaxis for this group of patients.

Choice 2: The risk of bleeding with chemoprophylaxis would outweigh any risk reduction of VTE

Score : -1

Choice Feedback: Incorrect. The overall benefits on the use of chemoprophylaxis in medical in-patients with cancer and in particular, the low molecular weight heparins,

is not clear. Whilst the benefits in the overall medical in-patient populations have been shown in terms of reduction of risk of VTE, this must be balanced against the risk of bleeding. A 1% risk of a major bleeding event in patients treated with low molecular weight heparins has been reported.

Choice 3: Enoxaparin is not associated with increased bleeding risks when used to treat advanced pancreatic cancer

Score : 1

Choice Feedback: Correct. A prospective evaluation of enoxaparin in patients receiving chemotherapy for advanced carcinoma of the pancreas found that this low molecular weight heparin was safe in terms that there was no increased incidence of major bleeding events. The patients were treated with agents known to be associated with an increased risk of VTE, such as cisplatin and no increased rates of severe bleeding events were noted (Ref: 27).

Choice 4: Chemoprophylaxis will reduce the incidence of VTE in high risk cancers

Score : 1

Choice Feedback: Correct. A report in the Lancet 2009 showed that the use of a low molecular weight heparin would reduce the incidence of VTE-related problems in patients with high and very high risk categories of cancer patients. The risk of a bleeding bleeding event was low and consistent with the use of these heparins in other, similar settings (Ref: 2).

Currently there are no international guidelines recommending the routine use of thromboprophylaxis in the ambulatory setting for cancer patients.

Synopsis

Epidemiology of VTE

Cancer confers a four- to six-fold increased risk of thrombosis compared with age- and sex-matched control groups, with patients undergoing surgery on a background of neoplastic disease having approximately twice the overall risk of developing a venous thromboembolism, and a 40% risk of a late (>21 days) post-operative VTE event. Cancer also confers a marked risk of recurrence of VTE, with oncology patients having a VTE recurrence rate of 2-3 times that of patients with no history of cancer. Risk of venous thromboembolism is also significantly increased by the therapies for cancer, including hormonal, chemo- , and radio-therapy. Newer anti-neoplastic agents, including anti-angiogenic and cytokine therapies similarly increase the risk of VTE.

Pathophysiology of VTE in Cancer

Fibrin and normal coagulation compounds have been found to be important factors in tumour adhesion and metastasis, with the presence of thrombotic plugs at sites of tumour growth suggesting a significant role in tumour growth and metastasis. The pro-thrombotic mechanisms of tumours can essentially be separated into general pro-thrombotic mechanisms (i.e. those that occur as part of a normal response to disease) and tumour-specific mechanisms (i.e. those that occur directly as a result of suffering from neoplastic disease). General pro-thrombotic mechanisms in neoplastic disease represent the host response to cancer, and consist of generic mechanistic responses to disease including the acute phase response, production of paraproteins,

inflammation, necrosis and haemodynamic disturbance, each of which serve to induce a pro-coagulant state.

Patients with cancer have been shown to have markedly elevated levels of Factors V, VIII, IX and XI and significantly increased markers of coagulation activation (eg. D-Dimers, FDP etc). In association with this increased generalised response to neoplasia, tumours themselves exert a considerable thrombogenic effect through their use of coagulation triggers, factors and mechanisms to perpetuate their own growth and survival. This occurs through cellular production of procoagulant, fibrinolytic and pro-aggregating factor production (Tissue factor, IL-1B, TNFa, VEGF, urokinase-type and tissue-type plasminogen activators, plasminogen-activator inhibitors 1 and 2 and plasminogen-activator receptor, ADP, and thrombin); release of pro-inflammatory and pro-angiogenic cytokines; and direct interaction with blood and vascular cells (endothelium, erythrocytes, leucocytes, platelets) through the function of adhesion molecules.

Risk Assessment

Admission Criteria. In line with the assessment of baseline VTE risk for all patients presenting to hospital for admission, the reason for the admission of Oncology patients should be reviewed in order to determine if they warrant VTE prophylaxis for any of the following high-risk procedures or injuries:

- Abdomino-pelvic, thoracic or orthopaedic surgery
- Major joint surgery and curative surgery for cancer
- Leg injury requiring surgery or prolonged immobilisation

- Prolonged surgery and/or prolonged immobilisation

Risk Assessment - Assessment of patient and condition-based risk factors

Oncology patients must be assessed for the full range of VTE risk factors as outlined in the NHMRC Summary Prevention of Venous Thromboembolism (VTE) in Patients Admitted to Australian Hospitals: Guideline Summary", however specific questioning must be directed towards cancer-specific risk factors, including:

- Previous VTE
- Active cancer
- Age (>40)
- Presence of:
- Malignant brain tumours
- Adenocarcinomas of the lung, ovary, pancreas, colon, stomach, prostate, kidney;
- Haemtaologic malignancies
- Use of non-surgical therapies for cancer including: Chemotherapy, Hormonal manipulation, Angiogenesis inhibitors, Thalidomide and Lenalidomide
- Presence of a CVC (particularly left-sided CVCs)
- Chest radiotherapy

The Khorana Risk Assessment score is a useful, clinically-validated method of assessing VTE risk specific to cancer patients.

Risk Assessment - Assess the risk of bleeding or contraindications to pharmacological prophylaxis. Assess the patient for:

- Significant renal impairment
- Current active major bleeding (at least 2 units RBC or other products/24hr)
- Current chronic, clinically significant, measurable bleeding over 48 hours - Inherited or acquired bleeding disorders
- Severe platelet dysfunction or thrombocytopaenia (Plts <50,000/ul; Severe platelet dysfunction; Uraemia; Medications; Myelodysplasia)
- Recent CNS bleeding
- Intracranial or spinal lesion
- Recent major surgical procedure of high bleeding risk
- Active PUD or ulcerative gastrointestinal disease
- Liver failure or prolonged obstructive jaundice
- Concomitant use of medications that may affect clotting
- Neuraxial block or recent lumbar puncture
- Intracranial or spinal lesion at high risk of bleeding
- High risk of falls

Risk Assessment - Assess the patient for any contraindications to mechanical prophylaxis. Patients should be assessed for:

- Any factor preventing correct fitting of stockings - Inflammatory conditions of the lower leg - Severe peripheral arterial disease - Diabetic neuropathy
- Severe lower limb oedema
- Severe lower limb deformity or inability to correctly fit stockings

- Peripheral arterial disease or arterial ulcers.

Selection of appropriate thromboprophylaxis in VTE patients

In patients with cancer undergoing abdominal surgery, evidence shows a similar efficacy for both LMWH and UFH with no difference in the incidence of side effects (haemorrhage, haematoma formation or need for transfusion) with studies showing that a four-week post-operative course of prophylaxis further reduces late VTE events.

In patients undergoing neurosurgery for cancer, evidence shows that neither LMWH or UFH are associated with serious haemorrhage and are more effective at preventing VTE that mechanical prophylaxis alone. Studies have shown that, while patients with glioma have a high incidence of delayed VTE, extended post-operative VTE prophylaxis is associated with a high risk of post-discharge bleeding, and is not recommended.

Patients with head and neck cancer experience a higher risk of VTE compared to patients undergoing maxillo-facial surgery for non-neoplastic disease, however they appear to remain relatively low-risk overall. Given the importance of haemostasis and vascular patency to the success of maxillo-facial procedures, staff should consider other VTE risk factors in assessing the role thromboprophylaxis in these patients.

In non-surgical cancer patients, evidence suggests that the use of LMWH VTE prophylaxis in inpatients results in a 50-70% reduction in VTE events. Consequently, the recommended practice is to commence inpatient medical oncology patients in LMWH or UFH at admission, and continuing until discharge. Current guidelines recommend the use of graduated compression stockings as mechanical prophylaxis in surgical and non-surgical oncology patients with contraindications to pharmacological thromboprophylaxis.

Management of established VTE in Oncology Patients

Current international guidelines recommend that patients with active cancer and confirmed proximal DVT or PE, be commenced on LMWH and continue the LMWH for 6 months. At 6 months the patient should be reviewed and the risks and benefits of continuing anticoagulation assessed. Similarly, international guidelines recommend that all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer are offered the following investigations for malignancy:

- History and targeted physical
- Chest X-ray
- Blood tests (CBE, Serum Ca2+, LFTs,)
- Urinalysis

Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients >40y/o who present with a first unprovoked DVT or PE and who do not have signs or symptoms of cancer on initial investigation.

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The recommended guidelines for this topic are:

- Prevention of Venous Thromboembolism (VTE) in Patients Admitted to Australian Hospitals: Guideline Summary. National Health and Medical Research Council. Clinical practice guideline for the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals. Melbourne: National Health and Medical Research Council; 2009.
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Case 768: VTE Prophylaxis in Surgical Patients

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Case Overview

This case study looks at some of the issues surrounding risk-management of venous thromboembolism (VTE) in surgical patients. The vignette starts with the presentation of a patient with an acute surgical problem and then focuses on measures that need to be considered to reduce the risk of VTE. The case is a real one - where the names and precise circumstances have been changed.

Learning Objectives

- An understanding of the risk factors associated with venous thromboembolism (VTE)
- A knowledge of the interventions required to reduce the risk of VTE

Question 1:
Question Information:

Mrs Jurinac is a 57-year-old woman who presents to the Emergency Department with a six hour history of severe upper abdominal pain radiating around to the back. She feels nauseated and wants to vomit but is unable to do so. She has difficulty giving this history and is acutely distressed. She is pale and sweating, with a blood pressure of 110/70 mmHg, pulse rate of 120/min and temperature of 37.4C. Her trachea is midline and breath sounds are clear on the left side but are reduced towards the right base. The percussion note has increased resonance at the right base. An intravenous line is inserted and blood samples collected for baseline biochemical investigations. A chest X-ray is performed (Images 1 - 2).

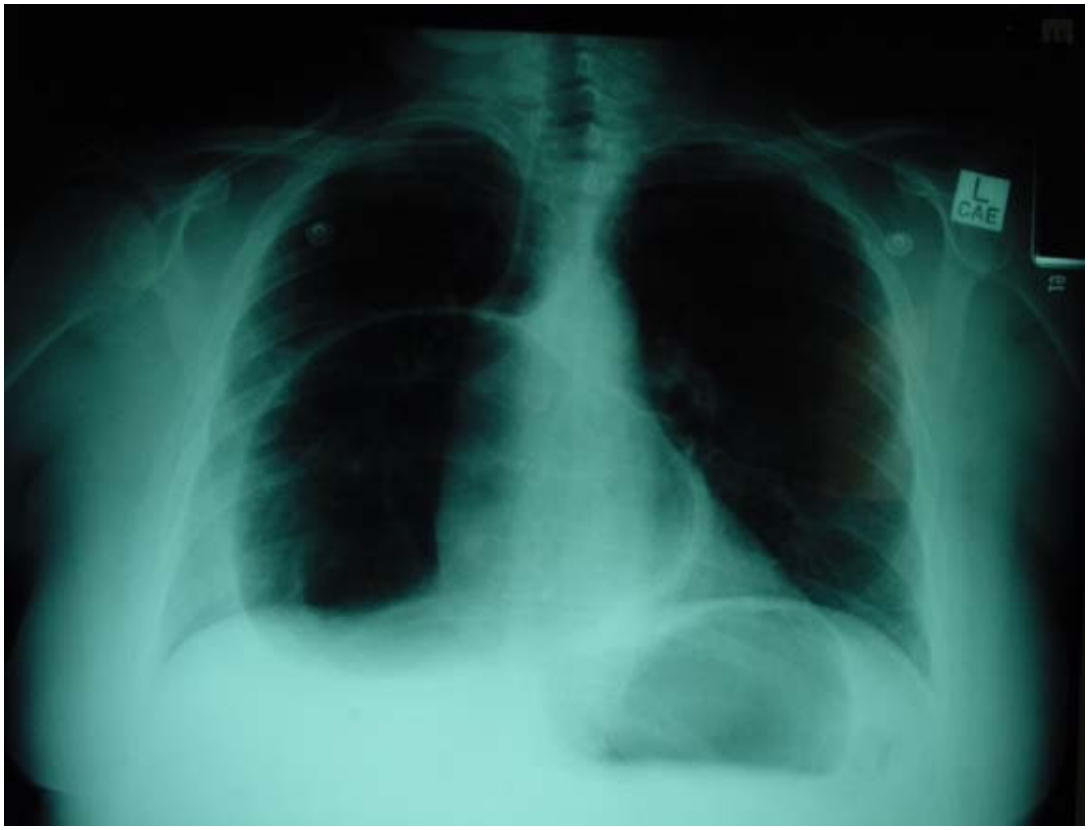


Image 1

Image 2 Not Available

Question:

Which one of the following is the most appropriate next step in management?

Choice 1: Chest tube and underwater-seal drain

Score : 0

Choice Feedback: Incorrect. The chest X-ray shows a large air-filled gastric bubble in the right chest.

Choice 2: Tube thoracostomy

Score : 0

Choice Feedback: Incorrect. This air-filled sac in the chest certainly needs decompression - but it would be achieved more effectively through the passage of a nasogastric tube.

Choice 3: Passage of a nasogastric tube

Score : 3

Choice Feedback: Correct. This is the classical appearance of a gastric volvulus. The stomach has volved around its long axis (organoaxial volvulus) with the proximal stomach above and hiatal defect and situated in the right chest, with the distal stomach visible below the diaphragem.

Choice 4: CT scan chest

Score : 0

Choice Feedback: Incorrect. There is already sufficient information to establish a diagnosis and institute a plan of management.

Choice 5: Electrocardiogram

Score : 0

Choice Feedback: Incorrect. There is little to suggest an acute cardiac event.

Question 2:
Question Information:

A nasogastric tube is passed and a large quantity of air is released, giving Mrs Jurinac immediate symptomatic relief. This is followed by a litre of blood-stained gastric contents. Mrs Jurinac is now able to give a history and says that she has known for a long time about her hiatus hernia, but it has never given her much bother. She had a chest X-ray performed about two years earlier (Images 1, 2) when she had developed chest pain after a blood clot had developed in her right leg. Duplex ultrasonography at that time confirmed the presence of a DVT and a CT pulmonary angiogram did not show any evidence of pulmonary embolus. Three years before that she had pneumonia and a chest X-ray then had shown the hernia. (Images 3, 4)

The condition of the patient has now improved considerably. Her abdominal pain has settled and she now longer feels nauseated. Her blood pressure is 124/80 mmHg and her pulse rate 90/min. Her abdomen is soft to palpation.

Image 1, Image 2, and Image 3 not available

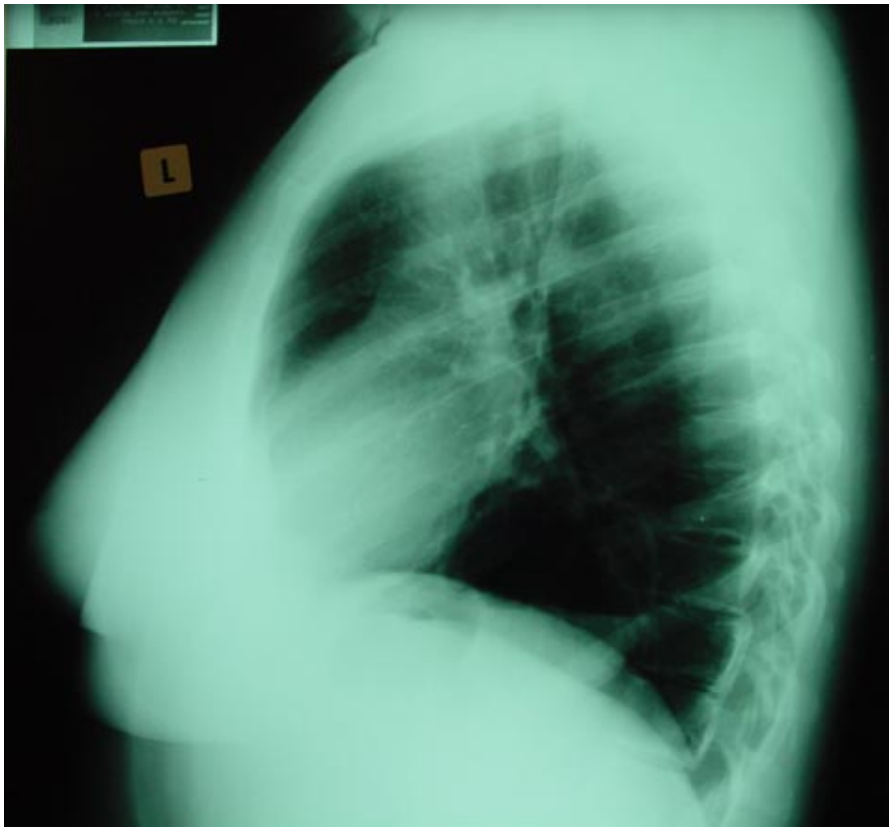


Image 4

Question:

Which one of the following is the most appropriate plan of management?

Choice 1: Discharge home with urgent surgical appointment

Score : 0

Choice Feedback: Incorrect. Whilst the intrathoracic component of the para-oesophageal hernia has been decompressed, more information is required on whether the obstruction has been relieved.

Choice 2: Barium meal

Score : 3

Choice Feedback: Correct. More information is required about her upper digestive tract. She still may be obstructed and it would be helpful to delineate the anatomy of the stomach as surgery will almost certainly be required.

Choice 3: Endoscopy

Score : 0

Choice Feedback: Incorrect. This will not give as much useful information about the anatomy of the upper digestive tract and any possible site of obstruction as a contrast study.

Choice 4: CT scan chest and abdomen

Score : 0

Choice Feedback: Possibly correct. A conventional contrast study will probably yield more useful information about the anatomy of the upper digestive tract and any possible site of obstruction.

Choice 5: Admit for gut rest

Score : 0

Choice Feedback: Incorrect.

Admit certainly, but this patient is going to require more than simple gut rest.

Question 3:
Question Information:

Arrangements are made to admit Mrs Jurinac to a surgical bed and a contrast study is performed (Images 1 - 3). This shows a coiled nasogastric tube in the proximal component of the chest. There is complete obstruction with no contrast flowing into the distal stomach. The site of obstruction is at the oesophageal hiatus. Arrangements are made for prompt surgical intervention. An assessment must be made of the risk factors for postoperative complications including venous thromboembolism. Different measures will be required according to her risk category. The risk categorisation will take into account:

- The individual risk factors of the patient
- The planned procedure

Guidelines exist to define high and low risk patients (2). (See References in the Synopsis section)

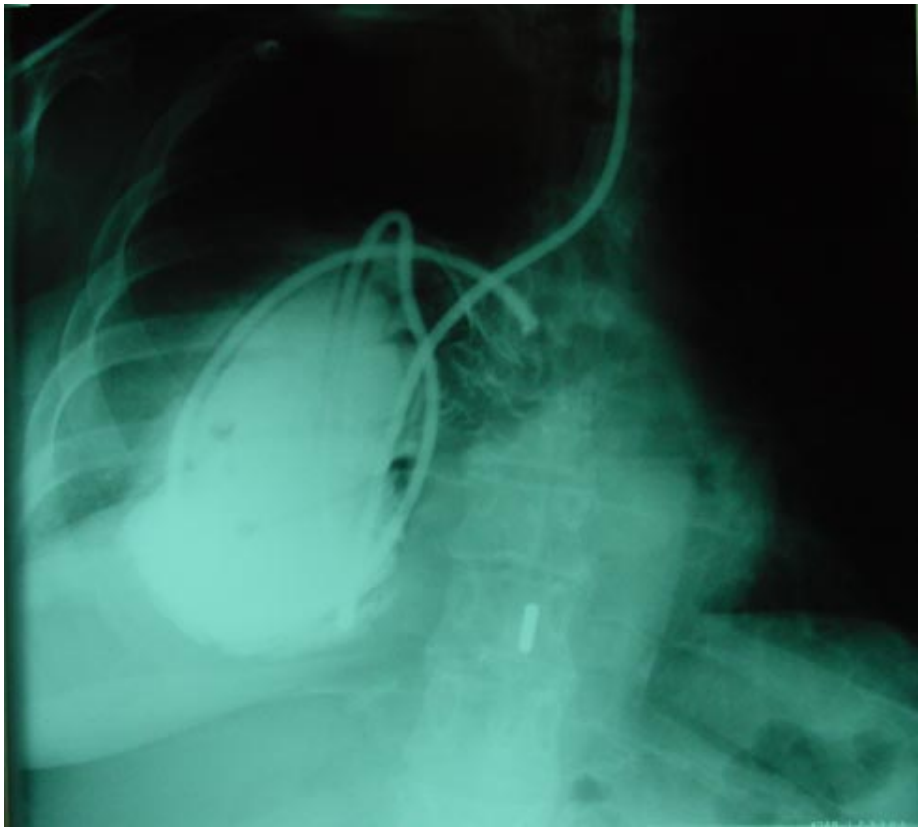


Image 1

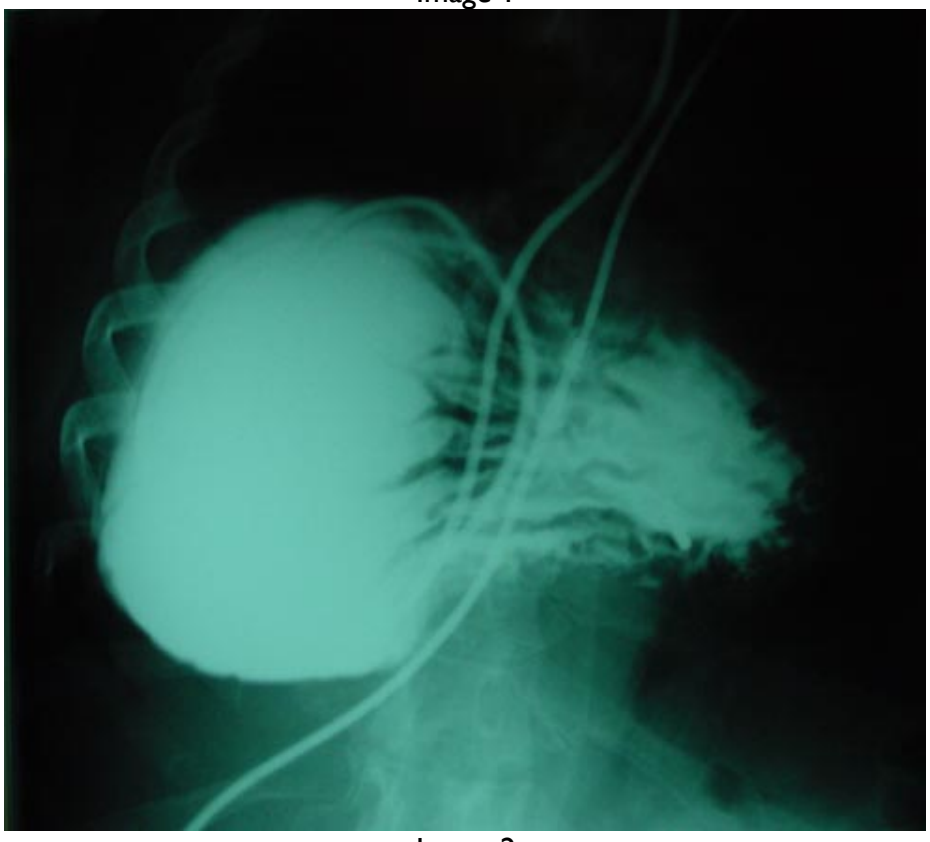


Image 2

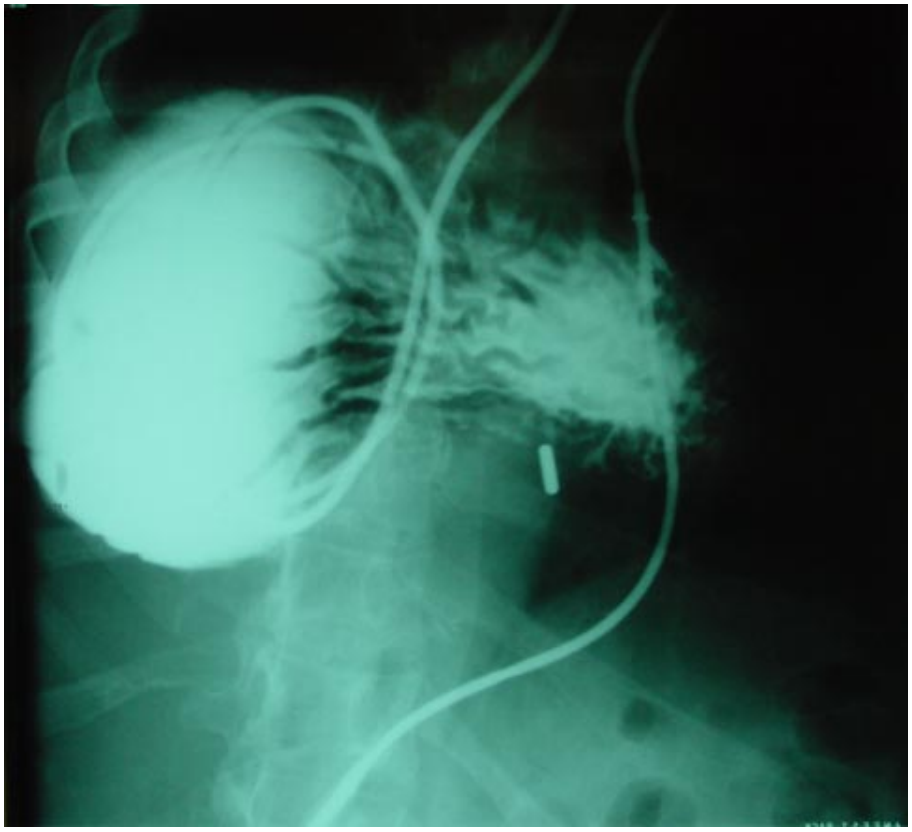


Image 3

Question:

Which of the following procedures would be classified as high risk?

Choice 1: Total knee replacement

Score : 1

Choice Feedback: Correct. Many forms of orthopaedic surgery are considered major risk for VTE. Some form of thromboprophylaxis must be used for patients undergoing total knee replacement. See the case study on orthopaedic surgery for more details.

Choice 2: Partial gastrectomy for carcinoma

Score : 1

Choice Feedback: Correct. It has been estimated that one third of patients undergoing surgery for malignancy will have venographic evidence of deep venous thrombosis (2). Abdominal surgery for any malignant process is defined as high risk for VTE and some form of thromboprophylaxis must be employed.

Choice 3: Laparoscopic cholecystectomy in a 25-year-old woman

Score : -1

Choice Feedback: Incorrect. In an otherwise fit and healthy person with no risk factors for VTE, a laparoscopic cholecystectomy would be considered a low risk procedure. Most of these procedures take less than 45 minutes to perform.

Choice 4: Laparoscopic fundoplication in a 30-year-old

Score : 0

Choice Feedback: Partially correct. According to international guidelines (6) a high risk procedure is one where there is major surgery in any patient aged over 40 years. Major surgery is defined as any form of intra-abdominal surgery or any operation of greater than 45 minutes duration. Many laparoscopic surgeons would probably not agree with this categorisation as most of these patients are relatively fit and are home within two days of the procedure.

Choice 5: Inguinal hernia repair in a 25-year-old man with a BMI of 32

Score : 1

Choice Feedback: Correct. Whilst inguinal hernia surgery might be considered a minor risk in terms of VTE occurrence, a BMI greater than 30 increases the risk substantially. In such circumstances the patient would be categorised as high risk.

Choice 6: Laparoscopic appendicectomy in a 20-year-old

Score : -1

Choice Feedback: Incorrect. Whilst this is obviously an abdominal procedure, in most instances it is a relatively minor one and can be classified as low risk. Most laparoscopic abdominal procedures where there is rapid recovery could be classified as low risk.

Choice 7: Laparoscopic appendicectomy in a 25-year-old with Crohn's disease

Score : 1

Choice Feedback: Correct. Inflammatory bowel disease is associated with an increased risk for first-time VTE. Unprovoked episodes of recurrent VTE in these patients is about 30% within five years of the initial episode. When considering long-

term anticoagulation in this group of patients, the risks of recurrent VTE must be balanced against the risks of haemorrhage (7).

Question 4 :
Question Information:

Mrs Jurinac's planned procedure is categorised as high risk. She is booked for a laparoscopic reduction and repair of her obstructed para-oesophageal hernia - which has volved. In addition to the type of procedure, there may be other factors that put her at increased risk of VTE.

Question:

Which of the following are accepted risk factors for VTE?

Choice 1: Morbid obesity

Score : 1

Choice Feedback: Correct. Obesity (BMI greater than 30) and its heavier cousin, morbid obesity (BMI greater than 40), is an important risk factor to take into account when looking at an individual's fitness for surgery.

Choice 2: Age greater than 60

Score : 1

Choice Feedback: Correct. Patients aged 60 and over undergoing a surgical procedure have their age as an individual risk factor for VTE.

Choice 3: Diabetes mellitus

Score : -1

Choice Feedback: Incorrect. Diabetes is not considered an individual risk factor for VTE.

Choice 4: History of deep venous thrombosis

Score : 1

Choice Feedback: Correct. This is an important individual risk factor for VTE.

Choice 5: Ulcerative colitis

Score : 1

Choice Feedback: Correct. Any patient with inflammatory bowel disease who is planned for any type of surgical intervention is at increased risk of VTE. A study published in the Archives of Surgery reported a significant increase in the incidence of DVT and pulmonary embolus in patients with inflammatory bowel disease undergoing surgery compared with patients without inflammatory bowel disease undergoing similar procedures (5).

Choice 6: Prolonged immobility two months prior to planned procedure

Score : -1

Choice Feedback: Incorrect. Any prolonged immobility within four weeks of the planned procedure would be considered an increased risk factor for VTE - but that risk diminishes as the time of immobility increases between the two events.

Choice 7: Hormone replacement therapy (HRT)

Score : 1

Choice Feedback: Correct. The risk of VTE is increased in patients taking HRT, particularly in the first year of treatment. A systemic review showed that HRT was

an independent risk factor (3). Similar risks exist for woman taking the oral contraceptive pill.

Choice 8: Cholangitis

Score : 0

Choice Feedback: Cholangitis per se is not a risk factor - but severe sepsis is an independent risk factor for VTE. What defines severe sepsis might be difficult to describe, but any patient who is hospitalised with a septic problem should probably be considered at increased risk for VTE.

Question 5:
Question Information:

Mrs Jurinac is at increased risk of VTE. She is about to undergo major abdominal surgery - although from a patient's viewpoint the procedure is often relatively minor as it can usually be undertaken laparoscopically and will only require two or three days in hospital before discharge home. Some measures must be taken to reduce the risk of VTE. It is standard practice for this type of surgery for patients to wearing sequential compression devices and have intermittent calf compression devices applied for the duration of the procedure.

Dependent venous pooling is real issue in these patients for two reasons. First, the raised intra-adbominal pressure of a laparoscopic procedure will hamper venous return and second, a considerable amount (up to 45 degrees from the horizontal) of reverse Trendelburg tilt is use to help access under the diaphragm. (Image) Used by themselves elastic graded compression stockings will reduce the postoperative incidence of DVT by up to 60% and when used in combination with pneumatic compression devices or low molecular weight heparin can reduce the incidence of such complications by up to 85% (3). These mechanical devices are not without their own problems.

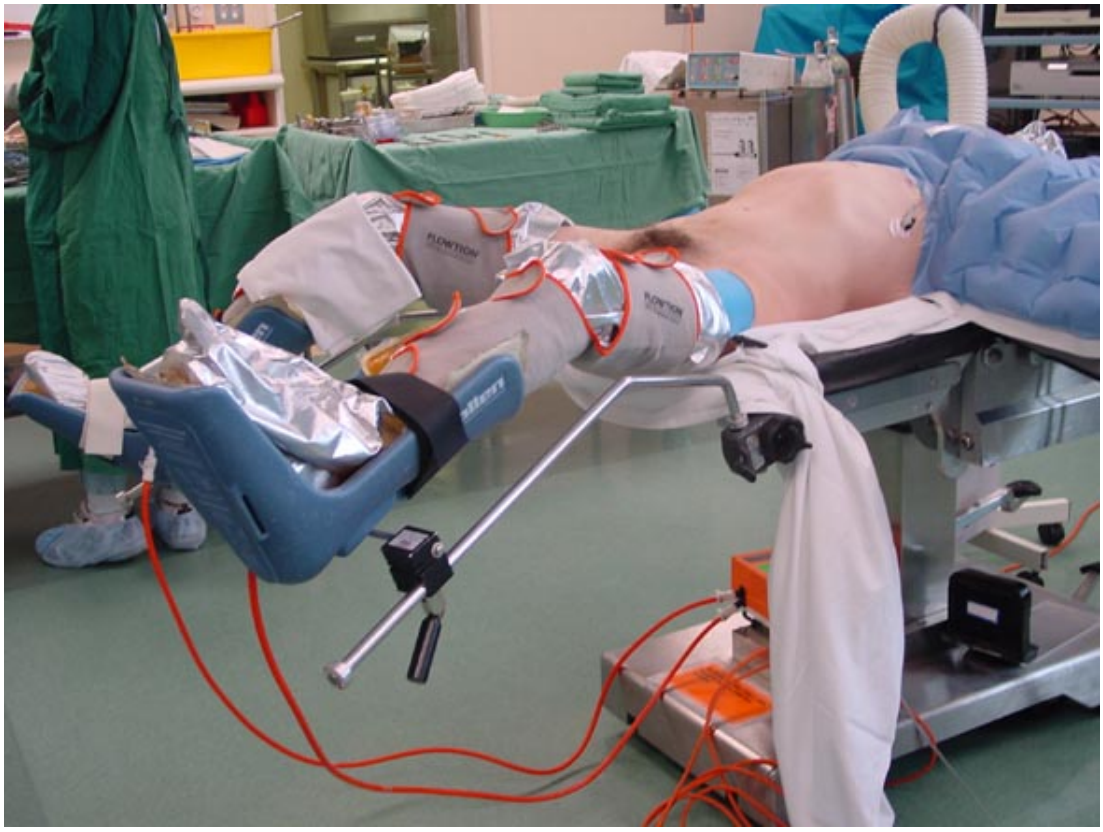


Image 1

Question:

Which of the following are contraindications to the use of mechanical compression devices?

Choice 1: Suspected presence of a DVT

Score : 1

Choice Feedback: Correct. If the patient is thought to have a DVT, then use of a compression device would increase the risk of dislodgement of that clot.

Choice 2: Intermittent claudication

Score : 1

Choice Feedback: Essentially correct. Mechanical compression devices must be used judiciously in patients with severe peripheral vascular insufficiency. Perhaps the

presence of intermittent claudication per se is not a contra-indication, but such symptoms must alert the clinician to the possibility of precipitating serious occlusion if such devices are used.

Choice 3: Varicose veins

Score : -1

Choice Feedback: Incorrect. The risk of VTE can be increased with varicose veins and these patients should have some sort of mechanical compression device applied during any surgical procedure.

Choice 4: Dependent oedema

Score : 1

Choice Feedback: Correct. Depending on the severity of the oedema, any decisions on the use of mechanical compression devices must be carefully thought through. Calf compression could potentially worsen any pre-existing oedema.

Choice 5: Recent skin graft

Score : 1

Choice Feedback: Correct. Any recent surgery to a lower limb would pose potential problems for mechanical compression devices, such as direct trauma to the operative site or impaired wound healing through reduced (albeit temporary) blood supply to that site.

Choice 6: Severe leg deformity

Score : 1

Choice Feedback: Correct. Any prolonged pressure over an area of acute angulation could risk tissue damage through pressure necrosis.

Choice 7: Lower limb psoriasis

Score : 0

Choice Feedback: Yes and no. Use of a pressure device would depend on the extent and severity of any underlying skin problem. A small patch of psoriasis would be of little consequence, but a large area of severe dermatitis might be aggravated with the use of a mechanical compression device.

Question 6:
Question Information:

Mrs Jurinac does not have any contraindications for the use of mechanical compression devices and arrangements are made for graded compression stockings to be fitting prior to surgery. In addition, pharmacological thromboprophylaxis should be considered. On the assumption that some form of thromboprophylaxis will be used in the immediate post-operative period (i.e. while the patient is still in hospital), it might be appropriate to consider continuing this pharmacoprophylaxis after discharge.

Question:

In addition to a prophylactic regimen in the immediate postoperative period, which of the following regimens would be appropriate for discharge?

Choice 1: Low molecular weight heparin for four weeks after discharge

Score : -1

Choice Feedback: Incorrect. It is now becoming standard practice to prescribe post-discharge pharmacological thromboprophylaxis for high risk groups of patients. This is done on the realisation that many patients remain relatively immobile and bed-bound for some time after discharge from hospital. Such patients include those undergoing hip or knee arthroplasty and it is recommended that these patients are maintained on some form of chemoprophylaxis for 28-35 days after surgery (ANZ Working Party). Mrs Jurinac has undergone major surgery - but a procedure with an expected rapid recovery to normal mobility - and has a history of DVT and is thus categorised as high risk. Some form of prophylaxis would be appropriate for the

postoperative period and a nominal period of a low molecular weight heparin for 14 days after discharge from hospital is recommended.

Choice 2: Enoxaparin started several hours after surgery and continued for 10 days

Score : 1

Choice Feedback: Correct. Use of a low molecular weight heparin would be appropriate and this should be continued for 10 days after the time of surgery. In other words, the chemical thromboprophylaxis must be continued for a period of time during convalescence at home.

Choice 3: Dabigatran for four weeks post surgery

Score : -1

Choice Feedback:

Incorrect. Even if it was decided to use a direct thrombin inhibitor rather than a low molecular weight heparin, the patient would not require its administration for more than two weeks.

Choice 4: Dalteparin for one week after discharge

Score : 1

Choice Feedback: Correct. This regimen would probably be appropriate. Assuming that the surgery can be done laparoscopically, the patient will spent a further two or three days in hospital and will required a total of about ten days of pharmological thromboprophylaxis.

Choice 5: Fondaparinux for one week after discharge

Score : 1

Choice Feedback: Correct. This regimen probably could be used, although this synthetic pentasaccharide Factor Xa inhibitor tends to be favoured for thromboprophylaxis in orthopaedic patients where the risks of VTE are greater and the patients tend to be given longer courses of preventative treatment. This longer time frame would theoretically increase the risk of heparin-induced thrombocytopaenia, thus making an agent such as fondoparinux a safer form of prophylaxis.

Question 7:
Question Information:

The timing of commencement will be influenced by certain factors such as the use of epidural or spinal anaesthesia. There are no guidelines for the timing of administration of pharmacological thromboprophylaxis with regard to the insertion or removal of epidural catheters. However, it is common practice to delay the use of anticoagulants for at least 12 hours after the insertion of the catheter. In certain circumstances the use of pharmacological thromboprophylaxis may not be appropriate and other solutions must be sought, such as insertion of a caval filter (Images 1 - 3). With respect to this case, there might be some situations in which the use of a caval filter would be appropriate.

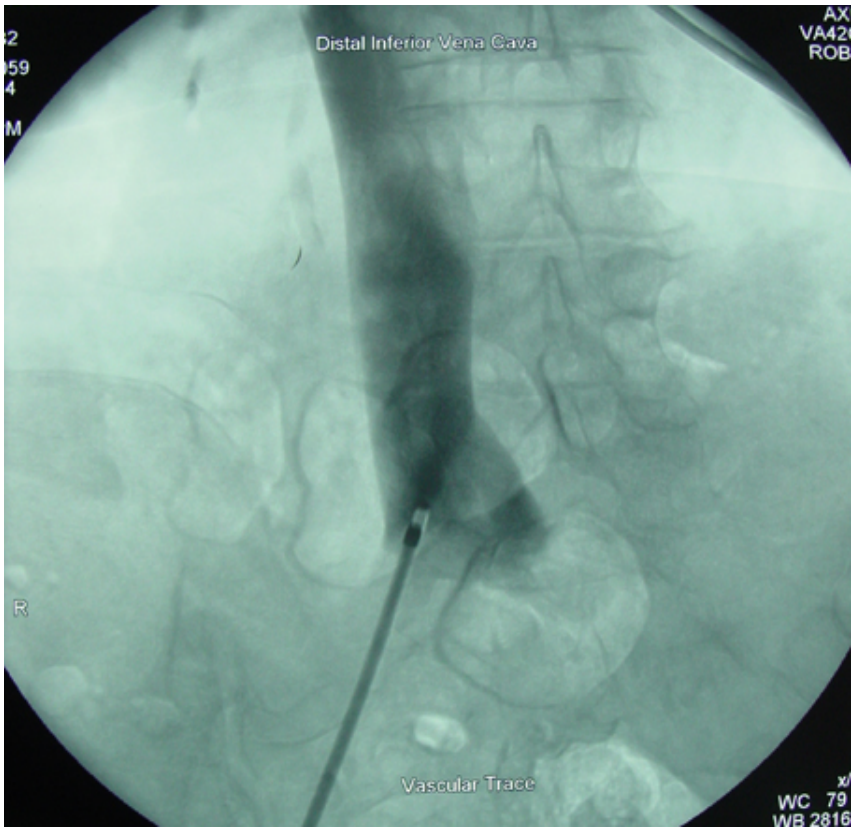
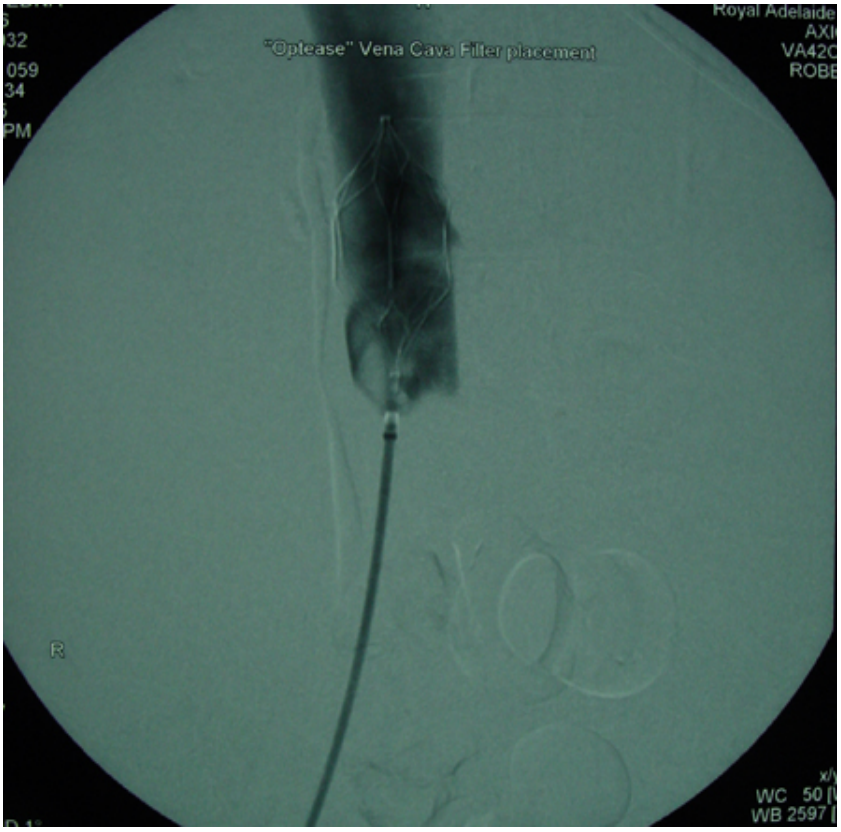


Image 1



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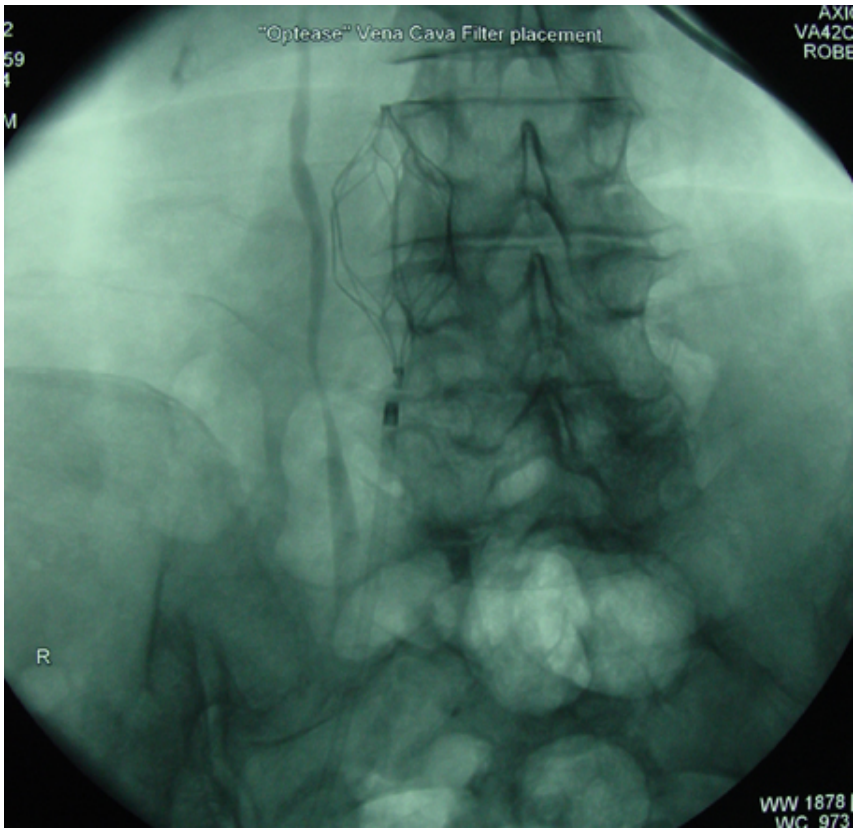

Image 3

Question:

In which of the following circumstances might use of a caval filter be appropriate?

Choice 1: Serum creatinine of 120 umol/L

Score : -1

Choice Feedback: Incorrect. Such a creatinine is borderline and would not necessarily be seen as renal impairment. If renal impairment was present, use of pharmacological prophylaxis would need to be judicious and whilst the factor Xa inhibitors might be contra-indicated, almost certainly this patient would still be suitable for a low molecular weight heparin.

Choice 2: Recent pulmonary embolus

Score : 1

Choice Feedback: Correct. Any patient being considered for surgery must be fully assessed for risk factors for VTE - and a recent pulmonary embolus is a very real risk for further problems. In such circumstances - and particularly if clot is still present in the dependent venous systems, some form of mechanical filter would be most appropriate. Such a patient would usually still be on some form of treatment (typically warfarin) for the pulmonary embolus, and this would need to be stopped for the period of surgical treatment of the gastric volvulus - thereby increasing the need for some other form of prophylaxis.

Choice 3: Recent haemorrhagic stroke

Score : 1

Choice Feedback: Correct. In such circumstances any form of pharmacological thromboprophylaxis would increase the risk of a further bleed and must be avoided. As the patient is at high risk of VTE, insertion of a caval filter to reduce the risk of pulmonary embolism would be quite appropriate.

Synopsis

Issues related to venous thromboembolism (VTE) occur with relative frequency in the surgical patient and are an important cause of post-operative morbidity. Hospitalised patients are over 100 times more likely to develop a DVT or pulmonary embolus compared with the rest of the community. Problems associated with VTE have a significant burden in Australia with approximately 30,000 people hospitalised each year as a consequence of VTE and an estimated 2,000 die from VTE . Pulmonary embolus remains the most common preventable cause of death in hospital. All surgical patients must be considered at increased risk for venous thromboembolic problems and the element of risk calculated on an individual basis. Risk assessment is made on the basis of:

- The nature of the planned procedure
- Individual factors pertinent to that patient
- The prophylactic measure to be considered

Surgical risk is judged to be either high or low. High risk procedures include:

- Hip and knee arthroplasty
- Cancer surgery
- Any intra-abdominal procedure
- Any procedure taking longer than 45 minutes

Individual risk factors include:

- Increasing age
- Previous venous thromboembolic problems
- Obesity

- Malignancy (including its treatment)
- Medications, including oestrogen therapy
- Sepsis
- Varicose veins
- Inflammatory bowel disease
- Dehydration
- Thrombophilia
- Prolonged immobility

Thromboprophylaxis comprises two main methods- mechanical and pharmacological prophylaxis. The most commonly used pharmacological agents in Australia are the heparins (low molecular weight heparin and unfractionated heparin sodium). Postoperative enoxaparin dose regimens may need to be varied according to the type of surgery and the general state of health of the patient. Co-morbidities such as renal impairment will determine the type of agent and dose to be used. For example, burnt and other critically ill patients have been documented with inadequate antifactor Xa levels and with conventional doses of prophylactic enoxaparin can result in increased risks of VTE. One study monitored antifactor Xa concentrations in burns patients and increased enoxaparin doses to meet target levels such that some patients required 70 mg enoxaparin every 12 hours. No adverse haemorrhage events were observed and the incidence of VTE events was reduced (4).

The place of the newer anticoagulants (direct thrombin inhibitors and factor Xa inhibitors) have yet to be defined in general surgical practice. Agents such as dabigatran and rivaroxaban have been shown to be as efficacious as the heparins in

the reduction of VTE risk in major joint replacement surgery and may prove more cost-effective. Data is still lacking as to any role these agents may have in other areas of surgery.

Mechanical prophylaxis options include thigh or knee length graduated compression stockings, pneumatic venous pumping devices that intermittently compress the calf muscles and devices that stimulate lower-limb muscle contraction. These devices are commonly used intra- and post-operatively and there are only a few circumstances in which their use might be precluded. These include:

- Dermatitis
- Gangrene
- Recent skin graft
- Severe peripheral vascular disease
- Severe lower limb oedema
- Proven or suspected DVT

The use of pharmaceutical and/or mechanical prophylactic measures and their planned use to reduce the risk of VTE must be balanced in terms of efficacy, cost-effectiveness and convenience. With the increasing recognition of the need to continue prophylaxis well into the convalescent period, a critical assessment of the various measures is required. The convenience of oral or subcutaneous preparations must be made on an individual basis and the risks of a serious bleeding event be weighed up against the risk of VTE. There are a number of contraindications to pharmacological prophylaxis and these include:

- Recent central nervous system bleeding

- Intracranial or spinal lesion at high risk for bleeding
- Current active major bleeding, defined as requiring at least two units of blood or blood products to be transfused in 24 hours
- Current chronic, clinically significant and measurable bleeding over 48 hours
- Thrombocytopenia (platelets less than 50,000/Î¼l)
- Severe platelet dysfunction
- Recent major surgical procedure at high risk for bleeding
- Underlying coagulopathy or coagulation factor abnormalities
- Regional axial anaesthesia or recent lumbar puncture for any reason
- High risk of falls

Vena caval filters are an important alternative in high risk patients when anticoagulation is contraindicated. Current evidence indicates that IVC filters are largely effective with breakthrough pulmonary emboli occurring in only between 0% to 6.2% of cases. Indications for vena caval filters include:

- Concurrent bleeding diatheses or active hemorrhage
- Recurrent VTE and PE despite conventional treatment
- Inability to achieve or maintain therapeutic anticoagulation or poor compliance with anticoagulant medications
- Pelvic surgery in the presence of extensive DVT
- Concurrent VTE and need to discontinue anticoagulation therapy before surgery
- High risk DVT- e.g. proximal spread of DVT

- Prophylaxis for patients at high risk of developing a VTE, where even a minor PE could be fatal. (e.g. severe trauma, hypercoaguable states, prolonged immobilization, severe cardiopulmonary disease)
- Any form of surgery on the 'super-obese' patient

Despite their increased use in trauma patients, a recent retrospective study did not find that use of caval filters did not lead to any reduction in mortality in an analysis of 451 trauma patients (14). Contraindications to implantation of IVC filters include:

- Lack of venous access
- Caval occlusion
- Uncorrectable coagulopathy
- Sepsis

Complications include:

- Misplacement or embolization of the filter
- Vascular injury or thrombosis
- Pneumothorax
- Air emboli

Long term IVC risks include:

- Recurrent PE
- IVC thrombosis
- Filter migration
- Filter fracture
- Penetration of the caval wall

Since caval filters only hinder clot migration and do not inhibit clot formation, all these patients should receive (unless contraindicated) some form of anticoagulation for a period appropriate to the thrombotic disorder.

Risk assessment models

Being alert to the potential problems of VTE, identifying risk factors (both general and individual), undertaking preventative measures, when combined with early post-operative mobilisation will produce a substantial reduction in the incidence of venous thromboembolic complications in surgical patients (9). Various risk assessment models for VTE exist. Software systems have been developed that identify at-risk hospitalised patients and warn the physician of the need to consider some form of VTE prophylaxis. In a study of one such system, the computer-alert system reduced the risk of a VTE-related complications by 41% (10). This model, developed by Kucher, was effective in identifying high risk patients (those with at least four of eight defined risk factors), but was less efficient in picking up the low risk patients - where 20% of patients with four or less factors did have a VTE-related complication. Another model is that devised by Rogers et al, which defines 15 variables which are associated with an increased risk of VTE (11). These variables can be used to predict a risk of VTE, but the complexity of the scoring system limits its applicability. Caprini developed a risk assessment model based on 30 variables, which can accurately stratify the risk for low and high-risk patients (12). However, it is a complex system to use and subsequent analysis has shown that some of the variables are not specific for VTE. In an effort to simplify these systems, Pannucci defined seven risk factors:

- History of VTE

- Current malignancy
- Age >60
- Male
- BMI >40
- Sepsis/septic shock/systemic inflammatory response syndrome
- Family history of VTE

This model is much simpler to apply and appears to stratify patients appropriately (13). A recent analysis of 13 studies, involving 14776 patients, found that chemoprophylaxis reduced the overall risk rate for postoperative VTE by 34% (15). However, the benefit only applied to those with a Caprini score of 7 or more. Some 75% of patients in these studies had a Caprini score of 6 or less - suggesting that many patients have unnecessary chemoprophylaxis - and this might expose them to the risk of bleeding complications. These data suggest that a more individualised approach should be taken to the use of chemoprophylaxis in patients with increased risk of VTE.

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Adelaide, Updated January 2017

Case 869: VTE Prophylaxis in Medical Patients

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Case Overview

This case will take the user through the assessment, choice and application of VTE prophylaxis in medical patients admitted to hospital.

Please note that, where available, staff should abide by local VTE prophylaxis and management policies, as these may take into account local clinical and economic factors that cannot be anticipated by this module.

Learning Objectives

- Identify the medical patient at risk of venous thromboembolic disease
- Assess the risk of venous thromboembolism in the medical patient
- Assess the risk of bleeding in the medical patient that is a candidate for VTE prophylaxis
- Correctly select an appropriate means of VTE prophylaxis for the medical patient
- Understand the epidemiology and pathophysiology of VTE in the medical patient

Question 1:
Question Information:

A 68-year-old man presents to the Emergency Department with a 12 hour history of cough and shortness of breath. Mr Benson has had these symptoms have been present for about two months, but got suddenly worse overnight. Other symptoms include worsening dyspnoea of exertion and ankle swelling. The medical officer of the general medical unit rostered for emergency admissions is asked to see the patient.

One of the considerations to be made will be the place of some form of prophylaxis to reduce the risk of venous thromboembolism (VTE) during the admission of this patient. The risk factors for VTE need to be considered. There are many patients with an acute medical illness who might be at increased risk of venous thromboembolism. These patients need to be identified early in the course of their illness and appropriate prophylaxis instituted.

Question:

Which of the following would be at increased risk of VTE?

Choice 1: Age over 40

Score : 1

Choice Feedback: Correct. Age per se is not a risk factor, but when combined with an acute medical illness and reduced mobility, patients in this age group must be considered for some form of VTE prophylaxis.

Choice 2: Stroke

Score : 1

Choice Feedback: Correct. These patients are at high risk. They are often elderly and immobile. A distinction between ischaemic and haemorrhagic stroke must be made early and the risk of haemorrhagic transformation be made before considering VTE prophylaxis.

Choice 3: Acute heart failure

Score : 1

Choice Feedback: Correct. Patients in the NYHA III/IV groups are at increased risk.

Choice 4: Acute respiratory failure

Score : 1

Choice Feedback: Correct. The patient who needs ventilatory support will be at even greater risk of VTE.

Question 2:
Question Information:

In addition to the immediate and precipitating cause for the admission, the patient might have other risk factors that can be identified from the history and physical examination.

Question:

Which of the following are recognised risk factors for VTE?

Choice 1: Hormone therapy

Score : 1

Choice Feedback: Correct. Medications such as the oral contraceptive pill and hormone replacement therapy put the patient at increased risk of VTE.

Choice 2: Dehydration

Score : 1

Choice Feedback: Correct. The patient who is admitted with a several day history of being unwell leading up to an acute admission might well be dehydrated - thereby increasing the risk of VTE.

Choice 3: Previously treated malignancy

Score : 1

Choice Feedback: Correct. Any previously treated malignancy - even though now cured and something of the past, leaves the patient at increased risk of VTE.

Choice 4: BMI of 25

Score : -1

Choice Feedback: Incorrect. This BMI is in the normal range. Those patients with a BMI of over 30 are at increased risk of VTE.

Choice 5: History of VTE

Score : 1

Choice Feedback: Correct. This is perhaps the most important risk factor to seek.

hoice 6: Varicose veins

Score : 1

Choice Feedback: Correct. Patients with varicose veins (venous stasis) are at increased risk of VTE events

Choice 7: Immobility prior to admission

Score : 1

Choice Feedback Correct. Among hospitalized patients, 50-75% of VTE events, including fatal pulmonary embolism, occur in the medical service.

Question 3:
Question Information:

Returning to the case of Mr Benson - he now provides some further information. His worsening of breathing occurred whilst lying in bed this morning. He does not have any fever, cough, palpitations or chest pain. He has had hypertension for 20 years and takes enalapril 5mg bd. He has a 40 pack-year smoking history and enjoys several glasses of beer with his friends at weekends. On examination he looks unwell, with a temperature of 37.4C, a tachypnoea of 18/min, blood pressure of 150/95 mmHg, pulse rate 105/min and an oxygen saturation breathing room air of 92%.

Question:

Which of the following diagnoses should be considered at this point?

Choice 1: Acute myocardial infarction (AMI)

Score : 1

Choice Feedback: Correct. AMI is characterised by symptoms including cardiac chest pain, nausea and vomiting, syncope, dyspnoea and fear of impending doom. Cardiac chest pain may radiate to the epigastrium, throat, arms and back. Although there is no chest pain in this case, one should never rule out AMI in such presentation, patients could present with exertional or resting dyspnoea due to impairment of the contractility of the left ventricle. The lack of pain could be due to underlying diabetic neuropathy impairing the normal pain sensation. The smoking history and hypertension are risk factors for coronary artery disease.

Choice 2: Acute pulmonary embolism

Score : 1

Choice Feedback: Correct. Common features of a pulmonary embolism (PE) include dyspnoea, pleuritic chest pain, tachypnoea, tachycardia and cough. Other features may include haemoptysis and cyanosis. Other symptoms of deep vein thrombosis such as leg swelling, leg pain may be present. Although he did not have a history of recent travel and had no chest pain, pulmonary embolism cannot be ruled out as a possible diagnosis.

Choice 3: Congestive heart failure (CCF)

Score : 2

Choice Feedback: Correct. The presentation is typical of CCF with progressive exertional dyspnoea, dyspnoea at rest and ankle swelling. Further physical examination and imaging will confirm the diagnosis.

Choice 4: Acute asthma exacerbation

Score : -1

Choice Feedback: Incorrect. Asthma can cause difficulty breathing. But with no previous history of asthma, no wheezing and cough, this is unlikely in this case. (Asthma is generally characterised by reccurent episodes of dyspnoea, wheezing, cough and chest tightness).

Choice 5: Cardiac tamponade

Score : 1

Choice Feedback: Correct. Typical presentation include dyspnoea, chest pain and palpitations. Cardiac tamponade can be caused by trauma, myocardial rupture

(related to myocardial infarction), infection (e.g. TB), malignancy, dissecting thoracic aortic aneurysm.

Choice 6: Pneumothorax

Score : -1

Choice Feedback: Incorrect. Spontaneous pneumothorax can cause sudden-onset chest pain and breathlessness. With a gradual presentation of dyspnoea for two months, this diagnosis is unlikely.

Choice 7: Pneumonia

Score : -1

Choice Feedback: Incorrect. Pneumonia is usually dominated by systemic features including fever, rigors, shivering, cough with productive sputum. Chest pain, anorexia, breathlessness may occur. Without fever, cough or any constitutional symptoms, it is unlikely that pneumonia is the primary underlying problem.

Question 4:
Question Information:

On further examination Mr Benson has a JVP of 7cm, and his apex is displaced 1cm lateral to the mid-clavicular line in the 6th intercostal space. Heart sounds are normal with no murmurs. On auscultation there are bibasal crepitations. Some sacral oedema is evident, as is bilateral ankle oedema. He does not have any hepatomegaly or ascites. Some investigations must be now be considered.

Question:

Which of the following investigations would be appropriate?

Choice 1: ECG

Score : 1

Choice Feedback: Correct. An ECG is valuable in looking for evidence of old myocardial infarction, acute ischaemia (such as AMI), arrhythmias and heart blocks.

Choice 2: Chest X-ray

Score : 1

Choice Feedback: Correct. A chest X-ray may show evidence of pulmonary congestion or oedema, cardiomegaly oe pleural effusion. It may rule out and a pneumothorax or pericardial effusion.

Choice 3: Complete blood examination

Score : 1

Choice Feedback: Correct. A CBE may provide evidence of anaemia exacerbating heart failure, or a raised WCC indicating infection.

Choice 4: Electrolytes, urea and creatinine

Score : 1

Choice Feedback: Correct. EUCs are important for the assessment of renal function, electrolyte disturbance and hyperkalaemia related to ACE inhibitor usage.

Choice 5: Troponin T/I

Score : 1

Choice Feedback: Correct. Troponin T/I is essential to rule out acute myocardial damage (e.g. acute coronary syndrome, NSTEMI or STEMI).

Choice 6: CT pulmonary angiogram (CTPA)

Score : -1

Choice Feedback: Incorrect. CTPA is not indicated in this case as there is no evidence of VTE or pulmonary embolism (no history of immobilisation, no risk factors for VTE, no chest pain, and no ECG evidence (e.g. RV strain or S1Q3T3), no unilateral leg swelling). CTPA would also subject the patient to unnecessary radiation.

Choice 7: V/Q Scan

Score : -1

Choice Feedback: Incorrect. V/Q scan is not indicated in this case as there is no evidence of VTE or pulmonary embolism (no history of immobilisation, no risk factors for VTE, no chest pain, and no ECG evidence (e.g. RV strain or S1Q3T3), no

unilateral leg swelling). V/Q scan would also subject the patient to unnecessary radiation.

Choice 8: Echocardiogram

Score : 1

Choice Feedback: Correct. An echocardiogram is useful to look for underlying valvular abnormality (e.g. mitral stenosis or regurgitation, aortic regurgitation) causing congestive heart failure, assessing myocardial (left ventricular function) and ruling out pericardial effusion.

Question 5:
Question Information:

A chest X-ray is performed. (Image)

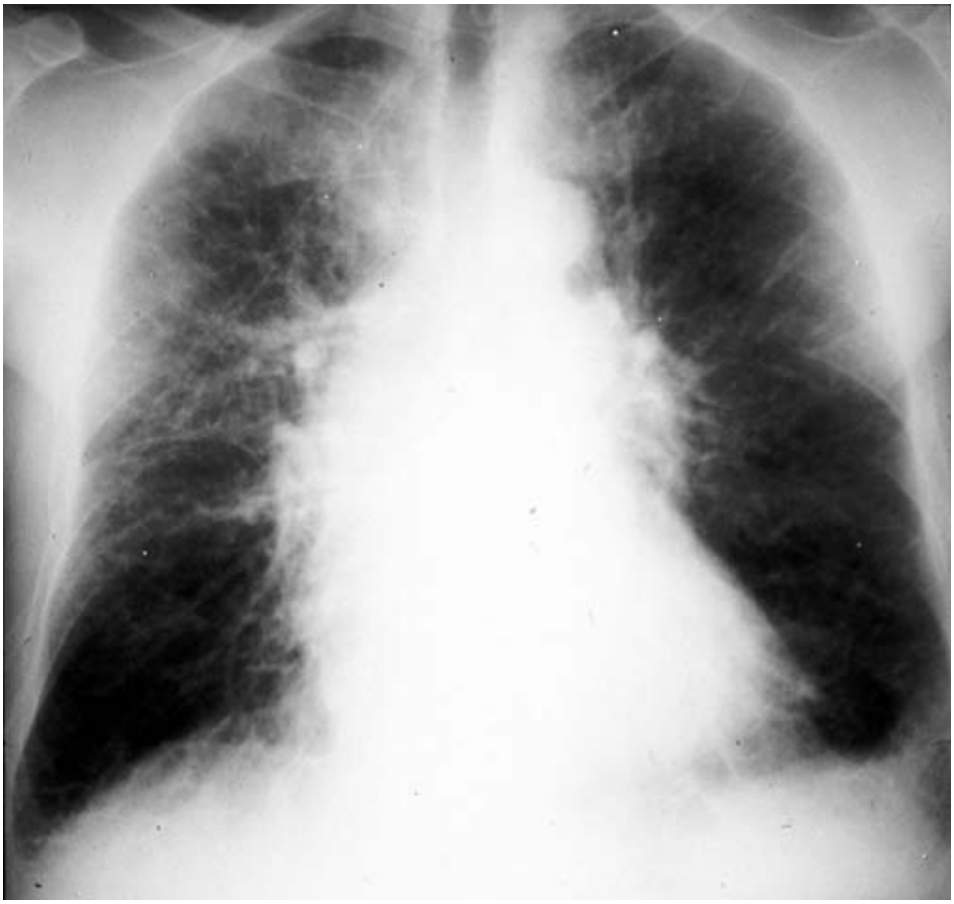

Image 1

Question:

Which one of the following is the most likely diagnosis?

Choice 1: Acute myocardial infarction (AMI)

Score : 0

Choice Feedback: Incorrect. The chest radiograph shows pulmonary congestion and cardiomegaly. There is no pleural effusion. The findings are compatible with the diagnosis of congestive heart failure.

Choice 2: Acute pulmonary embolism

Score : 0

Choice Feedback: Incorrect. The chest radiograph shows pulmonary congestion and cardiomegaly. There is no pleural effusion. The findings are compatible with the diagnosis of congestive heart failure. The chest radiograph of acute pulmonary embolism will show relative oligaemic lung fields with normal CTR.

Choice 3: Congestive heart failure

Score : 1

Choice Feedback: Correct. The chest X-ray shows an increased cardiothoracic ratio, pulmonary congestion and the presence of Kerley B lines. These findings are consistent with congestive cardiac failure.

Choice 4: Cardiac tamponade

Score : 0

Choice Feedback: Incorrect. In cardiac tamponade, the chest radiograph will show a globular heart with clear lung fields; the raised pressure of the tamponade results in compression to the atria and therefore reducing pre-load and right ventricular output to the lungs, hence producing clear lung fields.

Question 6:
Question Information:

An ECG is performed (Image 2)

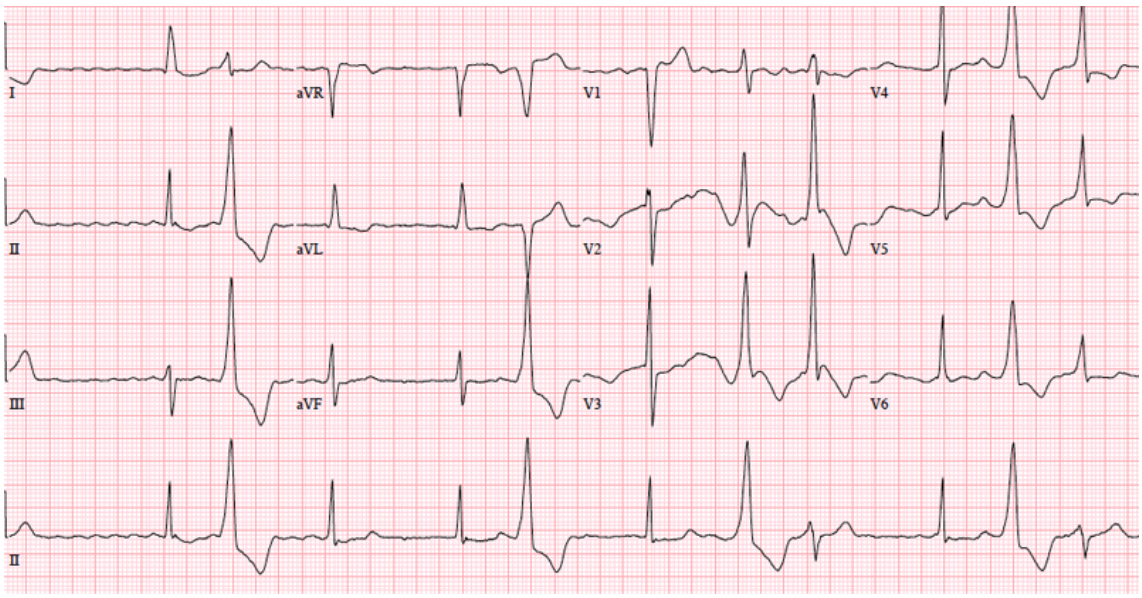

Image 1

Question:

What does the ECG show?

Choice 1: Acute STEMI

Score : 0

Choice Feedback: Incorrect. There is no ST elevation. The ECG showed fibrillatory waves (absence of discrete and normal P waves) and irregular QRS that is typical of atrial fibrillation. Here is an example of an acute inferior myocardial infarction. (Image 2)

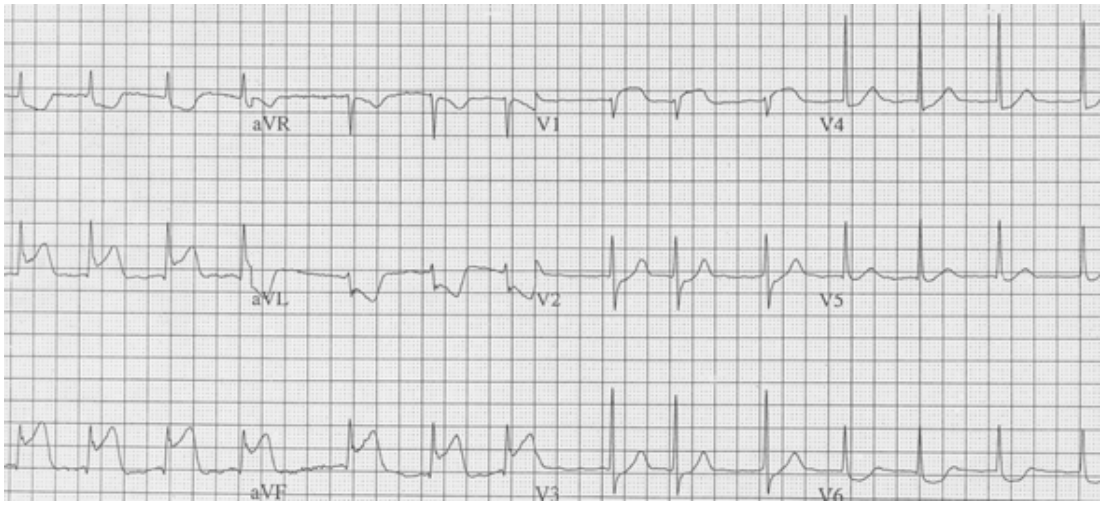

Image 2

Choice 2: First degree heart block

Score : 0

Choice Feedback: Incorrect. There is no P wave seen in the ECG and no prolonged PR intervals. The ECG showed fibrillatory waves (absence of discrete and normal P waves) and irregular QRS that is typical of atrial fibrillation. Here is an example of first degree heart block. (Image3)

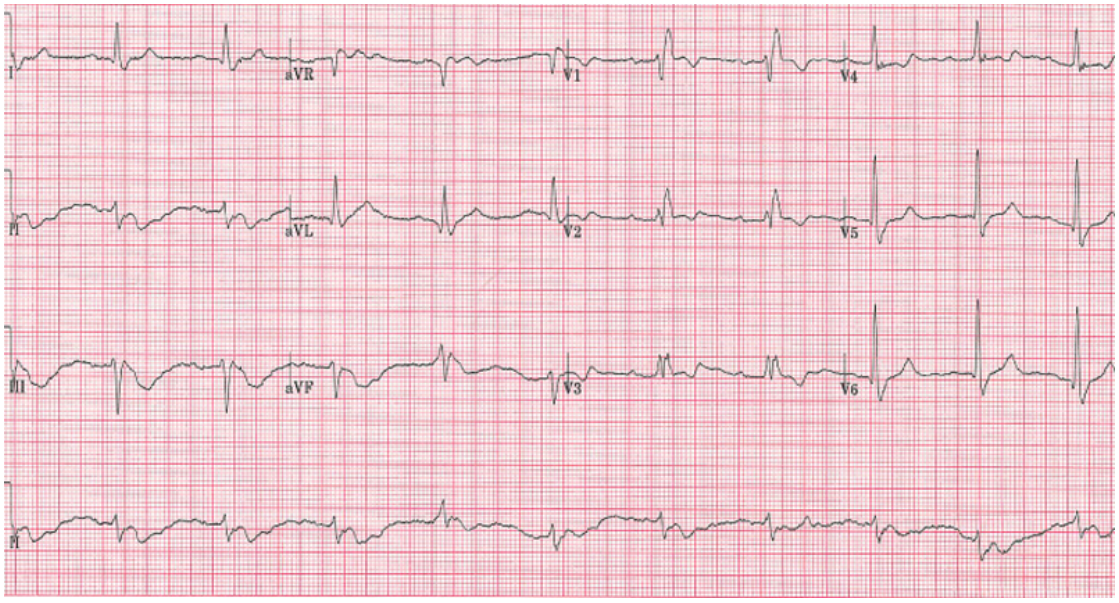

Image 3

Choice 3: Sinus tachycardia

Score : 0

Choice Feedback: Incorrect. In sinus tachycardia the ECG will show normal P waves followed by regular QRS and a normal PR interval. This ECG showed fibrillatory waves (absence of discrete and normal P waves) and irregular QRS that is typical of atrial fibrillation.

Choice 4: Atrial fibrillation

Score : 1

Choice Feedback: Correct

Choice 5: Atrial flutter

Score : 0

Choice Feedback: Incorrect. In atrial flutter the ECG will show a typical sawtooth pattern of flutter waves in between QRS. Atrial rate will usually be between 250-300 bpm. Here is an example of atrial flutter. (Image 4)

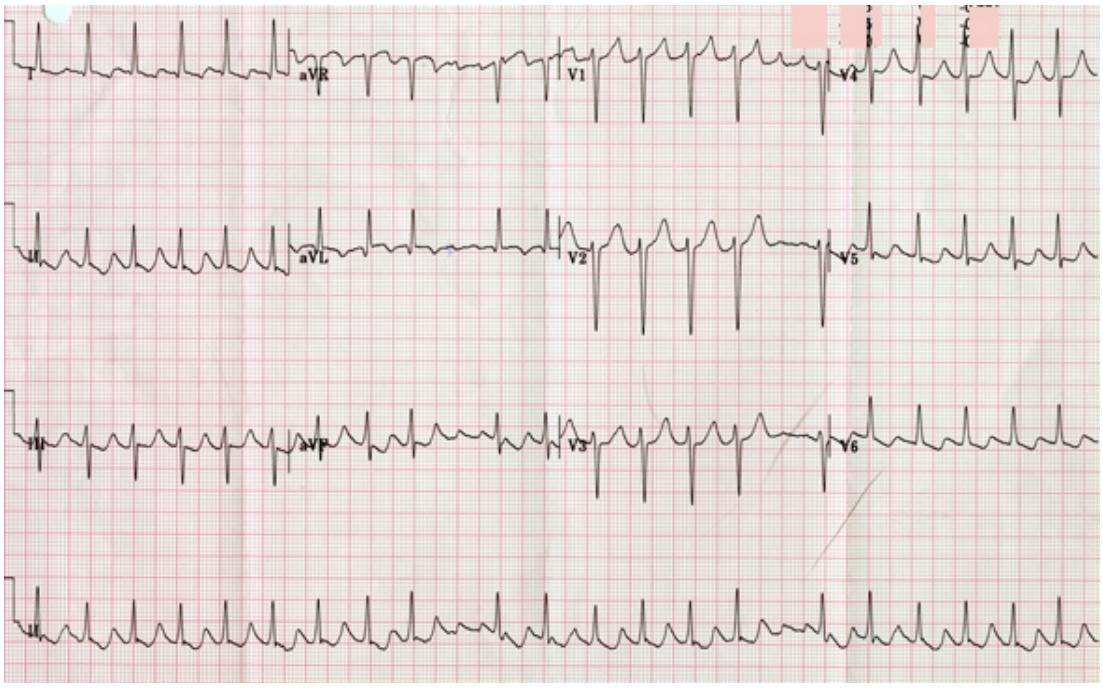

Image 4

Choice 6: S1Q3T3 pattern

Score : 0

Choice Feedback: Incorrect. This pattern could be seen in acute pulmonary embolism due to right ventricular strain, however it is not present in this ECG.

Question 7:
Question Information:

Mr. Benson is managed in the Emergency Department and transferred to the general medical ward. He is commenced on 40mg IV frusemide and low-dose potassium and magnesium supplementation. His condition slowly improves over the next three days, but the patient finds it difficult to mobilise and Mr Benson rarely leaves his bed during this time.

Question: (*Free text answer option*)

Describe how the risk of Mr. Benson developing a VTE can be predicted?

Feedback: The Padua Risk Prediction Score can be used to predict risk of VTE in hospitalised medical patients. It is used to estimate baseline risk for patients with low and high VTE risk. A high risk is a score of greater than, or equal to 4, based on the following scoring system:

- Active cancer =3 (Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the prvious six months)
- Previous VTE (with exclusion of superficial vein thrombosis) =3
- Reduced mobility = 3 (anticipated bed rest with bathroom privileges [either because of patient limitations or on physician orders] for at least 3 days)
- Already known thrombophilic condition = 3 (carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome)
- Recent (<1mo) trauma and/or surgery = 2

- Elderly age (>70) = 1
- Heart and/or respiratory failure = 1
- Acute myocardial infarction or ischaemic stroke = 1
- Acute infection and/or rheumatologic disorder = 1
- Obesity (BMI >30) = 1
- Ongoing hormonal treatment = 1

Question 8:
Question Information:

Mr. Benson clearly has a Padua Risk Score of 4, constituting a high risk of VTE. Given this risk, it is clear that some form of VTE prophylaxis will be required.

Question:

Which one of the following would be the most appropriate form of chemoprophylaxis?

Choice 1: Low molecular weight heparin

Score : 2

Choice Feedback: Correct. This is the most appropriate option. Comparison of low molecular weight heparin (LMWH) with no treatment for VTE prophylaxis in medical patients across six randomised controlled trials demonstrated significantly lower rates of symptomatic PE in those receiving LMWH than those receiving no treatment. In three other trials, patients receiving LMWH had significantly lower rates of proximal DVT compared with no treatment. Evidence-based guidelines currently recommend the use of anticoagulant thromboprophylaxis with LMWH for hospitalised patients at increased risk. These patients should be given either low-dose unfractionated heparin two or three times daily, or fondaparinux. For those patients at low risk of VTE, guidelines recommend against the use of pharmacologic or mechanical prophylaxis. For those patients who are actively bleeding, or at increased risk of bleeding, (e.g. patients suffering haemorrhagic stroke) the recommendation is for use of optimised mechanical prophylaxis. Current evidence

does not support the use of extended post-discharge pharmacological thromboprophylaxis in a acutely ill medical patients.

Choice 2: Unfractionated heparin

Score : 1

Choice Feedback: Correct. Recommendations for the use of VTE prophylaxis with unfractionated heparin (UFH) are dependent upon the inclusion and exclusion of particular studies. An analysis of four randomised controlled trials (RCTs) comparing UFH with no treatment did not demonstrate a clearly significant benefit to its use in prophylaxis. However, exclusion of one particular study that used autopsy to identify DVT in patients with infection resulted in a significant improvement in outcomes in the heparin-treated cohort. Similarly, two RCTs examining the use of UFH to prevent PE demonstrated a clear benefit in the heparin-treated group versus the not-treated controls.

Choice 3: Fondaparinux

Score : 0

Choice Feedback: Incorrect. Fondaparinux appeared to reduce rates of asymptomatic distal DVT in patients greater than 60 years of age, but not the rates of symptomatic DVT in one randomised controlled trial, with no difference between fondaparinux-treated and non-treated groups with regards to rates of bleeding or death. As a result, fondaparinux is one of the three available choices for anticoagulation in patients at risk of VTE in the medical setting, with choice of therapy made based on cost, patient compliance and local protocol.

Choice 4: Mechanical prophylaxis

Score : 0

Choice Feedback: Incorrect. For those patients who are actively bleeding, or at increased risk of bleeding, (e.g. patients suffering haemorrhagic stroke) the recommendation is for use of optimised mechanical prophylaxis. There is not enough evidence to currently recommend the routine use of mechanical prophylaxis in medical patients.

Synopsis

Medical patients have tended to be a neglected group when it comes to matters concerning their risk of a VTE complication during hospitalisation and convalescence. Many of these patients face an eight-fold increase in the risk of VTE during hospitalisation. The risks include:

- Any surgical procedure undertaken during that admission
- Previous VTE
- Active cancer
- Age > 40 (markedly increased risk when aged >70 years)
- Prolonged severe immobility
- Pregnancy and puerperium
- Marked obesity
- Oestrogen-containing HRT or OCP
- Certain types of thrombophilia
- Current use of a non-steroidal anti-inflammatory agent
- General anaesthesia
- The following medical conditions:
- Acute/acute on chronic chest infection
- Heart failure
- Respiratory failure
- Myocardial infarction
- Ischaemic stroke with immobility
- Some forms of cancer chemotherapy
- Acute inflammatory bowel disease

Patients with medical conditions require assessment of their risk of VTE using a validated scoring system (Caprini RIsk Assessment Model; Padua Prediction Score). Once their risk has been determined, an appropriate choice of VTE prophylaxis based on a comparison of risk of bleeding versus risk of VTE events needs to be made. In medical patients, the most-appropriate pharmacological forms of VTE prophylaxis are low-molecular weight heparin and unfractionated heparin. There are some important caveats in the use of pharmacological prophylaxis in medical patients.

Patients presenting with haemorrhagic stroke should not receive any form of pharmacologic prophylaxis due to the devastating consequences of intracranial haemorrhage in these patients. SImilarly, patients suffering a myocardial infarction will most likely be on some form of anticoagulant or antiplatelet therapy to treat pre-existing, and treat further, thrombosis. If cardiac patients require additional anticoagulation, the most appropriate choice of thromboprophylaxis is unfractionated heparin, as this drug can be readily reversed with protamine should operative or procedural (i.e. catheter) intervention be required. There is currently little evidence for the use of mechanical prophylaxis in medical patients, however each patient should be assessed for the use of graduated compression stockings should they be assessed as unsuitable for pharmacological prophylaxis.

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Case 873: VTE Prophylaxis in Obstetrics & Gynaecology

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Case Overview

This case looks at prophylaxis of deep vein thrombosis (DVT) and venous thromboembolism (VTE) in an uncomplicated pregnancy. It reviews the important parts of an obstetric history and risk factors that may influence the pregnancy and puerperium. The management of prophylaxis in the setting of ceasarean section is also addressed.

Please note that, where available, staff should abide by local VTE prophylaxis and management policies, as these may take into account local clinical and economic factors that cannot be anticipated by this module.

Learning Objectives

- Risk factors of VTE during pregnancy
- Mechanism of VTE development during pregnancy
- Management of thromboprophylaxis in normal vaginal delivery
- Management of thromboprophylaxis in caesarean section

Question 1:
Question Information:

Mrs Maria Galvany is a 32-year-old G3P1 who presents for her first antenatal triage appointment. You take a full medical history and discover that she has asthma and has previously undergone a laparoscopic appendicectomy. Her pregnancy began whilst she was still taking the combined oral contraceptive pill, however she has now ceased this medication. Her previous pregnancy was uneventful and she progressed to a spontaneous delivery of a healthy baby girl at 39+4 gestation. She has a significant family history of type two diabetes in her mother and maternal grandmother and her grandfather had a DVT following an orthopaedic procedure. As part of the current examination, Maria's weight and height measurements give her a BMI of 38.

Question:

Which of the above factors in her history most put Maria at an increased risk for VTE?

Choice 1: BMI 38

Score : 3

Choice Feedback: Correct. Increased BMI >30 is associated with an increased risk of VTE, with a risk that increases proportionally to BMI. Some studies also suggest a higher risk of associated pulmonary embolism with deep vein thrombosis with elevated BMI.

Choice 2: Gestational state

core : 3

Choice Feedback: Correct. Purely by being pregnant Maria places herself at an increased risk of VTE over the coming 9 months. Normal changes in the haematological system will results in hypercoagulability and compression on pelvic veins will result in peripheral stasis.

Choice 3: Age

Score : -1

Choice Feedback: Incorrect. Advanced maternal age is not considered an independent risk factor for VTE until 35.

Choice 4: Family history of DVT

Score : -1

Choice Feedback: Incorrect. Maria has reported a family history of a provoked deep vein thrombosis occurring in a second degree relative. This history does not increase her risk of VTE.

Choice 5: Combined oral contraceptive pill use

Score : -1

Choice Feedback: Incorrect. Whilst use of the COCP will give Maria a 3-fold increased risk of VTE outside of pregnancy, she has discontinued her usage of this medication.

Question 2:
Question Information:

Following the thorough history and questions regarding her grandfather's DVT, Maria would like to know some further statistics about her own risk for developing VTE during this pregnancy.

Question:

Which one of the following incidence ratios most accurately represents the likelihood of Maria developing a VTE-related problem?

Choice 1: 5 cases per 100,000 woman/years

Score : -1

Choice Feedback: Incorrect. This is the background risk of VTE in woman of reproductive age who are not using hormonal contraception.

Choice 2: 15 cases per 100,000 woman/years

Score : -1

Choice Feedback: Incorrect. This is the risk of VTE for non-pregnant women using combined oral contraception.

Choice 3: 60 cases per 100,000 woman/years

Score : 3

Choice Feedback: Correct. This is the risk of VTE during pregnancy. Due to the physiological changes of pregnancy, the risk of VTE is 12 times that of the background population risk.

Question 3:
Question Information:

In addition to her standard antenatal care, Maria is briefed on the risks of VTE in pregnancy and reassured that she is not at any increased risk compared with any other pregnant woman - but perhaps her obesity might slightly increase her risk. Maria continues to have routine antenatal care over her coming pregnancy. Unfortunately, Maria's baby is breech at 37 weeks. The patient and her partner decide to have an elective lower segment caesarean section.

Question:

Which of the following would be appropriate methods of thromboprophylaxis in preparation for theatre in this setting?

Choice 1: Heparin infusion

Score : -1

Choice Feedback: Incorrect. Maria has not had any thromboembolic complications throughout her pregnancy and does not need to be maintained on thromboprophylaxis prior to surgery. In cases where a heparin infusion is utilized due to events throughout the pregnancy, the infusion will still need to be stopped 6-8 hours prior to scheduled caesarean section for patient safety.

Choice 2: Graduated compression stockings

Score : 3

Choice Feedback: Correct. Graduated compression stockings are recommended for use within pregnancy and puerperium when fitted appropriately and should be placed on the patient prior to theatre.

Choice 3: Mechanical calf stimulators

Score : 2

Choice Feedback: Correct. Maria does have an increased risk of VTE due to her elevated BMI and the use of mechanical calf stimulators may be used throughout the surgery at the obstetric team's discretion.

Choice 4: Aspirin

Score : -1

Choice Feedback: Incorrect. Aspirin is not used for anticoagulant purposes in the third trimester and puerperium and would be inappropriate prior to theatre.

Question 4:
Question Information:

Maria undergoes a lower segment caesarean section under spinal anaesthesia. The procedure is performed quickly and easily and she is presented with a healthy baby boy with Apgar scores of 9 and 10. She is returned to the ward with an indwelling catheter and patient controlled anaesthesia. Some form of thromboprophylaxis should now be considered?

Question:

Which one of the following would be most appropriate?

Choice 1: Graduated compression stockings only

Score : 0

Choice Feedback: Incorrect. Whilst appropriately fitted graduated compression stockings do play a role in thromboprophylaxis after caesarean section, they will be inadequate to completely cover Maria, who is at slightly increased risk of VTE due to her elevated BMI.

Choice 2: Graduated compression stockings and enoxaparin 40mg SC daily for 7 days

Score : 3

Choice Feedback: Correct. This is the recommended treatment for patients undergoing caesarean section.

Choice 3: Enoxaparin 40mg SC daily for 6 weeks

Score : 0

Choice Feedback: Incorrect. Although this is the prophylactic dosage of enoxaparin, Maria is not at substantially increased risk to require thromboprophylaxis for the entirety of her puerperium.

Choice 4: Enoxaparin 100mg SC daily until mobilizing

core : -1

Choice Feedback: Incorrect. This is a therapeutic dosage of enoxaparin. Maria requires the prophylactic dosage only.

Synopsis

Deep vein thrombosis (DVT) and associated venous thromboembolism (VTE) are common complications of pregnancy within the Australia community, complicating 13 in 10 000 deliveries (Level B)(1). Although DVT and VTE can occur at any stage throughout pregnancy, the incidence is highest in the third trimester and first 6 weeks of the postnatal period (Level A) (2). The increased incidence of VTE in pregnancy can be explained through the use of Virchow's triad, with an observed hypercoaguable state, venous stasis and endothelial dysfunction in the gravid state. During pregnancy, the haematological system is preparing for multiple tasks including implantation and placentation, with resultant changes leading to a systemic prothrombotic state. Circulating levels of fibrinogen, factors VII, VIII, IX, X and XII and von Willebrand factor are markedly elevated, whilst free protein S is seen to dramatically decrease.

Physical changes within the peripheral venous system result in venous stasis secondary to compression of the inferior vena cava and pelvic veins from the gravid uterus (3). In addition to this naturally increased risk from pregnancy itself, there are multiple factors that should alert the physician of further risk to the patient of VTE. Pre-existing factors include a personal history of VTE, thrombophilia, antiphospholipid syndrome, age >35, obesity and smoking. Obstetric risk factors include caesarean section, pre eclampsia, multiple pregnancy, PPH >1 litre and requiring transfusion and prolonged labour (4). All potential risk factors should be screened in the first trimester triage visit through a detailed history. Patients who are identified to be at increased risk of DVT or VTE throughout their pregnancy

should be reviewed by a consultant obstetrician as early as possible in their pregnancy and the role of thromboprophylaxis planned (5).

The exact method and regimen of thromboprophylaxis should be managed by an obstetric team and will be determined by the identifiable risk factors within each case. Heparins are almost always the medication of choice as, unlike Warfain, they will not cross the placenta and thus have minimal effect on the unborn fetus (6).

In low risk women who have undergone a normal vaginal delivery, early mobilization, maintaining adequate hydration and compression devices (e.g. graduated compression stockings) are usually sufficient. In cases subjected to high risk profiles, thromboprophylaxis consisting of subcutaneous low molecular weight heparin may be initiated at any time during the pregnancy and continued for up to 6 weeks following the pregnancy. At this time, the patient's ongoing VTE risk outside of pregnancy will need to be reviewed (4). Finally, patients undergoing caesarean section should be considered individually for thromboprophylaxis. There is minimal data on the success of thromboprophylaxis in this group due to difficulty in establishing and recruiting for significant trials, however it is theorized that women undergoing ceasarean section may be up to 5 times more likely to develop venous thromboembolism than those progressing to vaginal deliveries (Level A and B) (1,7,8). These women should all be considered for graduated compression stockings before and after the procedure, mechanical calf stimulators in theatre, and thromboprophylaxis from 6 hours after surgery (4).

References

1. Thrombotic risk during pregnancy: a population study. Lindqvist P, Dahlback B, Marsal K. Obstet Gynecol. 1999 Oct;94(4):595-9. (Level B)

2. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. J Thromb Haemost 2008;6:632-7. (Level A)

3. Obstetrics: Normal and Problem Pregnancies. Gabbe, 5th edition. Chapter 41: Thromboembolic disorders. Published 2007 Churchill Livingstone

4. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. Green-top Guideline No. 37a. Royal College of Obstetricians and Gynaecologists. www.rcog.org.uk/files/rcog-corp/GTG37aReducingRiskThrombosis.pdf Reviewed November 2009

5. South Australian Perinatal Practice Guidelines. Chapter 74: Venous thromboembolism prophylaxis in pregnancy. www.health.sa.gov.au/PPG Reviewed 28 July 2004

6. Position statement: anticoagulation in pregnancy and the puerperium. A working group on behalf of the Obstetric Medicine Group. Med J Aust 2001; 175(5): 258-263.

7. Thromboprophylaxis and pregnancy: two randomized controlled pilot trials that used low-molecular-weight heparin. Gates S, Brocklehurst P, Ayers S, Bowler U. Am J Obstet Gynecol 2004; 191:1296. (Level A)

8. Maternal mortality and severe morbidity associated with low-risk planned caesarean delivery versus planned vaginal delivery at term. Liu S, Liston RM, Joseph KS, Heaman M, Sauve R, Kramer MS, et al. CMAJ 2007;176:455-60. (Level B)

9. Venous thromboembolism and hormonal contraception. Green-top Guideline No. 40. Royal College of Obstetricians and Gynaecologists. www.rcog.org.uk/cinical-guidance/venous-thromboembolism-and-hormonal-conraception-green-top-40 Reviewed July 2010

The recommended guidelines for this topic are:

- Prevention of Venous Thromboembolism (VTE) in Patients Admitted to Australian Hospitals: Guideline Summary. National Health and Medical Research Council. Clinical practice guideline for the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals. Melbourne: National Health and Medical Research Council; 2009.

Case 886 VTE Prophylaxis in Orthopaedic Surgery Patients

Authors and Affiliations

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University of AdelaideThis case study takes the user through some of the issues involved in the assessment and management of thromboprophylaxis in the orthopaedic surgery patient.

Case Overview

Learning Objectives

- Identify the orthopaedic surgery patient at risk of venous thromboembolic disease
- Assess the risk of venous thromboembolism in the orthopaedic surgery patient
- Assess the risk of bleeding in the orthopaedic surgery patient that is a candidate for VTE prophylaxis
- Correctly select an appropriate means of VTE prophylaxis for the orthopaedic surgery patient

Question 1:
Question Information:

You are working as the ward doctor on a busy city-based orthopaedic surgery unit. A number of patients have required elective admission, transfer from the Emergency Department and post-operative follow-up, all of whom require assessment and management of their risk of venous thromboembolism. Mr. Harvey is a 69-year-old man who has returned from the high dependency unit following a total replacement of his right hip two days ago. He has a background history of myocardial infarction five years ago, which was managed with two bare metal stents, although he has not had any recurrence of his anginal symptoms since he was treated.

Question:

Which one of the following is the most important next step in management?

Choice 1: Enoxaparin

Score : 0

Choice Feedback: Incorrect. In order to prescribe a low-molecular weight heparin for prophylaxis, one must first consider the risk of the patient bleeding. Only then can the risks associated with VTE be weighed against the risks of prescribing an anticoagulant.

Choice 2: Mobilisation and cessation of any earlier VTE prophylaxis

Score : 0

Choice Feedback: Incorrect. Patients with total hip replacements are at high risk of VTE, and should continue VTE prophylaxis beyond the immediate post-procedure period, regardless of mobilisation.

Choice 3: Assessment of renal function and risk of bleeding

Score : 1

Choice Feedback: Correct. Mr. Harvey should be assessed for his risk of bleeding prior to the administration of any anticoagulant. Certain conditions impose a higher risk of bleeding on those patients potentially requiring thromboprophylaxis, including significant renal impairment, active major bleeding, chronic, active and clinically significant bleeding over 48 hours, inherited or acquired bleeding disorders, and other medical conditions.

Choice 4: Unfractionated heparin (UFH)

Score : 0

Choice Feedback: While UFH is a useful and readily-reversible anticoagulant, it should not be prescribed for use in VTE prophylaxis, without there at first being some assessment of the risk of adverse outcomes, including significant haemorrhage.

Question 2:
Question Information:

Mr. Harvey states that other than his heart attack a few years ago, he has no other significant problems. He has never suffered any allergies and has never had an adverse reaction to heparin, although the first time that he used it was during his heart attack. Mr. Harvey normally takes aspirin 100mg daily, on the advice of his cardiologist, although this had been held perioperatively. He also regularly takes atorvastatin 40mg nocte, and metoprolol 25mg BD, for a "funny rhythm thing" that began after his stents were placed. He has no history of bleeding diatheses, renal disease, hepatic dysfunction or haematological malignancy.

His examination reveals a generally relatively-fit looking man, clearly post-operative, resting comfortably in bed. His legs are neurovascularly-intact bilaterally, and there is no calf-swelling, tenderness or peripheral oedema. His chest and abdominal examinations are clear, although palpation of peripheral pulses and auscultation reveals a heart rate of 87bpm with an irregularly-irregular pulse. His post-op ECG is shown (Image).

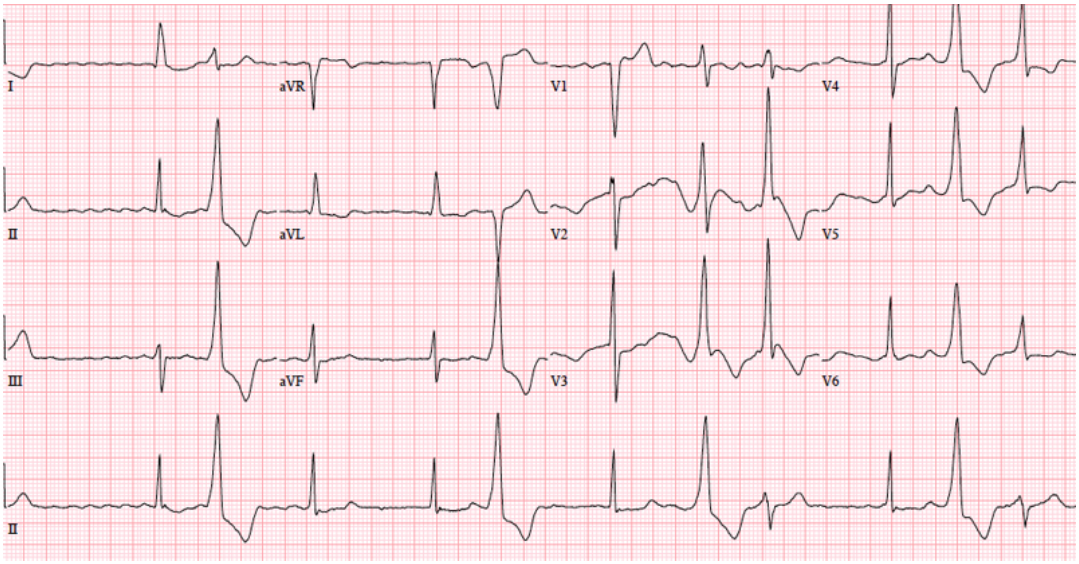

Image 1

Question:

Which of the following are important risk factors for bleeding to consider in the orthopaedic surgery patient requiring pharmacological prophylaxis?

Choice 1: Current active major bleeding

Score : 1

Choice Feedback: Correct. Any patient with active bleeding, or requiring transfusion of at least two units of red cells or other blood products in 24 hours is considered to be at significant risk for continued bleeding with pharmacological VTE prophylaxis.

Choice 2: Bleeding disorders

Score : 1

Choice Feedback: Correct. Bleeding disorders, such as haemophilia, are significant risk factors for increased bleeding with pharmacological VTE prophylaxis.

Choice 3: Thrombocytopaenia (platelets less than 70,000/ul)

Score : -1

Choice Feedback: Incorrect. While thrombocytopaenia with a platelet count of less than 50,000/ul is considered a significant patient-related risk factor for bleeding with pharmacological VTE prophylaxis, those patients with a higher platelet count would warrant further investigation and assessment of their VTE risk, as they may still qualify for VTE prophylaxis. Consideration also needs to be given to choice of pharmacological agent in these patients, as the use of heparin may be contraindicated if there is history of heparin-induced thrombocytopaenia.

Choice 4: Clinically significant bleeding over 36 hours

Score : -1

Choice Feedback: Incorrect. Chronic, clinically significant bleeding over 48 hours is a relative contraindication to pharmacological VTE prophylaxis, however bleeding risk and thrombosis risk must be individually assessed for each patient, and the role of chronic bleeding considered in light of other patient factors.

Choice 5: Concomitant use of anti-platelet, anti-clotting, selective- and non-selective non-steroidal antiinflammatory drugs or thrombolytic agents

Score : 1

Choice Feedback:Correct. Concomitant use of agents that also affect the coagulation and haemostatic mechanisms could lead to severe bleeding through a number of mechanisms, including potentiating the effect of the other drug, reduced metabolism or excretion of one or both drugs, or dual-effect with complementary medications.

Question 3:
Question Information:

Mr. Harvey has undergone a procedure that is known to increase risk for venous thromboembolism, however the choice to use pharmacological prophylaxis in this patient is confounded by his cardiac and medication history.

Question:

What is the risk of Mr. Harvey developing a post-operative venous thrombosis?

Choice 1: 10-20%

core : 0

Choice Feedback: Incorrect. Mr. Harvey has an age within the range of 61-74 years old, and has experienced a hip fracture. According to the Caprini Risk Assessment Tool, a scoring system validated in the assessment of VTE risk in surgical patients, Mr. Harvey has a "Highest Risk" level for VTE development, with a risk incidence of 40-80%.

Choice 2: 10-20%

Score : 0

Choice Feedback:Incorrect. Mr. Harvey has an age within the range of 61-74 years old, and has experienced a hip fracture. According to the Caprini Risk Assessment Tool, a scoring system validated in the assessment of VTE risk in surgical patients, Mr. Harvey has a "Highest Risk" level for VTE development, with a risk incidence of 40-80%.

Choice 3: 20-40%

Score : 0

Choice Feedback: Incorrect. Mr. Harvey has an age within the range of 61-74 years old, and has experienced a hip fracture. According to the Caprini Risk Assessment Tool, a scoring system validated in the assessment of VTE risk in surgical patients, Mr. Harvey has a "Highest Risk" level for VTE development, with a risk incidence of 40-80%.

Choice 4: 40-80%

Score : 1

Choice Feedback: Correct. Mr. Harvey has an age within the range of 61-74 years old, and has experienced a hip fracture. According to the Caprini Risk Assessment Tool, a scoring system validated in the assessment of VTE risk in surgical patients, Mr. Harvey has a "Highest Risk" level for VTE development, with a risk incidence of 40-80%.

Question 4:
Question Information:

Given Mr. Harvey is at high-risk of VTE post-operatively, it is decided that he should receive VTE prophylaxis.

Question:

Which of the following pharmacological, non-pharmacological or combination therapies is most appropriate for this patient?

Choice 1: Fondaparinux 2.5mg SC daily injection for 35 days

Score : 0

Choice Feedback: Incorrect. While Fondaparinux is one of the two recommended anti-thrombotic agents for VTE prophylaxis post-hip fracture surgery, and if initiated should be continued for up to 35 days post-operatively, it is not the most appropriate choice in this patient. Given his history of cardiac disease, and pre-operative use of aspirin to manage these issues, it is most appropriate to commence Mr. Harvey on Enoxaparin 40mg SC daily and aspirin 100mg daily (his pre-operative dose). His enoxaparin dosing should continue for 35 days post-operatively. While non-pharmacological prophylaxis (i.e. use of a foot pump, intermittent pneumatic compression device or TED stockings) is often prescribed to patients post-orthopaedic surgery, there is no evidence to support their use in addition to pharmacological prophylaxis.

Choice 2: Aspirin, 100mg once daily

Score : 0

Choice Feedback: Incorrect. Aspirin alone, especially at doses of less than 160mg/day, has not been shown to be effective in venous thromboembolism prophylaxis. Given his history of cardiac disease, and pre-operative use of aspirin to manage these issues, it is most appropriate to commence Mr. Harvey on Enoxaparin 40mg SC daily and aspirin 100mg daily (his pre-operative dose). His enoxaparin dosing should continue for 35 days post-operatively. While non-pharmacological prophylaxis (i.e. use of a foot pump, intermittent pneumatic compression device or TED stockings) is often prescribed to patients post-orthopaedic surgery, there is no evidence to support their use in addition to pharmacological prophylaxis.

Choice 3: Low molecular weight heparin, 40mg SC Daily for 35 days

Score : 0

Choice Feedback: Incorrect. While LMWH is one of the two recommended agents for VTE prophylaxis post-hip fracture surgery, it is not the most appropriate therapy in this patient. Given his history of cardiac disease, and pre-operative use of aspirin to manage these issues, it is most appropriate to commence Mr. Harvey on Enoxaparin 40mg SC daily and aspirin 100mg daily (his pre-operative dose). His enoxaparin dosing should continue for 35 days post-operatively. While non-pharmacological prophylaxis (i.e. use of a foot pump, intermittent pneumatic compression device or TED stockings) is often prescribed to patients post-orthopaedic surgery, there is no evidence to support their use in addition to pharmacological prophylaxis.

Choice 4: Fondaparinux 2.5mg SC daily injection for 35 days and Intermittent Pneumatic Compression

Score : 0

Choice Feedback: Incorrect. Use of intermittent pneumatic compression is warranted if there are contraindications to the use of pharmacological prophylaxis. There is no evidence to support their sole use, or use in combination therapy, when options for pharmacological prophylaxis are available. Given his history of cardiac disease, and pre-operative use of aspirin to manage these issues, it is most appropriate to commence Mr. Harvey on Enoxaparin 40mg SC daily and aspirin 100mg daily (his pre-operative dose). His enoxaparin dosing should continue for 35 days post-operatively. While non-pharmacological prophylaxis (i.e. use of a foot pump, intermittent pneumatic compression device or TED stockings) is often prescribed to patients post-orthopaedic surgery, there is no evidence to support their use in addition to pharmacological prophylaxis.

Choice 5: Use of intermittent pneumatic compression devices

Score : 0

Choice Feedback: Incorrect. Use of intermittent pneumatic compression is warranted if there are contraindications to the use of pharmacological prophylaxis. There is no evidence to support their sole use, or use in combination therapy, when options for pharmacological prophylaxis are available. Given his history of cardiac disease, and pre-operative use of aspirin to manage these issues, it is most appropriate to commence Mr. Harvey on Enoxaparin 40mg SC daily and aspirin 100mg daily (his pre-operative dose). His enoxaparin dosing should continue for 35 days post-operatively. While non-pharmacological prophylaxis (i.e. use of a foot pump, intermittent pneumatic compression device or TED stockings) is often

prescribed to patients post-orthopaedic surgery, there is no evidence to support their use in addition to pharmacological prophylaxis.

Choice 6: Low molecular weight heparin, 40mg SC Daily for 35 days and Aspirin 100mg PO Daily

Score : 1

Choice Feedback: Correct. Given his history of cardiac disease, and pre-operative use of aspirin to manage these issues, it is most appropriate to commence Mr. Harvey on Enoxaparin 40mg SC daily and aspirin 100mg daily (his pre-operative dose). His enoxaparin dosing should continue for 35 days post-operatively. While non-pharmacological prophylaxis (i.e. use of a foot pump, intermittent pneumatic compression device or TED stockings) is often prescribed to patients post-orthopaedic surgery, there is no evidence to support their use in addition to pharmacological prophylaxis.

Choice 7: Low molecular weight heparin, 40mg SC Daily for 35 days and Intermittent Pneumatic Compression

Score : 0

Choice Feedback: Incorrect. Use of intermittent pneumatic compression is warranted if there are contraindications to the use of pharmacological prophylaxis. There is no evidence to support their sole use, or use in combination therapy, when options for pharmacological prophylaxis are available. Given his history of cardiac disease, and pre-operative use of aspirin to manage these issues, it is most appropriate to commence Mr. Harvey on Enoxaparin 40mg SC daily and aspirin 100mg daily (his pre-operative dose). His enoxaparin dosing should continue for 35

days post-operatively. While non-pharmacological prophylaxis (i.e. use of a foot pump, intermittent pneumatic compression device or TED stockings) is often prescribed to patients post-orthopaedic surgery, there is no evidence to support their use in addition to pharmacological prophylaxis.

Synopsis

Mr. Harvey completes his post-operative physiotherapy, and is discharged home with supports to the care of his daughter eight days after his operation. Visits from the Hospital at Home service are arranged to assist with his enoxaparin administration over the remaining 27 days of pharmacological VTE prophylaxis that he requires.

Orthopaedic surgery patients are amongst some of the highest-risk patients for the development of VTE due to the advanced age of the patient, multiple peri-operative co-morbidities, the frequent presentation with pre-operative trauma, and the nature of the surgical insult that patients experience. Novel medications available for pharmacological thromboprophylaxis in orthopaedic surgery include:

- **Fondaparinux**, a synthetic Factor Xa inhibitor that acts by binding selectively to antithrombin III and increasing it's inherent rate of natural inhibition of Factor Xa by approximately 300 times.
- **Rivaroxaban**, a highly-selective, direct Factor Xa inhibitor, thus modifying FXa-mediated conversion of prothrombin to thrombin via the prothrombinase complex. The drug acts to prevent or terminate the explosive burst of thrombin generation that occurs with prothrombinase-bound FXa (300,000 x greater than free FXa).
- **Dabigatran etexilate**, a novel prodrug that is metabolised to dabigatran in the blood and liver. It is a competitive and reversible direct thrombin inhibitor (inhibiting free and fibrin-bound thrombin, and thrombin-induced platelet aggregation), thus preventing the conversion of fibrinogen to fibrin.

Recommendations for orthopaedic surgery patients

Current guidelines note the high risk (40-80% incidence) of VTE in patients not receiving thromboprophylaxis when having orthopaedic surgery. All patients undergoing orthopaedic surgery for hip or knee replacement, or surgery for hip fracture, or those being treated for fracture of the lower limb requiring immobilisation, require VTE prophylaxis. Current guidelines recommend the use of low-molecular weight heparin, or fondaparinux sub-cutaneous injections, or rivaroxaban or dabigatran oral therapy for the provision of pharmacological prophylaxis, based on patient suitability, cost, supply and local protocols.

Some caution continues to be advised on the use of rivaroxaban and dabigatran, as these drugs are relatively new on the market and are not yet as well-validated as MWH and fondaparinux. Current guidelines recommend the use of either enoxaparin or fondaparinux, in the absence of contraindications, for up to 35 days following surgery for hip fracture, or the use of LMWH, fondaparinux, rivaroxaban or dabigatran for 35 days following elective total hip replacement. If LMWH is to be used, it has been demonstrated that the addition of low-dose aspirin provides additional thrombo-prophylactic benefits. In patients undergoing total knee replacement, use of LMWH, fondaparinux, rivaroxaban, or dabigatran is recommended for 14 days following surgery, unless contraindicated, with care again being taken to ensure correct dosing the older patients, those with weight less than 50kg or those with impaired renal function. Patients undergoing elective knee arthroscopy do not require VTE prophylaxis, unless they are immbolised in some

way. For patients with lower leg fractures requiring immobilisation, the current recommendation is for the use of pharmacological prophylaxis for the entire period of immobilisation of the limb, ceasing on removal of the cast or brace.

Care must be taken with the use of pharmacological prophylaxis in patients weighing less than 50kg, the elderly, and in patients with renal impairment. This is particularly true for the newer thromboprophylactic agents, due to increased risks of bleeding. Non-pharmacological thromboprophylaxis. Some patients (i.e. those at increased risk of bleeding, those with co-morbidities precluding the use of pharmacological thromboprophylaxis, or those sensitive to the effects of pharmacological prophylactic agents) will require non-pharmacological interventions to reduce their risk of VTE. Current guidelines recommend the use of foot pumps, intermittent pneumatic compression and TED stockings in orthopaedic surgery patients unable to receive pharmacological thromboprohylaxis.

There is little evidence to suggest that their concomitant use with pharmacological thromboprophylaxis confers added benefit, however there is no evidence that intercurrent use with medications confers any additional risk to patients. Before using mechanical prophylaxis, patients should be assessed to ensure that they do not have any contraindications, including:

- Suspected or proven peripheral arterial disease
- Peripheral arterial bypass grafting
- Peripheral neuropathy or other causes of sensory impairment
- Local conditions in which stockings may cause damage e.g. fragile tissue paper skin, leg ulcers, dermatitis, gangrene or recent skin graft

- Known allergy to material of manufacture
- Cardiac failure
- Massive leg oedema
- Pulmonary oedema from congestive cardiac failure
- Unusual leg shape or size
- Major limb deformity preventing correct fit.

At all times, decisions regarding appropriate choice of thromboprophylaxis should be made in light of locally-available guidelines, protocols, and materials.

Further Reading

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Case 887: End-of-Module Questions

Authors and Affiliations

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Case Overview

These questions constitute the final assessment in the VTE prophylaxis module. On completion of these questions, candidates will be provided with a certificate of completion.

Learning Objectives

Question 1:
Question Information:

A 59-year-old man is admitted to hospital for chemotherapy of a locally advanced carcinoma of the stomach. Two weeks ago he recovered from an episode of left leg cellulitis for which he was bed-bound for three days. Three years ago he had a myocardial infarction from which he made a good recovery. His BMI is 29. He is considered for some form of prophylaxis against venous thromboembolism.

Question:

Which one of the following would place him at greatest risk of such a complication.

Choice 1: The underlying malignancy
Score : 1
Choice Feedback: Correct

Choice 2: The myocardial infarction
Score : 0
Choice Feedback: Incorrect

Choice 3: His weight
Score : 0
Choice Feedback: Incorrect

Choice 4: The recent episode of cellulitis
Score : 0
Choice Feedback: Incorrect

Choice 5: The period of immobility
Score : 0
Choice Feedback: Incorrect

Question 2:
Question Information:

A 68-year-old woman is admitted to hospital with a three day history vomiting. She had recently been started on chemotherapy for inoperable carcinoma of the pancreas. Two weeks ago a biliary stent had been inserted to relieve her jaundice. This procedure had been complicated by a bleed from sphincterotomy site. She has been taking diclofenac for pain relief. The patient is cachectic and dehydrated. Her serum biochemistry demonstrates a markefly elevated creatinine and urea. Her LFTs are grossly deranged. The patient is given intravenous fluids to correct her dehydration. Some consideration is given to measures to be taken to reduce her risk of venous thromboembolism.

Question:

Which one of the following regimens would be most appropriate?

Choice 1: Warfarin
Score : 0
Choice Feedback: Incorrect

Choice 2: Enoxaparin
Score : 0
Choice Feedback: Incorrect

Choice 3: Dabigatrin
Score : 0
Choice Feedback: Incorrect

Choice 4: Graduated Compression Stockings
Score : 1
Choice Feedback: Correct

Choice 5: Unfractionated heparin
Score : 0
Choice Feedback: Incorrect

Question 3:
Question Information:

A 28 year old man is brought to the Emergency Department following a motor vehicle accident at a low speed. He was the unrestrained passenger in the vehicle, striking his legs against the dashboard during the collision. Primary and secondary surveys reveal a stable patient with a shortened and externally rotated right leg. A FAST scan does not show any free intra-peritoneal or peri-cardial fluid. The chest X-ray does not show any evidence of a pneumothorax or rib fractures, and a CT of the brain shows no signs of acute intracranial pathology. The patient remains haemodynamically stable on transfer to the orthopaedic surgery unit.

Question:

Which of the following is the most appropriate choice of pharmacological prophylaxis?

Choice 1: Low molecular weight heparin
Score : 0
Choice Feedback: Incorrect

Choice 2: Fondaparinux
Score : 1
Choice Feedback: Correct

Choice 3: Score : 0
Choice Feedback: Incorrect

Choice 4:
Score : 0
Choice Feedback: Incorrect

Choice 5: Aspirin
Score : 0
Choice Feedback: Incorrect

Question 4:
Question Information:

A 73-year-old man is retrieved from a rural property following an accident on his ride-on lawnmower. He was trapped, face-down, beneath the vehicle for 2 hours prior to extrication. He was stabilised at the scene and retrieved to the nearest major trauma centre. On examination he has a severe crush injury of the left hand, multiple rib fractures, and fluid in Morrisons pouch. The patient is supported in a pelvic brace. His blood pressure is 83/54 mmHg despite 2 litres of 0.9% NaCl. He is scheduled for emergency surgery.

Question:

Which one of the following is the most appropriate approach to post-operative VTE prophylaxis?

Choice 1: Commence fondaparinux once adequate haemostasis has been achieved
Score : 0
Choice Feedback: Incorrect

Choice 2: Commence use of calf-compression stockings only
Score : 0
Choice Feedback: Incorrect

Choice 3: No VTE prophylaxis is required
Score : 0
Choice Feedback: Incorrect

Choice 4: Commence low-molecular weight heparin once adequate haemostasis has been achieved.
Score : 1
Choice Feedback: Correct

Choice 5: Commence Dabigatran etexilate once adequate haemostasis has been achieved.
Score : 0
Choice Feedback: Incorrect

Question 5:
Question Information:

A 30-year-old woman who is G2P1 presents at 37 weeks gestation with a two day history of pain and swelling in her right calf. She has also noticed some breathless during this time. Her previous pregnancy was uneventful. There is some tenderness and redness of the calf and examination of the chest is unremarkable.

Question:

Which one of the following is the most appropriate initial investigation?

Choice 1: CT pulmonary
Score : 0
Choice Feedback: Incorrect

Choice 2: Ventilation-perfusion scan
Score : 1
Choice Feedback: Correct

Choice 3: Chest X-ray
Score : 0
Choice Feedback: Incorrect

Choice 4: Duplex scan of lower limbs
Score : 0
Choice Feedback: Incorrect

Choice 5: D-dimer
Score : 0
Choice Feedback: Incorrect

Question 6:
Question Information:

A 40-year-old man is admitted to the medical ward for intravenous antibiotics to manage an uncomplicated cellulitis of his left calf. An ultrasound scan shows no evidence of DVT. He is otherwise healthy and mobilises around the ward; he can often be found outside of the hospital talking to other patients. He is a non-smoker and drinks 1-2 standard drinks per week. He weighs 98kg.

Question:

Which one of the following is the most appropriate choice of VTE prophylaxis?

Choice 1: Graduated calf compression stockings
Score : 0
Choice Feedback: Incorrect

Choice 2: No VTE prophylaxis is required
Score : 1
Choice Feedback: Correct

Choice 3: Aspirin, 100mg PO daily
Score : 0
Choice Feedback: Incorrect

Choice 4: Enoxaparin, 100mg Daily, subcut
Score : 0
Choice Feedback: Incorrect

Choice 5: Low-dose unfractionated heparin
Score : 0
Choice Feedback: Incorrect

Question 7:
Question Information:

A 73-year-old man is hospitalised with an haemorrhagic stroke, proven on CT scan. As part of the rehabilitation program, consideration must be given to prophylaxis against venous thromboembolism. Immediately prior to the stroke the patient enjoyed an active life, although he had hurt his back recently and had been taking paracetamol immediately prior to his admission. Apart from some right-sided motor weakness in his arm, hand and leg, the physical examination is unremarkable. His serum biochemistry is shown. (Image) Haemoglobin 128 g/L (130 - 175) Platelets 130 x 10^9/L (150 - 450)

Question:

Which one of the following regimens would be most appropriate?

Choice 1: Calf compression stockings
Score : 1
Choice Feedback: Correct

Choice 2: Aspirin
Score : 0
Choice Feedback: Incorrect

Choice 3: Enoxaparin
Score : 0
Choice Feedback: Incorrect

Choice 4: Dabigatran
Score : 0
Choice Feedback: Incorrect

Choice 5: Warfarin
Score : 0
Choice Feedback: Incorrect

Question 8:
Question Information:

An otherwise fit 64-year-old man is about to undergo a partial gastrectomy for carcinoma. He will require some measures to minimise the risk of venous thromboembolic complications during his hospitalisation.

Question:

Which one of the following is the most appropriate intervention?

Choice 1: Pneumatic calf compression during surgery only
Score : 0
Choice Feedback: Incorrect

Choice 2: Sequential calf compression stockings until discharge
Score : 0
Choice Feedback: Incorrect

Choice 3: Enoxaparin starting at commencement of surgery until
Score : 0
Choice Feedback: Incorrect

Choice 4: Enoxaparin starting immediately after surgery and given until discharge
Score : 0
Choice Feedback: Incorrect

Choice 5: Enoxaparin given immediately after surgery and continued for 14 days after discharge
Score : 1
Choice Feedback:Correct

Question 9:
Question Information:

A 35-year-old woman is admitted for an elective laparoscopic cholecystectomy, planned as a day case procedure. Apart from an episode of biliary colic two months earlier, she is in good health and there is nothing of note in the past medical history. She is on the oral contraceptive pill. With regard to minimising the risk of venous thrombo-embolic (VTE) complications, graded calf compression stockings will be applied before and during the operation. Measures need to be taken to reduce her risk of a venous thrombo-embolic event

Question:

Which one of the following is the most appropriate management?

Choice 1: Intraoperative pneumatic calf compression and perioperative enoxaparin until mobile
Score : 1
Choice Feedback: Correct

Choice 2: Intraoperative pneumatic calf compression and postoperative enoxaparin for two weeks
Score : 0
Choice Feedback: Incorrect

Choice 3: Intraoperative pneumatic calf compression and postoperative enoxaparin for four weeks
Score : 0
Choice Feedback: Incorrect

Choice 4: No additional measures are required
Score : 0
Choice Feedback: Incorrect

Choice 5: Pneumatic calf compression devices during
Score : 0
Choice Feedback: Incorrect

Question 10:
Question Information:

A 72-year-old man is about to start a course of chemotherapy for a recently diagnosed small cell carcinoma of the lung. Consideration is being given to the most appropriate chemoprophylaxis to reduce his risk of VTE. Apart from his lung cancer the patient does not have any other apparent health issues and is still leading an active life. His pre-chemotherapy laboratory results are reviewed. His Hb was 98g/L, his leucocyte count 12.5x10^9/L and his platelet count was 450x10^9/L.

Question:

Which one of the following regimens would be most appropriate choice of anticoagulant drug?

Choice 1: Warfarin
Score : 0
Choice Feedback: Incorrect

Choice 2: Enoxaparin
Score : 1
Choice Feedback: Correct

Choice 3: Unfractionated heparin
Score : 0
Choice Feedback: Incorrect

Choice 4: Dabigatran
Score : 0
Choice Feedback: Incorrect

Choice 5: Aspirin
Score : 0
Choice Feedback: Incorrect

Section 3. Studies Performed

Chapter 9. Online Learning In Venous thromboembolism Education: A Randomised Controlled Trial

Conducted in the Discipline of Surgery, School of Medicine, University of Adelaide, Adelaide, SA 5000, Australia

Statement of Authorship

Title of Paper	Online Learning In Venous thromboembolism Education: A Randomised Controlled Trial
Publication Status	☐ Published ☐ Accepted for Publication ☒ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	

Principal Author

Name of Principal Author (Candidate)	Eamon Patrick Raith		
Contribution to the Paper	Project design, data collection, data analysis, manuscript preparation		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	8/1/19

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Abstract

Introduction: A venous thromboembolism prophylaxis (VTE) e-learning module was developed and a randomised controlled educational trial was conducted to investigate its educational benefit in improving knowledge of thromboprophylaxis guidelines.

Methods: Medical students were randomised into control (n=144) and intervention (n=148) groups. Pre- and post-test scores were compared within and between groups. Students were retested six months later.

Results: 292 Students completed the study. Mean baseline scores were similar between groups (40.8% vs. 41.6%, p=0.750; control vs. intervention). No statistically significant improvement was observed between groups (41.1% vs. 44.7%, p=0.242; control vs. intervention) or between baseline and post-intervention scores in the intervention group (41.6% vs. 44.7%, p= 0.241). Re-testing at six months demonstrated improvement in all scores.

Conclusion: Use of an online learning module was not immediately associated with improved scores relating to knowledge of thromboprophylaxis. Scores improved six months post-intervention, suggesting a possible role for blended learning in this field.

Introduction

Venous thromboembolism (VTE) is a common, multi-factorial disease, with incidence rates between 0.75 to 2.69 per 1,000 of population. Adherence to global thromboprophylaxis guidelines has decreased over time, primarily due to poor implementation of post-discharge guidelines.[117] Educational interventions to improve thromboprophylaxis management have had variable and limited success.[111,118]

e-Learning has been demonstrated to promote self-directed learning, provide flexible learning opportunities, and engage learners in collaborative learning communities,[119] however, only two studies demonstrated transfer of skills from e-learning to the clinical surgical environment, and there is no evidence that the use of e-learning improves patient outcomes in surgery.[120]

Wolpin et al published a paper in 2011 describing a the efficacy of an online training module for VTE prophylaxis, provided to 69 residents and fellows from two medical centers.[111] They identified a trend for knowledge gains related to VTE guidelines on post-test for clinicians with a 14.5% increase in content mastery ($p=0.05$). Although effect size was small (0.23), the authors noted an overall improvement in knowledge mastery relating to VTE prophylaxis between pre- and post-tests, but no additional knowledge gain through the use of question/response case studies.[111]

The aim of this study was to assess the educational benefit of using an online, case-based learning system to deliver educational material relating to VTE prophylaxis across medical and surgical specialties.[111]

Methods

The University of Adelaide Office of Research Ethics, Compliance and Integrity (H-2012-057) and The University of Notre Dame, Australia, Human Research Ethics Committee (013093S) approved this study.

Study design

A randomised controlled educational trial was designed and conducted based on methodologies described by Wolpin et al and Farah et al.[111,125] A six-month online course on venous thromboembolism prophylaxis was provided to fifth year medical students at The University of Adelaide for each six-month semester, for two consecutive years. All fifth year medical students were enrolled in the course (published on www.emedici.com) in each year, and the content of the course was examinable in the end of year 'barrier' examination. Enrolment in the course was not contingent upon participation in the study, and all students ultimately had access to the same learning material.

Students were eligible for participation in the RCT if they were a fifth-year (penultimate-year) medical student at The University of Adelaide.

Students were excluded if:

1. They refused consent to participate in the study (however, students still had access to the educational material).

2. They were currently enrolled in their obstetrics & gynaecology/paediatric medicine semester (Students were able to enrol in the course and the study in the alternate semester).

The online module was made available to two annual cohorts of students, across 4 semesters, over two years. Students had to complete the module within a single semester.

Five case-based learning modules teaching the fundamentals of VTE prophylaxis in Oncology, Surgery, General Medicine, Obstetrics & Gynaecology, and Orthopaedics, according to national[37] and international[38] guidelines. In addition, twenty assessment questions were constructed. These were divided into three modules; the "Baseline Assessment Module" and the "Final Assessment Module", each composed of ten questions, with equal representation of the taught specialty areas, and a Control Group-only Assessment Module containing all twenty questions.

Students were enrolled into the course at the beginning of the semester. They had six months to complete the learning material, in their own time and at their own pace. Once enrolled in the course students were shown an introductory page at their first login. This page explained the study that was being conducted, the principles around data collection for the study, and emphasized that all students would receive equal access to the learning material regardless of participation. Students were then invited to consent to participate in the study. Participating students were then automatically randomised to intervention or control groups (Figure 9.1).

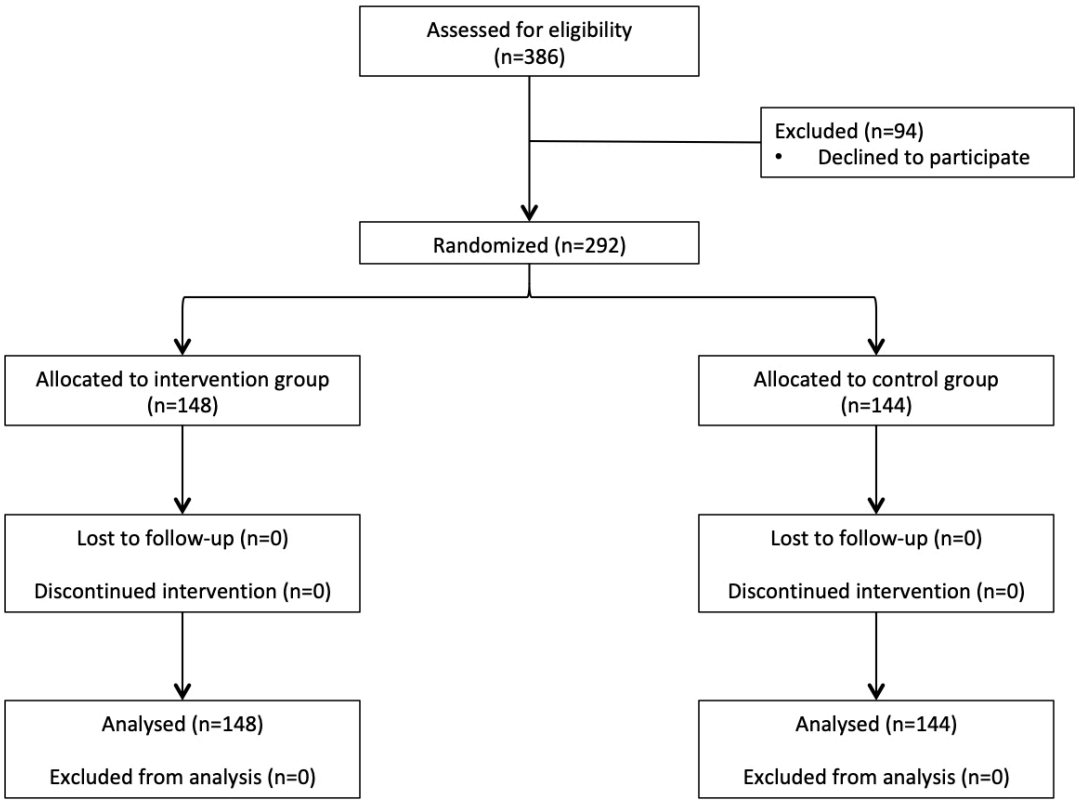

Figure 9.1 CONSORT Diagram.

Recruitment and allocation of subjects to control and intervention groups

Students randomised to the control group were required to complete the 'Control-Group-only Assessment Module' (labelled 'Baseline Assessment Questions' on their screen). Once completed, they then had free access to the learning modules.

Students randomised to the intervention group completed ten baseline assessment questions (the same as questions 1-10 in the Control Group-only Assessment Module) then had access to the learning material. At the completion of the learning material, students in the intervention group then completed a Final Assessment Module of ten questions (the same as questions 11-20 in the Control Group-only Assessment Module) (Figures 9.2 & 9.3).

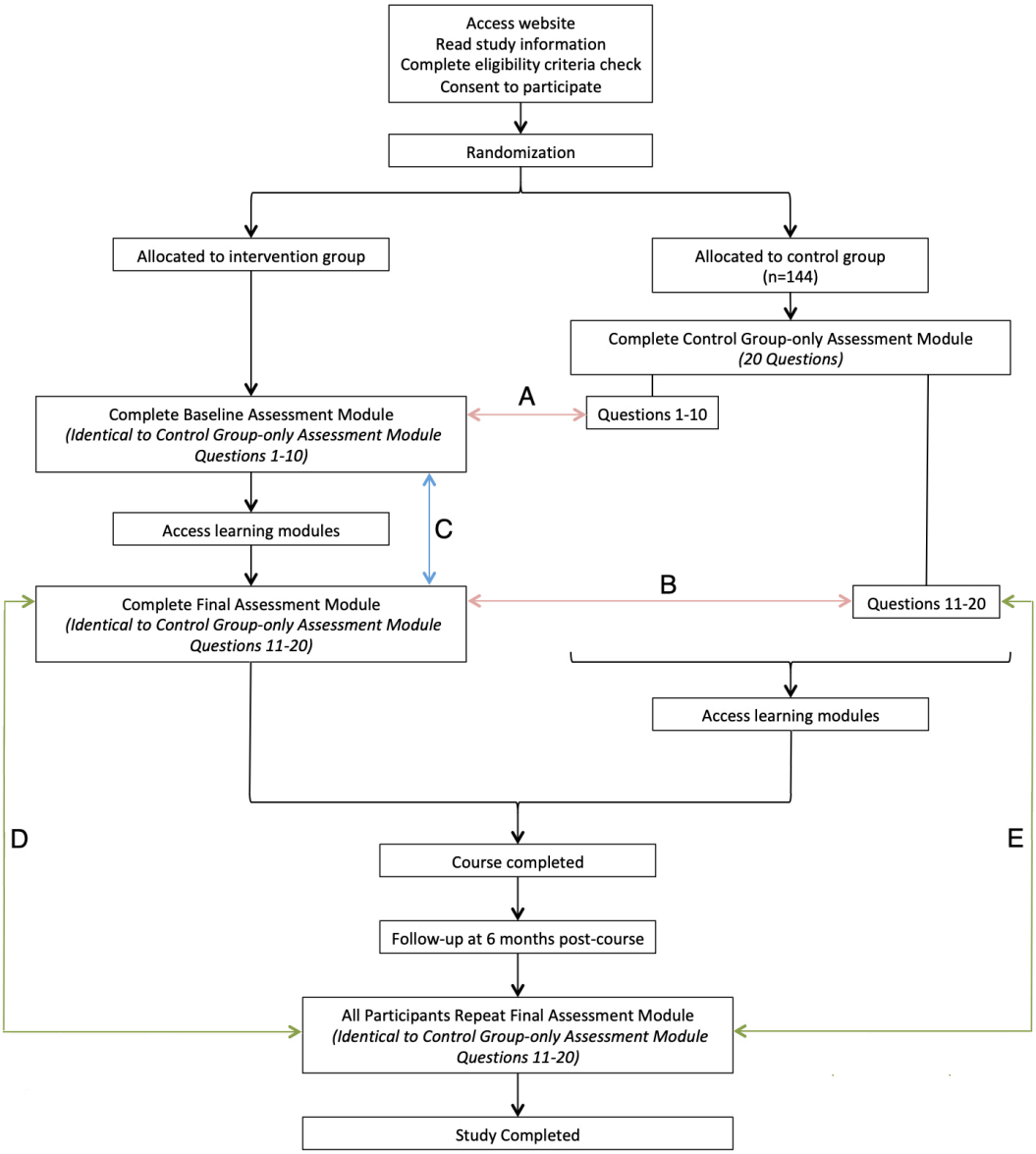

Figure 9.2 Graphic representation of trial process for students randomised to control and intervention groups.

A, Comparison of scores between groups (Control Group-only Assessment Module Questions 1-10 vs the ten-question Intervention Group Baseline Assessment Module. The questions used to establish baseline knowledge are identical between the two groups. B, Comparison of scores between groups (Control Grouponly Assessment Module Questions 11-20 vs the ten-question Intervention Group Final Assessment Module. The questions are identical between the two groups. C, Comparison of scores between Intervention Group Final Assessment Module and Intervention Group Baseline Assessment Module. D & E, Comparison of scores from six-month follow up with Intervention Group Final Assessment Module, to assess persistence of knowledge post-online learning program

Questions were grouped in this way to allow comparison between intervention and control groups at baseline and following intervention group completion of the learning material (Figure 9.3, red groups and arrows), and to allow comparison within the intervention group pre- and post-intervention (Figure 9.3, blue arrows).

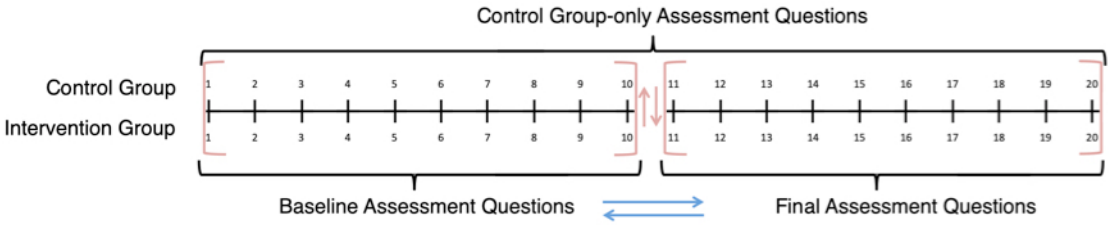

Figure 9.3 Breakdown of questions between control and intervention groups.

Both groups undertook all twenty questions. The control group undertook all twenty questions in the Control Group-Only Assessment Module; they then had access to the learning material. This approach provided a baseline for pre- and postintervention comparison between the control and intervention groups. The intervention group completed the ten-question Intervention Group Baseline Assessment Module, which is equivalent to questions 1-10 in the Control Group-Only Assessment Module. After accessing the learning material, the Intervention group completed the ten-question Intervention Group Final Assessment Module, which is equivalent to questions 11-20 completed in the Control Group-Only Assessment Module. Comparison of scores was then performed between intervention and control groups at baseline and following the intervention group's completion of the learning material (red groupings and red arrows). Scores were also compared within the intervention group pre- and post-intervention (blue arrows)

Six months after completion of the course, all students were followed-up and asked to complete the Final Assessment Module questions (Control Group-only Questions 11-20) again, to assess persistence of learning effect. The study was then completed.

Outcomes

The primary outcome was difference in mean scores between the intervention group versus control group for final-assessment questions (Control Group-only assessment questions 11-20).

Secondary outcomes were;

1) Differences in mean scores between baseline assessment questions and final assessment questions in the intervention group.

2) Differences in mean scores between questions 1-10 and 11-20 in the control group.

3) Differences in mean score between questions 11-20 in the Control Group and repeat Final Assessment Module questions/Control Group-only Questions 11-20 conducted at 6-months follow-up, and

4) Differences in mean scores between Intervention Group final-assessment questions and repeat Final Assessment Module questions/Control Group-only Questions 11-20 conducted at 6-months follow-up.

Statistical Analysis

All analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Group comparisons were conducted using linear regression, linear mixed-effects models and Student's *t*-tests for normally distributed data. Descriptive results are reported as frequencies (%), means (standard deviations) or medians [interquartile ranges]. Inferential statistics are presented with estimates, 95% confidence intervals and P values. For linear mixed-effects models (used for comparison of scores between baseline questions and final-assessment questions in the intervention group, or questions 1-10 vs 11-20 for the control group), assumptions of a linear model were upheld. A mixed effects model was used as scores within student would be more similar, more correlated, than scores between students, leading to erroneous standard errors and P values if not controlled for.

We also explored a novel variable, the improvement score (described by Khatib et al[135]), equivalent to the post-intervention score minus the pre-intervention score. For the control group this is reported as the score for questions 11-20 minus the score for questions 1-10, and for the intervention group the score for final-assessment questions minus the score for baseline questions.

Based on the study by Wolpin et al,[111] we calculated a requisite sample size of 200-270 participants, based on a minimum-anticipated score improvement of 14.5% (p=0.05).

Results

386 students were eligible for participation in the study. 94 students declined to participate, resulting in a total cohort of 292 students. No students actively withdrew from the study. Completion of modules was variable; some students completed all modules and cases, some completed only the initial module, regardless of randomization. Given that this likely represents real-world engagement with an e-learning tool all analyses were completed on the basis of intention-to-treat. Mean scores and mean time-per-module are presented in table 1.

144 students were randomised to the control arm of the study. Mean score for baseline questions 1-10 was 0.408 (40.8%) (SD, 0.175), and for baseline questions 11-20 was 0.411 (41.1%) (SD, 0.215). 148 students were randomised to the intervention group. Mean score for baseline questions (equivalent to control-group baseline questions 1-10) was 0.416 (41.6%) (SD, 0.180), and mean score for final-assessment questions was 0.447 (44.7%) (SD, 0.278) (Table 1).

	Control Group		Intervention Group		Six Month Follow-Up Group
	Q 1-10	Q11-20	Baseline Questions	Final-assessment Questions	
Number of students, n	144		148		155
Mean Score, n, % (SD[a])	0.408, 40.8% (0.175)	0.41, 41.1% (0.215)	0.416, 41.6% (0.180)	0.447, 44.7% (0.278)	0.569, 56.9% (0.141)
Frequency of deciles of scores, n (%)					
0%	4 (2.8%)	15 (10.4%)	3 (2%)	34 (23%)	0 (0%)
10%	7 (4.9%)	3 (2.1%)	5 (3.4%)	1 (0.7%)	0 (0%)
20%	14 (9.7%)	15 (10.4%)	13 (8.8%)	7 (4.7%)	1 (0.6%)
30%	23 (16%)	16 (11.1%)	33 (22.3%)	14 (9.5%)	9 (5.8%)
40%	36 (25%)	24 (16.7%)	35 (23.6%)	23 (15.5%)	20 (12.9%)
50%	35 (24.3%)	35 (24.3%)	34 (23%)	34 (23%)	42 (27.1%)
60%	17 (11.8%)	20 (13.9%)	12 (8.1%)	22 (14.9%)	36 (23.2%)
70%	4 (2.8%)	9 (6.3%)	5 (3.4%)	10 (6.8%)	30 (19.4%)
80%	2 (1.4%)	6 (4.2%)	5 (3.4%)	1 (0.7%)	16 (03%)
90%	1 (0.7%)	1 (0.7%)	1 (0.7%)	2 (1.4%)	1 (0.6%)
100%	1 (0.7%)	0 (0%)	2 (1.4%)	0 (0%)	0 (0%)
Mean time to completion of questions, seconds (SD)	1056.80 (804.14)	791.26 (975.20)	770.36 (469.64)	471.23 (434.87)	N/A[b]

Table 9.1 Descriptive and frequency data for control, intervention and follow-up groups.

[a]SD represented Standard Deviation. [b]Time to completion of questions was unable to be collected for the follow-up group. Data collection occurred in a group setting; as a result, data was collected in an off-line format, with a 30-minute time limit for the entire group.

Among the control group's first ten questions (baseline questions 1-10), the median score was 0.4 (40%), as it was for questions 11-20. For questions 1-10 in the control group, the most frequent score was 0.4 (40%), representing 25% of all scores. 4 (2.8%) students scored zero, one student (0.7%) scored 100%. For questions 11-20 the most frequent score was 0.5 (50%), obtained by 35 students (24.3%). 15 students

(10.4%) scored zero in questions 11-20; 1 student (0.7%) scored 90% in questions 11-20. No student scored 100% (Table 9.1).

In the intervention group's baseline questions, the median score was 0.4 (40%) for the baseline questions, and 0.5 (50%) for the final-assessment questions. The most frequent result was 0.4 (40%) (35 students, 23.6%). 3 students (2%) scored zero. 2 students (1.4%) scored 100%. For the intervention group's final-assessment questions, the most frequent results were zero and 0.6 (60%) (34 students, 23%, respectively). 2 students (1.4%) scored 100% (Table 9.1).

Student's *t*-test for paired samples was used to compare mean scores between pre- and post-test questions, within groups. An independent Student's *t*-test was used for comparison of mean scores between groups (Table 9.2). There was no statistically-significant difference between any set of pre- or post-test questions, or between intervention and control groups. The difference between mean scores for questions 11-20 in the control group and mean scores for questions 1-10 in the control group was 0.003 ($t(143)= 0.163$, 95%CI, 0.034-0.04; $p=0.871$). The difference between mean baseline scores for the intervention group and the mean score for questions 1-10 of the control group was 0.008 ($t(290)= 0.379$, 95%CI, -0.033-0.049; $p=0.705$). The difference between mean scores for the final-assessment questions versus the baseline questions in the intervention group was 0.030 ($t(147)= 1.176$, 95%CI, 0.02-0.08; $p= 0.241$). The difference between mean scores between the final-assessment questions for the intervention group versus questions 11-20 for the control group was 0.036 ($t(290)= 1.219$, 95%CI, -0.022-0.093; $p=0.224$).

	Control Group (n=144)	Intervention Group (n=148)	
Q1-10/Baseline (mean, [SD])	40.8% [0.175]	41.6% [0.180]	0.008, t(290)= 0.379, 95%CI, -0.033-0.049; p=0.705
Q11-20/Final-Assessment (mean, [SD])	41.1% [0.215]	44.7% [0.278]	0.036, t(290)= 1.219, 95%CI, -0.022-0.093; p=0.224
	0.003, t(143)= 0.163 95%CI, 0.034-0.04; p=0.871	0.030, t(147)= 1.176, 95%CI, 0.02-0.08; p= 0.241	

Table 9.2 Difference in mean scores within groups (columns) and between groups (rows).

Linear regression modelling demonstrated no statistically significant difference between mean scores for questions 1-10 in the control group and baseline questions in the intervention group. Both mean scores were 0.4 (40%) (p=0.70). Similarly, there was no significant difference between mean scores for questions 11-20 in the control group and final-assessment questions in the intervention group. Both mean scores were 0.4 (40%) (p=0.22).

The improvement score[135] was calculated for the control and intervention groups, as described above. The mean improvement score for the control group was 0.003 (SD, 0.20). The mean improvement score for the intervention group was 0.03 (SD, 0.31). Student's *t*-test was used to compare means between intervention group

improvement scores and control group improvement scores. The difference was 0.03 (95% CI, 0.03-0.09; p=0.33).

A linear mixed effects model was used to investigate the association between performance in questions 1-10 and scores for questions 11-20 in the control group. There was no significant difference between mean score for questions 1-10 and questions 11-20, adjusted for clustering on student; both scores were 0.4 (40%) (p=0.90).

The same analysis was performed for the intervention group, examining the association between score in the baseline questions and score in the final-assessment questions. There was no significant difference between mean scores; in both cases the mean score was 0.4 (40%) (p=0.27).

Follow-Up

After completion of the study, students were followed up, and asked to re-sit the final-assessment questions in order to assess knowledge retention after six months. 155 students participated in the follow-up questions.

The mean score was 0.57 (57%) (SD, 0.14), the median score was 0.5 (50%). The most frequent score was 0.5 (50%), attained by 42 students (27.1%). 1 student (0.6%) scored 0.20 (20%), the lowest score. The highest score, 0.9 (90%), was attained by one student (0.6%).

To investigate the association between Question 11-20 score for the control group and all scores at six months follow-up, a linear regression model was used. There is a statistically significant difference between mean Question 11-20 score in the control group versus scores at six months follow-up (global P value<0.0001) (Table 9.3). Mean q11-20 score for the control group is 0.41 and for the follow-up group is 0.57. Mean q11-20 score is 0.16 units lower in the control group than it is in the follow-up group (estimate=-0.16, 95%CI, -0.20 to -0.12).

	Control Group (n=144)	**Intervention Group (n=148)**
Q11-20/Final-Assessment (mean, [SD])	41.1% [0.215]	44.7% [0.278]
Six-Month Follow-Up Qs (n=155)	56.9% [0.141]	
	0.16, 95%CI, 0.12-0.20 p≤0.001	0.12, 95%CI, 0.07-0.17 p≤0.001

Table 9.3 Difference in mean scores at six months follow-up compared with initial scores

A linear regression model was also used to investigate the association between outcome score for the intervention group and all scores at six months follow-up. There is a statistically significant difference between mean final-assessment questions score in the intervention versus scores at six months follow-up (global P value<0.0001). Mean final-assessment questions score for the intervention group is 0.45 and for the follow-up group is 0.57. Mean final-assessment questions score is

0.12 units lower in the intervention group than it is in the follow-up group (estimate=-0.12, 95%CI, -0.17 to -0.07).

Discussion

We have shown that the introduction of an online VTE prophylaxis teaching module did not result in any statistically significant immediate benefits in terms of knowledge gained, however, repeat testing at six months demonstrated an improvement in test scores.

Wolpin et al[111] reported positive results from two online educational interventions, demonstrating a 14.5% increase in content mastery related to VTE guidelines, yet no additional increase in knowledge gain with additional question/response case studies, an alternate finding to that reported by Casebeer et al.[111,137] Watt et al report the effect of educational interventions on thromboprophylaxis prescribing patterns among junior doctors. In this study, results of an audit around VTE prescribing practice were presented to Junior Doctors as part of a teaching session focussed on areas targeted for improvement. A further educational intervention (verbal feedback) was provided to senior medical staff. The authors report generally-appropriate thromboprophylaxis prescribing (80.6-92.9%), but poor compliance with guidelines, and no improvement in teaching following educational interventions.[118]

Computer- and technology-aided learning can be effective in improving skills and examination outcomes, with faster uptake of more material leading to a reduction in training time by up to one-third.[96,138,139] E-learning has been demonstrated to be associated with fewer costs than traditional teaching modalities and has a high

degree of learner-satisfaction, although evidence of outcomes (in terms of knowledge-gain and knowledge-retention) has been variable.[92]

In this study, there was no statistical difference in mean scores between control and intervention groups at baseline testing, or between the intervention group post-online module and the control group. Performance in the baseline questions (questions 1-10 in the control group) did not appear to correlate with results in the final-assessment questions (questions 11-20 in the control group) in either group. The mean improvement score (MIS) (post-intervention MCQ minus pre-intervention score)[135] was not statistically significantly different between groups.

Interestingly, students followed up six months after completion of the module demonstrated a statistically significant improvement in scores, with follow-up group mean score rising to 0.57 compared to 0.41 for control group questions 11-20 ($p<0.0001$) and 0.45 for intervention group final-assessment questions ($p<0.0001$).

These results contrast with Wolpin et al's findings that the use of an online learning tool lead to an improvement in total knowledge mastery around the topic of VTE prophylaxis, however they appear to support the finding that the use of case-based modules did not lead to an increase in knowledge.

Students completed the module during Year 5 of their undergraduate medical degree program. At the University where this trial was conducted Year 5 is also the year in which students sit their final examinations. As per the tripartite model of learning, medical students tend to begin their training as deep learners, but may move

towards strategic learning approaches due to the demands of their course, with strategic learning demonstrating a positive correlation with final exam marks.[96,140,141] It is possible that students took a strategic approach to the module, as the content represents a small, yet examinable, component of the undergraduate curriculum. This may be reflected in the amount of time students spent on the modules, with students spending a longer period of time on pre-test questions (Control group, mean time 1056.8 seconds (17.61 minutes) [SD 804.14]; Intervention group, mean time 769 seconds (12.82 minutes) [SD 465.06]) than on post-test questions (Control group, mean time 791.26 seconds (13.19 minutes) [SD 975.20]; Intervention group, mean time 466.18 seconds (7.77 minutes) [SD 431.15].

The results may also be partially explained by the cases included in the module. The module provided education and testing on cases in Oncology, General Surgery, General Medicine, Obstetrics & Gynaecology, and Orthopaedics. Variation in student and junior doctor knowledge surrounding VTE prophylaxis, and prescribing compliance, has been reported across medical and surgical specialties.[118,142] It is possible that students' scores on more familiar areas (particularly thromboprophylaxis in surgery and orthopaedics) confounded scores for less-familiar specialties, such as obstetrics & gynaecology.

The improvement in scores at six months post-study is difficult to explain, but may represent knowledge application in the ward environment (where students are exposed to junior medical staff considering and prescribing thromboprophylaxis in various scenarios). This suggests, in line with other reported studies,[110,143] that a blended-learning approach (combining virtual learning environment and face-to-face

interactions)[96] may lead to a greater improvement in knowledge surrounding thromboprophylaxis, however, our study was not designed to measure this effect.

Our study has a number of strengths and limitations. This is a large, appropriately-powered randomised controlled educational trial that aimed to examine the effect of an online educational intervention on knowledge surrounding VTE prophylaxis. It was adequately powered to detect an effect at a p-value of 0.05. Students were randomised into approximately equal groups (144 vs 148 students) and received an educational intervention as per the trial design. Analysis was conducted on an intention-to-treat basis.

Our study was limited by potential bias in the form of students conducting additional reading outside the module, and seeking advice or input from senior staff or other students. This truly reflects real-world use of e-learning material, however, and therefore better measures the effectiveness of our online learning module.

Conclusion

The use of an online learning module on VTE prophylaxis across multiple specialties did not demonstrate a statistically significant improvement in mean scores in pre- and post- testing, or between intervention and control groups. Repeating the Final Assessment Module questions/Control Group-only Questions 11-20 at six months was associated with a statistically significant improvement in mean scores when compared to results for the control group (Control Group-only Questions questions 11-20) and the intervention group (Final Assessment Module questions). The study findings do suggest, however, that a blended-learning approach may result in improved knowledge mastery surrounding VTE prophylaxis.

Chapter 10. Factors Associated With Test Performance In Venous Thromboembolism E-Learning: A Subgroup Analysis of the OLIVE Trial.

Conducted in the Discipline of Surgery, School of Medicine, University of Adelaide, Adelaide, SA 5000, Australia

Statement of Authorship

Title of Paper	Factors Associated With Test Performance In Venous Thromboembolism E-Learning: A Subgroup Analysis of the OLIVE Trial.
Publication Status	☐ Published ☐ Accepted for Publication ☒ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	

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Name of Principal Author (Candidate)	Eamon Patrick Raith		
Contribution to the Paper	Project design, data collection, data analysis, manuscript preparation		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Abstract

Introduction: A venous thromboembolism prophylaxis (VTE) e-learning module was developed and a randomised controlled educational trial was conducted to investigate its educational benefit in improving knowledge of thromboprophylaxis guidelines.

Methods: Medical students were randomised into control (n=144) and intervention (n=148) groups. Pre- and post-test scores were compared within and between groups. Students were retested six months later. In order to determine the relevant effects of scores and times for completion for each case on overall performance, and correlation with performance in other cases and in the final assessments, a subgroup analysis was performed.

Results: 292 Students completed the study. Mean baseline scores were similar between groups (40.8% vs. 41.6%, p=0.750; control vs. intervention). Students in the control group spent more time on the baseline assessment questions, and on the final assessment questions than the intervention group. Students in the intervention group out-performed students in the control group in scores for the medical and orthopaedic surgery cases. Analysis of correlation of performance between cases demonstrated that performance in the eMedici VTE Prophylaxis Module appears to be associated with performance in areas of medicine in which students had prior experience, or were currently rotating.

Conclusion: Use of an online learning module was not immediately associated with improved scores relating to knowledge of thromboprophylaxis. Scores improved six

months post-intervention. While e-learning in isolation may not lead to immediate knowledge improvement among medical students, the use of e-learning in a blended learning strategy with clinical exposure appears to lead to improvement in knowledge outcomes.

Introduction

The Online Learning in Venous thrombombolism Education (OLIVE) study[144] was a randomised controlled trial that aimed to measure the effect of e-learning intervention on the knowledge base regarding venous thromboembolism prophylaxis of medical students in their final examinable year of study. The trial, which was conducted at The University of Adelaide, South Australia, recruited 386 medical students in their final examinable year of training. The primary end point was comparison of post-intervention test scores. In this study, the use of an e-learning module did not appear to provide immediate improvement in student knowledge of VTE prophylaxis, however there were significant improvements in all students' scores on repeat testing at 6 months follow-up.

It was unclear as to why this increase in test scores occurred; while it may have represented an unintentional blended-learning effect (i.e. students were more cognoscente of VTE prophylaxis principles, and focused on those techniques while on clinical rotations), we were not certain that the initial results may have been skewed by students potentially performing very well in modules for specialty areas that have a traditionally high awareness of the role of VTE prophylaxis (e.g. the orthopaedic surgery case, or the oncology case), while under-performing in less-familiar areas. In this article, we examine the sub-groups of the OLIVE trial with a view to examining the relative contribution of case-based factors to overall outcomes.

Methods

The University of Adelaide Office of Research Ethics, Compliance and Integrity (H-2012-057) and The University of Notre Dame, Australia, Human Research Ethics Committee (013093S) approved this study.

A randomized controlled educational trial was designed and conducted based on methodologies described by Wolpin et al and Farah et al.[111,125] Medical Students in their penultimate year at The University of Adelaide were asked to participate in a randomized controlled educational trial. Students were eligible for participation if they were a fifth-year (penultimate-year) medical student at The University of Adelaide.

Students were excluded if they met any of the following criteria:

1. They refused consent to participate in the study (however, students still had access to the educational material).
2. They were currently enrolled in their obstetrics & gynaecology/paediatric medicine semester (due to the specific and high-volume workload of this semester, and associated end-of-rotation assessments).

The online module was made available to two years of students, across 4 semesters. Students had to complete the module within a single semester.

After consenting to participate in the study students were randomized to one of two groups (control vs. intervention) (Figure 10.1).

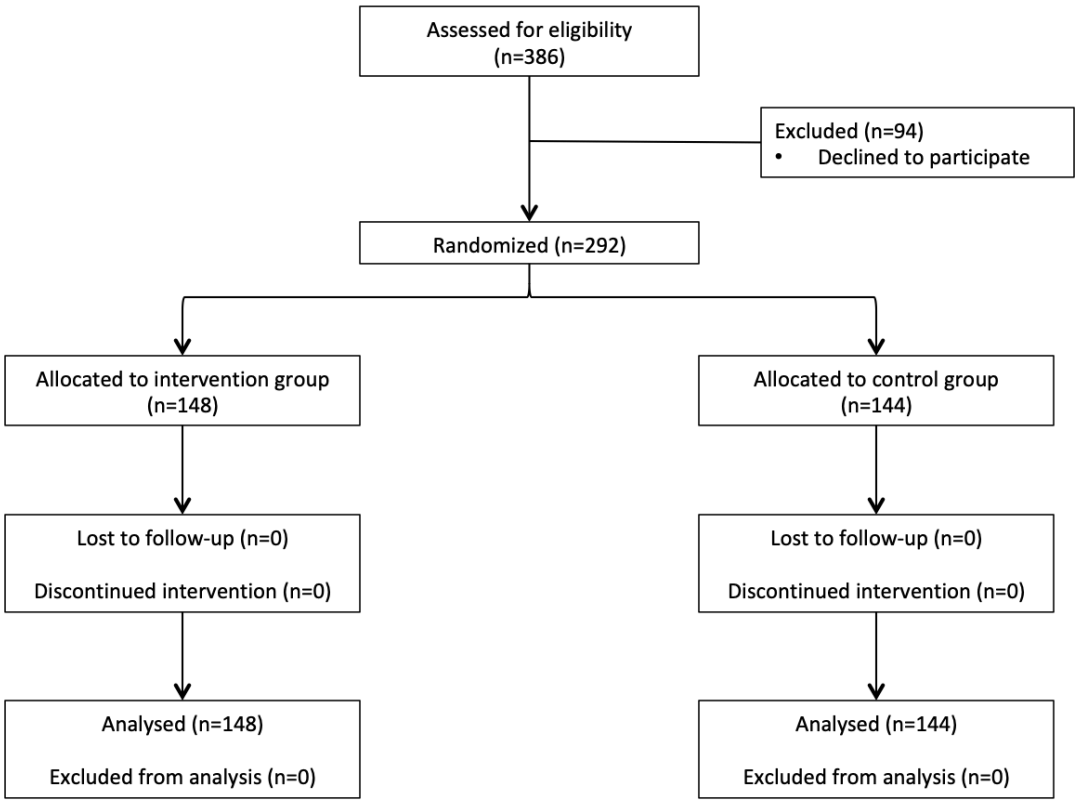

Figure 10.1 CONSORT Diagram.

Recruitment and allocation of subjects to control and intervention groups

The control group undertook an initial baseline-assessment case of twenty questions, assessing their knowledge surrounding VTE prophylaxis across the specialties of Oncology, Surgery, General Medicine, Obstetrics & Gynaecology, and Orthopaedics. They were then given access to the online educational modules.

The intervention group undertook a baseline assessment case composed of ten questions assessing their knowledge surrounding VTE prophylaxis across the specialties of Oncology, Surgery, General Medicine, Obstetrics & Gynaecology, and Orthopaedics. These were identical to Questions 1-10 completed by the control group. The intervention group were then given access to five case-based modules teaching the fundamentals of VTE prophylaxis in Oncology, Surgery, General

Medicine, Obstetrics & Gynaecology, and Orthopaedics, according to national[37] and international[38] guidelines. Following completion of these modules, students completed a 10 question post-test, matched to questions 11-20 completed as a baseline assessment by the control group. Six months after completion of the course, all students were followed-up and asked to complete the 10 post-test questions/control group questions 11-20 again. The study was then completed.

In order to determine the relevant effects of scores and times for completion for each case on overall performance, and correlation with performance in other cases and in the final assessments, a subgroup analysis was performed.

Statistical Analysis

All analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Group comparisons were conducted using linear regression, linear mixed-effects models and Student's *t*-tests for normally distributed data. Descriptive results are reported as frequencies (%), means (standard deviations) or medians [interquartile ranges]. Inferential statistics are presented with estimates, 95% confidence intervals and P values. For linear mixed-effects models (used for comparison of scores between baseline questions and final-assessment questions in the intervention group, or questions 1-10 vs 11-20 for the control group), assumptions of a linear model were upheld. A mixed effects model was used as scores within student would be more similar, more correlated, than scores between students, leading to erroneous standard errors and P values if not controlled for.

Results

Participants

386 students were eligible for participation in the study. 94 students declined to participate, resulting in a total cohort of 292 students. No students actively withdrew from the study. Completion of modules was variable; some students completed all modules and cases, some completed only the initial module, regardless of randomization. Given that this likely represents real-world engagement with an e-learning tool all analyses were completed on the basis of intention-to-treat.

Scores and times

144 students were randomized to the control arm of the study. Mean score for baseline questions 1-10 was 0.408 (40.8%) (SD, 0.175), and for baseline questions 11-20 was 0.411 (41.1%) (SD, 0.215). 148 students were randomized to the intervention group. Mean score for baseline questions (equivalent to control-group baseline questions 1-10) was 0.416 (41.6%) (SD, 0.180), and mean score for final-assessment questions was 0.447 (44.7%) (SD, 0.278). Students in the control group spent almost double the amount of time on the baseline assessment case questions as the intervention group (1353.15 secs, or 22.6 mins, versus 771.6 secs, or 12.86 mins).

Independent samples t-tests demonstrated a number of differences between the control and intervention groups. There was a statistically significant difference in time spent on baseline assessment questions between control and intervention groups ($t_{4.916}$, $p<0.001$), and significant differences between the intervention and control groups for post-test scores in the medical (mean score 0.568 vs. 0.537, $t_{-0.796}$, $p=0.024$) and orthopaedic VTE prophylaxis cases (mean score 0.407 vs. 0.223, $t_{6.903}$, $p<0.001$).

There was a statistically-significant difference between groups in the amount of time spent on the final assessment questions, with students in the intervention group spending less time on the questions compared with controls (469.34sec [7.8mins] vs 791.26secs [13.2mins], $p<0.01$).

Correlation Results

Assessment of correlation between scores for individual cases by randomisation group was conducted using Pearson's correlation coefficient for baseline assessment questions and final assessment questions for all participants, control group and intervention group. A summary of all results is presented in table 10.1.

		Baseline Assessment Questions, Score	Baseline Assessment Questions, Time	Oncology Case, Score	Oncology Case, Time	Surgical Case, Score	Surgical Case, Time	Medical Case, Score	Medical Case, Time	Obstetric & Gynaecology Case, Score	Obstetric & Gynaecology Case, Time	Orthopaedic Case, Score	Orthopaedic Case, Time	Final Assessment Questions, Score
All (Whole Cohort)	Baseline Assessment Questions, Score													
	Baseline Assessment Questions, Time	0.018												
	Oncology Case, Score	**0.120**	-0.021											
	Oncology Case, Time	0.064	**0.147**	0.193										
	Surgical Case, Score	0.096	0.072	**0.143**	0.096									
	Surgical Case, Time	-0.031	**0.134**	0.075	*0.164*	0.194								
	Medical Case, Score	0.110	**0.149**	0.380	0.272	0.341	*0.176*							
	Medical Case. Time	0.010	0.263	*0.158*	0.318	0.185	0.364	0.468						
	Obstetric & Gynaecology Case, Score	**0.117**	0.113	0.299	0.243	0.284	0.084	0.687	0.327					
	Obstetric & Gynaecology Case, Time	0.005	0.083	0.067	0.095	0.059	0.051	**0.145**	**0.120**	*0.154*				
	Orthopaedic Case, Score	0.067	-0.006	0.332	**0.140**	0.301	0.080	0.598	0.280	*0.582*	**0.119**			
	Orthopaedic Case, Time	-0.032	*0.288*	**0.142**	*0.159*	0.109	*0.260*	*0.332*	*0.284*	*0.174*	**0.129**	0.349		
	Final Assessment Questions, Score	*0.257*	0.051	*0.176*	*0.171*	*0.162*	0.047	*0.418*	*0.173*	0.351	0.088	0.435	0.270	
	Final Assessment Questions, Time	-0.009	0.805	-0.051	0.093	0.016	0.020	0.066	0.202	0.092	0.028	0.028	**0.135**	*0.156*
Control Group	Baseline Assessment Questions, Score													
	Baseline Assessment Questions, Time	-0.029												
	Oncology Case, Score	0.103	-0.044											
	Oncology Case, Time	0.000	0.155	**0.168**										
	Surgical Case, Score	0.114	**0.189**	0.286	0.272									
	Surgical Case, Time	0.070	**0.186**	0.136	0.414	0.326								
	Medical Case, Score	0.080	**0.186**	0.364	0.319	0.764	0.409							
	Medical Case. Time	0.070	0.320	0.140	0.323	0.416	0.388	0.445						
	Obstetric & Gynaecology Case, Score	0.109	**0.182**	*0.292*	**0.212**	*0.685*	0.283	*0.693*	0.296					
	Obstetric & Gynaecology Case, Time	0.058	*0.257*	0.070	**0.194**	*0.356*	0.279	*0.343*	0.314	0.299				
	Orthopaedic Case, Score	0.041	**0.178**	*0.373*	*0.297*	*0.552*	**0.205**	*0.655*	*0.248*	0.702	**0.190**			
	Orthopaedic Case, Time	-0.050	*0.404*	0.121	*0.236*	*0.235*	*0.220*	*0.324*	*0.232*	*0.219*	0.397	0.277		
	Final Assessment Questions, Score	*0.462*	0.029	0.110	**0.183**	**0.172**	**0.203**	*0.231*	-0.001	0.106	0.084	0.139	**0.188**	
	Final Assessment Questions, Time	-0.008	*0.876*	-0.117	0.056	-0.019	0.063	-0.057	**0.169**	-0.007	0.052	-0.026	0.120	0.000

Intervention Group	Baseline Assessment Questions, Score													
	Baseline Assessment Questions, Time	**0.184**												
	Oncology Case, Score	**0.187**	0.147											
	Oncology Case, Time	0.144	**0.200**	0.291										
	Surgical Case, Score	0.091	0.087	0.071	0.000									
	Surgical Case, Time	-0.089	0.263	0.041	0.010	0.150								
	Medical Case, Score	0.140	**0.178**	0.496	**0.206**	0.144	0.046							
	Medical Case. Time	-0.059	0.275	*0.232*	0.311	0.070	0.384	0.495						
	Obstetric & Gynaecology Case, Score	0.122	0.076	0.389	0.286	0.102	-0.025	0.680	0.359					
	Obstetric & Gynaecology Case, Time	-0.013	0.070	0.123	0.080	0.007	0.007	0.100	0.070	0.127				
	Orthopaedic Case, Score	0.079	0.064	0.486	0.030	**0.199**	0.004	0.639	0.329	0.551	0.099			
	Orthopaedic Case, Time	-0.020	*0.256*	*0.224*	0.064	0.042	0.290	0.336	0.339	0.119	0.057	0.393		
	Final Assessment Questions, Score	0.110	*0.219*	0.360	**0.170**	0.154	-0.024	0.582	0.328	0.532	0.092	0.598	0.328	
	Final Assessment Questions, Time	0.001	0.299	0.296	*0.230*	0.127	0.023	0.419	0.376	0.392	0.060	0.387	0.280	0.539

Table 10.1 Correlation between scores and times across the study cohort, control group and intervention group during the Online Learning in Venous thromboembolism Education (OLIVE) randomised controlled trial.

Numbers in boldface type indicate p≤0.05; italiscised type indicates p≤0.01; a solid box indicated results with p≤0.001. Data shown are all correlation coefficients, so the original units of measurement are not stated in the column headings. Data for case times was seconds, and for scores was percentage

All participants

Statistically significant correlations ($p \leq 0.05$) were widespread throughout the dataset, however correlation was generally only weakly positive (r 0.25-0.5), or very weakly positive (r=0.1 to 0.25).

Moderate positive correlation (r=0.5-0.75) was present between the medical case score and the obstetric case score (r=0.687, p<0.001), and the orthopaedic case score (r=0.598, p<0.01). Moderate positive correlation was also present between the obstetric case score, and performance in the orthopaedic case (r=0.582, p<0.01).

Control group

Students in the control group had access to the e-learning modules after completion of the baseline assessment module. The scores for questions 11-20 in that module (identical to the ten final assessment questions in the intervention group)[144], were then compared to scores for questions 1-10 (identical to the ten baseline assessment questions applied to the intervention group). There were again multiple weak or very weak correlations present within the control group dataset.

Strongly positive correlations were present between performance in the surgical case and performance in the medical case (r=0.764, p<0.01) and time spent on baseline assessment questions and time spent on final assessment questions (r=0.76, p<0.01). Moderate positive correlations were present between performance in the surgical case and performance in the obstetric (r=0.685, p<0.01) and orthopaedic (r=0.552, P<0.01) cases, performance in the medical case and performance in the orthopaedic case (r=0.655, p<0.01), performance in the obstetric case and

performance in the orthopaedic case ($r=0.702$, $p<0.01$). There were no non-weak correlations between performance in any case, or amount of time spent on any case, and performance in the final assessment questions.

Intervention group

Multiple weak or very weak, yet statistically significant, correlations were present within the intervention group dataset. There were no strongly positive correlations present.

Performance in the medical case demonstrated moderate positive correlation with performance in the obstetric ($r=0.680$, $p<0.01$) case. Performance in the obstetrics case was moderately correlated with performance in the orthopaedic case ($r=0.551$, $p<0.01$).

Performance in the final assessment was moderately positively correlated with performance in the medical case ($r=0.582$, $p<0.01$), the obstetrics case ($r=0.532$, $p<0.01$), and the orthopaedic case ($r=0.598$, $p<0.01$). Time spent on the final assessment demonstrated moderate positive correlation with performance in the final assessment ($r=0.539$, $p<0.01$).

Discussion

In the randomized controlled OLIVE study, the use of case-based e-learning modules did not demonstrate a statistically-significant improvement in student knowledge compared to controls, however all students across both groups significantly improved their scores on re-testing at six months. We hypothesised that this non-difference in scores may relate to either differences in time spent on questions between the groups, and performance in specific cases in the intervention group, with students potentially performing very well in modules for specialty areas that have a traditionally high awareness of the role of VTE prophylaxis (e.g. the orthopaedic surgery case, or the oncology case), while under-performing in less-familiar areas.

Students in the intervention group spent significantly less time on the final assessment questions than students in the control group, and time spent on questions demonstrated a moderate positive correlation with outcomes in the final assessment for this group. By the time students completed the final assessment questions they had been able to access the eMedici system for six months, and had completed seven cases related to VTE prophylaxis. It may be that this result represents e-learning fatigue, and after prolonged exposure to the module students may have become bored of the learning material and rushed through the final assessment. Alternatively, students were given open access to the module for the duration of the semester, although it was clear to students that the module had to be completed by the end of semester; as a result, the reduced time spent on final assessment questions may represent last-minute module completion by students. It is a recognised limitation of e-learning that a high degree of motivation is required to

complete the educational tasks,[94,95] and the duration of access to this module may have inadvertently reduced student motivation for completion by providing too much convenience in the context of their other studies. We suggest that future research into e-learning interventions in medical education should examine such instructional design factors.

As hypothesised, performance in the medical and orthopaedics cases was moderately correlated with performance in the final assessment questions for the intervention group, as was performance in the obstetrics case. At the time of the study, all fourth year medical students at The University of Adelaide completed mandatory rotations in General Medicine, General Surgery and Orthopaedic Surgery, with the remainder of the year consisting of non-mandatory selective specialty rotations. This result may therefore represent pre-existing knowledge of the provision of VTE prophylaxs in general medicine and orthopaedic surgery among this cohort of students (who would have completed rotations in general medicine and orthopaedic surgery in the preceding year of their studies), and a possible confounding blended-learning effect, as the fifth year of the medical degree program is the year in which students undertake obstetrics and gynaecology terms at our institution.

Students in the control group had access to the e-learning cases after completing 20 questions in a baseline assessment module, with questions 1-10 identical to the baseline assessment questions completed by the intervention group, and questions 11-20 identical to the final assessment questions completed by the intervention group. As a result, strong correlation between time spent on baseline and final

assessment questions in this group is unsurprising, as these questions were completed in the same sitting. Moderate correlation was present between performance in the surgical case and performance in the orthopaedic and obstetric cases in the control group, which may again represent application of knowledge gained from rotations in the previous academic year (general surgery and orthopaedics) and an unintended, confounding blended learning effect (obstetrics and gynaecology).

Interestingly, analysis of pooled data for both groups indicated a strongly positive correlation between performance in the oncology case and performance in the final assessment questions. This result cannot be readily be explained, but may represent an area of practice that was not familiar to students, and hence attracted additional attention to the learning material, however this correlation was not duplicated in analysis of the control and intervention groups.

In conclusion, performance in the eMedici VTE Prophylaxis Module appears to be associated with performance in areas of medicine in which students had prior experience, or were currently rotating. This fits with findings when students were followed up at six months, demonstrating global improvement in knowledge of VTE prophylaxis,[144] and suggests that while e-learning in isolation may not lead to immediate knowledge improvement among medical students (a finding consistent with the results of a systematic review by Vaona et al[105]), the use of e-learning in a blended learning strategy with clinical exposure appears to lead to improvement in knowledge outcomes. We suggest that future research in this area should focus on the conduct of well-designed randomised controlled trials comparing the use of

blended e-learning and clinical teaching strategies with traditional clinical teaching methods.

Chapter 11. Computers in Medical Education: Evaluation of Instructional Ergonomics in the Online Learning in Venous thromboembolism Education Study

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Statement of Authorship

Title of Paper	Computers in Medical Education: Evaluation of Instructional Ergonomics in the Online Learning in Venous thromboembolism Education Study
Publication Status	☐ Published ☐ Accepted for Publication ☒ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	

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Name of Principal Author (Candidate)	Eamon Patrick Raith		
Contribution to the Paper	Project design, data collection, data analysis, manuscript preparation		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Abstract

Background

The use of online learning has become ubiquitous in medical education, with broad uptake across a range of countries and healthcare systems. Despite this rapid uptake and implementation of e-learning facilities, there has been limited investigation of instructional ergonomics and human factors in the delivery of online medical education. The purpose of this study was to describe the instructional ergonomic factors associated with the use of an online module used to teach undergraduate medical students about venous thromboembolism prophylaxis.

Method

After completion of a six-month online course on venous thromboembolism prophylaxis students completed a questionnaire covering the domains of administration and support, access, usage, technical performance, general usability, student expectations, content and instructional design, and testing and assessment.

Results

Most of the students provided positive comments on the delivery of the course. Students predominantly studied at home, and preferred study location was associated with technical performance of the module. Some issues surrounding usability were reported, in keeping with issues previously reported in the literature.

Conclusion

The results indicate the importance of usability testing in designing online medical education resources, suggest the importance of supporting online learning through

the provision of physical learning spaces and infrastructure within the clinical setting, and highlight the importance of considering human factors in the design and assessment of e-learning material for medical and surgical education.

Introduction

Twenty years ago members of this research group, and others, described the use of a computer-aided learning package developed to promote learning during a surgical rotation as part of an undergraduate medical curriculum. The study demonstrated that most students provided positive comments on the learning material, and were interested in seeing computer-aided learning introduced to the medical curriculum.[124] At that time it was noted that computers and e-learning had a limited role in medical education due to difficulties with keeping pace with technological development, professional reluctance to embrace new technological methods of instruction, and low computer literacy amongst medical students.[124]

Online learning has become a powerful and challenging tool in medical education, aimed at lowering the cost of education, increasing educational capacity and improving the sharing of learning resources.[119] Uptake of e-learning has occurred globally and variation in per-capita income has been no barrier to the use of this medium.[145] Usability is a key factor in the efficacy of e-learning, and e-learning material design must account for variations in abilities and disabilities amongst learners.[146] Consideration must be given to the capabilities of the user, and technical support must be readily available.[146]

Human factors, or ergonomics, is defined by the International Ergonomics Association as "…the scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data and methods to design in order to optimize human well-being and overall system performance"[147] The concept of educational

ergonomics was proposed by Kao in 1976, who described the five concepts of learning ergonomics, instructional ergonomics, ergonomics of educational facilities, ergonomics of educational equipment and the ergonomics of educational environment[148] According to Kao, instructional ergonomics is a sub-set of educational ergonomics addressing delivery, presentation and communication of knowledge, and includes the ergonomics of "teaching machines and self-instructional devices"[148] Since Kao's original paper, the use of multimedia and the design of educational technology has received significant attention, yet there remains an ongoing need for how student interaction with new technologies influences performance and learning.[149]

eMedici is a website providing an open-ended series of case-studies across medical and surgical specialties, primarily aimed at medical students, at our institution.[122] We conducted an educational randomized controlled trial (the Online Leaning In Venous thromboembolism Education (OLIVE) Study) that aimed to investigate a new module's utility in improving knowledge of thromboprophylaxis guidelines.[144] As part of this trial we collected descriptive data surrounding the usability of the eMedici module. This paper reports the results of our analysis of human factors associated with online learning in the undergraduate medical environment.

Methods

The University of Adelaide Office of Research Ethics, Compliance and Integrity (H-2012-057) and The University of Notre Dame, Australia, Human Research Ethics Committee (013093S) approved this study.

A six-month online course on venous thromboembolism prophylaxis was provided to fifth year medical students at The University of Adelaide for each six-month semester, for two consecutive years. All fifth year medical students were enrolled in the course (published on www.emedici.com) in each year, and the content of the course was examinable in the end of year 'barrier' examination. Enrolment in the course was not contingent upon participation in the OLIVE study, and all students ultimately had access to the same learning material.

A questionnaire was developed based on a modification of the student reaction questionnaire proposed by Pike and Huddleston.[131] Students were asked to complete the questionnaire on completion of the eMedici module. The questionnaire covered the domains of administration and support, access, usage, technical performance, general usability, student expectations, content and instructional design and testing and assessment. At the end of the questionnaire students were asked to provide an overall rating for the course. Data was collected through a combination of Likert scales and drop-down options.

Five-point Likert scales were used for the majority of questions, with a score of one representing total disagreement with the questions, and a score of five representing strong agreement. Where no answer was provided a score of zero was allocated,

and data was not included in the analysis. Three questions relating to location of study, module completion and formal assessment of the information contained within the module used drop-down text options.

All forms were de-identified and then reviewed by the lead author. Statistical advice was provided by a qualified statistician, and analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for presentation and analysis of ordinal data [136]. Independent associations between categorical data were explored by the chi-square test, with statistical significance set at a p value of ≤ 0.05.

The survey form, and associated descriptive statistics for this study are presented in Table 11.1 (Presented as a supplemental appendix, S1, in the article for publication).

Results

Administration and support

The majority of students agreed or strongly agreed that they received comprehensive registration and login instructions (75.9%), that help was available in resolving issues relating to connection to eMedici (76.1%), and that help was available to manage issues regarding the course software (54.3%). 40.3% of students were uncertain, or had no opinion, as to the fact that an instructor or mentor was available as course support.

Access to eMedici

66.4% of students agreed or strongly agreed that they had physical facilities available to the to access eMedici. Almost all students (87.9%) found it easy to log in to eMedici. Most students felt that support was available when they encountered problems with the software, and that support helped resolve problems.

EMedici usage

The majority of students undertook the online learning tasks in their own home (77.3%). The next most frequent approach was to study at a combination of home, on-campus or at university-affiliated hospitals (6%) (Figure 1). 87.3% of students completed all cases within the eMedici module. The vast majority of students felt that they were able to set the pace of their learning (92.6%) and were free from interruptions during their study (79.9%). There was significant variability in whether students felt they received allocated work or study time to complete the module. The majority of students felt they had adequate time to complete the module.

Technical performance

The majority of students felt that the eMedici program ran quickly on the machine they used (87.2%) and without any technical glitches (71%). 30.9% of students reported the eMedici platform crashing or 'freezing up' during use.

A chi-square analysis was performed to assess the association between location of study and technical performance. There was no association between reported location of study and the speed at which eMedici ran on the machine used (p = 0.447). Studying at home was associated with the eMedici module running without any technical glitches (p = 0.01) and never crashing (p = 0).

General usability

The majority of students found the eMedici module usable, with a clear on-screen layout, legible text on-screen, easy-to-understand and operate navigation controls, and easy course navigability. While the majority of students reported that they never accidentally exited the course, the number who did was surprisingly high (39.6%).

Student expectations

Students did not expect the course to be difficult (66.5%), and most reported that the subject-matter (venous thromboprophylaxis across multiple specialties) was interesting (79.1%). The majority of students found the module engaging (75.1%) and relevant to their future practice (93.3%). Students anticipated using the material learned on the course, and felt confident in applying what they had learned.

Content and Instructional Design

Student expectations of statements of case objectives, case structure, level of module content, case context, content presentation, currency, image quality and sequencing were met for the majority of students. Students reported a high degree of interaction with the module (65.7%) and found those interactions meaningful (69.2%). 53% of students disagreed with the statement that "There was opportunity for skills practice associated with the module.

Testing and Assessment

The majority of students felt that the length of the module was sufficient to meet the stated objectives of the module. 54.7% of students did not believe the cases were formally assessed, and 59.7% did not feel that they were informed as to how the test results were used.

Overall rating

The majority of students rated the course satisfactory or totally satisfactory (77.4%).

Conclusion

Our study describes the ergonomic factors related to the delivery of a venous thromboembolism prevention program via an e-learning modality. Most students were satisfied with the course delivery and content, however a number of usability and browsing problems were detected, consistent with previously reported findings [150].

Usability problems in the e-learning environment bear similarities to usability problems in other systems, and relate to compatibility, consistency, feedback, error management and satisfaction [150]. It appears that a large number of students were unaware of the administrative support available to them, and that the majority of students were unaware of the module's assessment requirements, and how the results of the module were being used, despite this information being displayed on the opening screen of the module, and informed consent being required to access the remainder of the module. A surprising number of students accidently exited the module during use. These findings may indicate a recall error on the part of the students, however, it is more likely that they represent the effects of extraneous cognitive load (for example, whilst 80% of students stated that they were free from distractions in the home environment, this is a subjective assessment susceptible to recall bias, and the number of distractions may be higher) and demonstrate the importance of usability and usability testing. Cognitive load theory (CLT) aims to use a model of human cognitive architecture to design instructional principles and strategies and is becoming more apparent in medical education, particularly in the application of teaching complex tasks [151]. CLT assumes that intrinsic and extraneous cognitive loads are additive, and the sum of these loads may surpass working

memory capacity during complex task learning [151]. Similarly, the cognitive theory of multimedia learning highlights the importance of the working memory in learning, and emphasizes it's short-term (<30 secs), limited capacity for processing information [152]. Mayer recommends the elimination of extraneous material, highlighting essential material and placing printed words near corresponding graphics as principles for reducing extraneous processing in the design of online learning material. He also recommends the combined use of words and pictures, the presentation of words in conversational or polite style and the use (where appropriate) of a human voice rather than a machine voice to foster generative processing when using multimedia lessons [152].

Usability testing is not widely recognised in the development of medical education resources [153,154]. Usability testing across the technological approach (navigation, learnability, accessibility, consistency and visual design) and the instructional design (interactivity, content and resources, media use, learning strategies design and learner guidance and support) of e-learning material has been recommended in the literature [154] and has been demonstrated to result in significant improvements in usability [153]. As such, formal usability testing should form a component of instructional design.

Chi-squared analysis demonstrated that studying at home was associated with the eMedici module running without any technical glitches ($p = 0.01$) and never crashing ($p = 0$). Information technology infrastructure has been demonstrated to be a requirement for e-learning system success, and impacts on the perceived usefulness, user satisfaction, customer value and organizational value associated with the

learning system. Development and maintenance of IT infrastructure is key to the outcomes of e-learning systems, and requires careful investment and support. [155] The findings of our study may demonstrate inadequate information technology infrastructure support, and provision of physical learning spaces, for e-learning systems outside of the students' home study environment.

This study has a number of strengths. As a descriptive study of human factors impacting on e-learning delivery, it assesses eight ergonomic domains; administration and support, access, usage, technical performance, general usability, student expectations, content and instructional design, and testing and assessment. The study has value as a measure of human factors related to the use of this educational module, and is reproducible, allowing for trends analysis and future usability testing. The study has also identified a potential area for further study in medical e-learning, namely the role of information technology infrastructure.

The study is limited as a descriptive study, and as such can only report our direct findings and cannot draw causal inferences. The human factors survey was conducted on completion of the online module, and as a result may be subject to recall bias from the participants.

In conclusion, this study demonstrates the importance of usability testing in the development of e-learning material, the importance of the consideration of human factors and instructional ergonomics in the construction of online courses, and has highlighted the importance of information technology infrastructure and study location as areas of potential future research in the field of online medical education.

It also highlights the positive approach that most students have to on-line learning as an educational tool.

Question	N	Mean Score	Std. Deviation	Score Percentiles		
				Median	25th	75th
Q1: I received comprehensive eMedici registration/log-in instructions	149	3.78	0.829	4	4	4
Q2: Help was available in resolving issues with connection to eMedici	149	3.79	0.903	4	3	4
Q3: Help was available in issues running the courseware	149	3.58	0.871	4	3	4
Q4: An instructor or mentor was available to support the course	149	3.19	0.911	3	3	4
Q5: Physical facilities to access eMedici were available	149	3.64	0.987	4	3	4
Q6: It was easy logging into eMedici	149	4.11	0.737	4	4	5
Q7: Support was available on encountered problems	149	3.71	0.824	4	3	4
Q8: The support helped resolve problems	149	3.69	0.821	4	3	4
Q11: I was able to go at my own pace	149	4.17	0.566	4	4	5
Q12: I was free from interruptions during the module	149	3.86	0.771	4	4	4
Q13: I was allocated work/study time to complete the module	149	2.79	1.043	3	2	4
Q14: The allowed time (4 months) was sufficient for the program content	148	3.87	0.703	4	3	4
Q15: The eMedici program ran quickly on the machine I used	149	4.05	0.645	4	4	4
Q16: The module ran without any technical glitches	148	3.74	0.927	4	3	4
Q17: The module never crashed or 'froze up'	149	3.66	0.949	4	3	4
Q18: The screen layout was clear	149	3.93	0.736	4	4	4
Q19: Text on screen was legible	149	4.13	0.596	4	4	4
Q20: The navigation controls were easy to understand	149	4.04	0.656	4	4	4
Q21: The controls were straightforward to operate	149	4.03	0.62	4	4	4
Q22: It was easy to navigate around the course	149	3.96	0.706	4	4	4
Q23: It was easy to return to pieces of content already viewed	149	3.71	0.872	4	3	4
Q24: I never accidently exited the course	149	3.46	1.056	4	3	4
Q25: The module was consistent with my expectations	149	3.88	0.58	4	4	4
Q26: The module is known to be a difficult module	149	3.28	0.752	3	3	4
Q27: The subject-matter of the module was interesting	148	3.84	0.625	4	4	4

Q28: The module held my attention	149	3.77	0.641	4	3.5	4
Q29: The module is relevant to my future work as a Doctor	149	4.41	0.637	4	4	5
Q30: I anticipate using what I learnt on this course	149	4.18	0.668	4	4	5
Q31: I would be confident in applying what was learnt on this course	149	3.58	0.823	4	3	4
Q32: Module and case objectives were clearly stated	149	3.95	0.585	4	4	4
Q33: Cases were well-structured	149	3.9	0.685	4	4	4
Q34: The breakdown of content in the course was logical	149	3.89	0.642	4	4	4
Q35: The content of the module was at an appropriate level of detail	149	3.83	0.672	4	4	4
Q36: The content of the module was presented in the right context	149	3.95	0.602	4	4	4
Q37: The content was presented and explained clearly	149	3.88	0.636	4	4	4
Q38: The content was up to date	149	3.91	0.63	4	4	4
Q39: Still images were of good quality	149	3.7	0.913	4	3	4
Q40: Content sequencing was logical	149	3.92	0.61	4	4	4
Q41: There was a high degree of interaction with the module	149	3.68	0.717	4	3	4
Q42: The interactions with the module were meaningful	149	3.77	0.748	4	3	4
Q43: There was opportunity for skills practice associated with the module	149	3.28	0.886	3	3	4
Q44: The length of the module was sufficient for the module objectives	149	3.81	0.619	4	4	4
Q46: The test instructions were easy to understand	149	3.93	0.534	4	4	4
Q47: The mechanism for answering questions was straight-forward	149	3.89	0.628	4	4	4
Q48: The assessment was a fair reflection of the information covered in the cases	149	3.59	0.814	4	3	4
Q49: Notification of whether test results were recorded (or not) was given	149	3.46	0.889	4	3	4
Q50: I was informed as to how the test results were used	149	3.14	0.987	3	3	4
Q51: There was post-test feedback	149	3.5	0.991	4	3	4
Q52: Overall course rating (1 = totally unsatisfactory, 5 = Totally satisfactory)	148	3.81	0.732	4	4	4

Table 11.1 Descriptive data (mean score, median score and scores at 25th and 75th percentiles) for completed survey

Section 4. Thesis Synopsis

Chapter 12. Thesis Synopsis

The outcomes of the research contained within this PhD thesis have advanced our understanding of online educational methodologies and the utility of online learning in delivering clinical practice outcomes in isolation, although much work still remains before we are able to delineate the precise role of online learning in a blended model of medical education.

The basis of this work was an understanding that online learning was associated with an increase in knowledge gain and retention by resident medical officers, resulting in an increase in content mastery related to VTE guidelines. The original study underlying this work demonstrated a 14.5% increase in in content mastery among resident medical officers, although this occurred with a small effect size (0.23).[111] The authors of this original study demonstrated an overall improvement in knowledge mastery relating to VTE prophylaxis between pre- and post-tests, however, no additional knowledge gain through use of question/response cases was demonstrated.

In the late 1990 'Medici' was released at the University of Adelaide as an e-learning tool. This CD-ROM-based learning program was designed to provide students with educational material related to their surgical terms.[124] This program was translated to the online environment in the early 2000s, resulting in the publication, and use, of eMedici at the University of Adelaide, as part of the undergraduate medical education program.

The aim of this body of work was to assess the educational benefit of using an online case-based learning system (eMedici) to deliver material relating to VTE prophylaxis across multiple disciplines with a view to improving understanding of VTE prophylaxis requirements in fifth-year medical students at The University of Adelaide.

The first step in this project was characterising the utility of online education in the medical education literature. E-learning has been readily absorbed into medical education, and is now a key component of many courses, at both the undergraduate and graduate level. There is a suggestion in the evidence that e-learning brings multiple non-learning based benefits, including flexibility, cost savings and the opportunity for deliberate and distributed practice, that traditional learning cannot provide.

We conducted a randomised controlled trial determing the efficacy of online learning on application of knowledge related to VTE among medical students approaching their final examinations (of which this subject was included).

A venous thromboembolism prophylaxis (VTE) e-learning module was developed and a randomised controlled trial was conducted to investigate its educational benefit in improving knowledge of thromboprophylaxis guidelines. Medical students were randomised into control and intervention groups. We demonstrated that mean baseline scores were similar between groups, and that no statistically significant improvement was observed between groups or between baseline and post-intervention scores in the intervention group. Re-testing at six months

demonstrated improvement in all scores.

In conclusion, use of an online learning module was not immediately associated with improved scores relating to knowledge of thromboprophylaxis. Scores improved six months post-intervention, suggesting a possible role for blended learning in this field.

Our second paper describes a subgroup analysis of a randomised controlled educational trial, performed with a view to determine the relevant effects of scores and times for completion for each case on overall performance, and correlation with performance in other cases and in the final assessments. We demonstrated that that performance in the eMedici VTE Prophylaxis Module appears to be associated with performance in areas of medicine in which students had prior experience, or were currently rotating. This supports our finding in the first article that e-learning may be of limited utility when used in isolation, but may represent an important component of a blended learning strategy to teach clinical material.

In our third paper, we describe the results of a survey of human factors and instructional ergonomics, conducted as part of a project to assess the utility of e-learning material in teaching medical students about venous thromboembolism prophylaxis. This project was designed following the WolpinStudy[111], which appeared to demonstrate that the use of an online VTE education package resulted in increased knowledge mastery among Medical Residents. We elected to include research around human factors in the online delivery of medical education in our project, as this is an under-investigated area in medical training. In short, we demonstrated that usability testing is important in designing online medical education

resources, the importance of supporting online learning through the provision of physical learning spaces and infrastructure, and highlight the importance of considering human factors in the design of e-learning material.

We have characterised the use of online education in the instruction of clinical undergraduate medical students in their learning around VTE prophylaxis. In summary, we suggest that online learning material related to the provision of VTE prophylaxis is provided as part of a blended learning environment, wherein students are able to apply their theoretical knowledge of VTE prophylaxis to simulated real-world scenarios.

The importance of this project will only become clear in the fullness of time, with repeated assessment of the role of online learning in undergraduate medical knowledge and the utility of e-learning in broader medical education. Application of e-learning resources to medical education will inevitably continue, and the measurement of the effectiveness of these resources will inevitably lead to improved educational delivery.

Until that time, additional questions have been generated from this research. It is unclear as to whether the benefits of blended learning occur with early exposure to clinical scenarios, versus exposure after absorption of theoretical knowledge, particularly in e-learning scenarios. An important question is, is association between completion of e-learning and completion of clinical rotation related to outcomes? Similarly, well-designed randomised controlled trials comparing the use of blended e-

learning and clinical teaching strategies with traditional clinical teaching methods are required in the future.

Section 5. References

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