Extended Thromboprophylaxis following Major Open Abdominopelvic Surgery for Malignancy: A Review of Efficacy, Safety and Economic Impact.

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CITATION LISTING OF INCLUDED PUBLICATIONS:

1. Heijkoop B, Parker N, Kiroff G and Spernat D. Effectiveness and safety of inpatient versus extended venous thromboembolism prophylaxis with heparin following major pelvic surgery for malignancy: protocol for a systematic review. Systematic Reviews. (2019)8:249. Available from https://doi.org/10.1186/s13643-019-1179-1

2. Heijkoop B, Nadi S, Spernat D and Kiroff G. Extended versus inpatient thromboprophylaxis with heparins following major open abdominopelvic surgery for malignancy: a systematic review of efficacy and safety. Perioperative Medicine. (2020)9:7. Available from https://doi.org/10.1186/s13741-020-0137-8

ABSTRACT:

The primary aim of this project was to perform a systematic review and meta-analysis of the currently available literature, comparing the effectiveness and safety of inpatient versus extended venous thromboembolism (VTE) prophylaxis with heparin following major open abdominal or pelvic surgery for malignancy. A secondary aim was to use the results of this review to evaluate the economic implications of providing extended pharmacological VTE prophylaxis in this population.

A protocol for a systematic review of the literature was first developed, registered and published. Systematic literature review and meta-analysis were then performed in accordance with the protocol, and the results published. Finally, the results of the literature review were compared to literature estimates of the incidence and cost of VTE events in the absence of pharmacological prophylaxis, and current cost of Enoxaparin on the Pharmaceutical Benefits Scheme (PBS) in Australia, and a further manuscript produced which is currently submitted for consideration of publication.

The result of the literature review was that no significant difference was found in either postoperative VTE rates or bleeding complications when comparing patients receiving extended duration versus inpatient only heparin VTE prophylaxis following major open abdominopelvic surgery for malignancy. However, the available contemporaneously published evidence was limited and of poor quality so this finding must be interpreted with caution.

Regarding the secondary aim, cost analysis based on results of the literature review found the cost of providing extended duration heparin VTE prophylaxis to be less than that of treating predicted VTE events without prophylaxis, and therefore financially justifiable. However, if the initial finding of no significant difference in postoperative VTE events with extended compared to inpatient prophylaxis is assumed to be correct, on a purely financial basis inpatient only duration prophylaxis may be a more efficient use of resources.

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I would also like to recognise the invaluable advice and guidance provided by Dr David Tivey and Mr Ning Ma of Research and Evaluation, Incorporating ASERNIP-S, Royal Australasian College of Surgeons, Adelaide, Australia, in developing the protocol and search strategy and conducting literature review and analysis, as well as the contribution from Mr Sinan Nadi in acting as a second reviewer of articles identified on literature search.

Finally, I would like to acknowledge and sincerely thank my supervisors A/Prof George Kiroff and Mr Dan Spernat for first encouraging me to enrol in the Degree and continuing to tirelessly support and guide me through each step of the process.

MAIN BODY CHAPTER 1: CONTEXTUAL STATEMENT

VTE is a not only a common postoperative complication, but also a significant cause of morbidity and mortality[1] in surgical patients leading to an associated burden on the healthcare system. Consequently, it is important that all reasonable steps are taken to minimise patients' risk of developing VTE postoperatively, to both optimise individual patient's outcomes and minimise unnecessary expenditure on a preventable disease in a healthcare system which has an ultimately finite supply of resources. Prophylactic treatments for VTE are widely used, however optimum duration of prophylaxis remains unknown as yet. Despite this, extended duration treatment is being increasingly used in many patient populations.

The following commentary provides the reader with the background context to the project, reviewing the established field of knowledge and current literature regarding VTE, current prophylactic treatments of VTE and the relationship to the aims of the project.

Pathophysiology of VTE

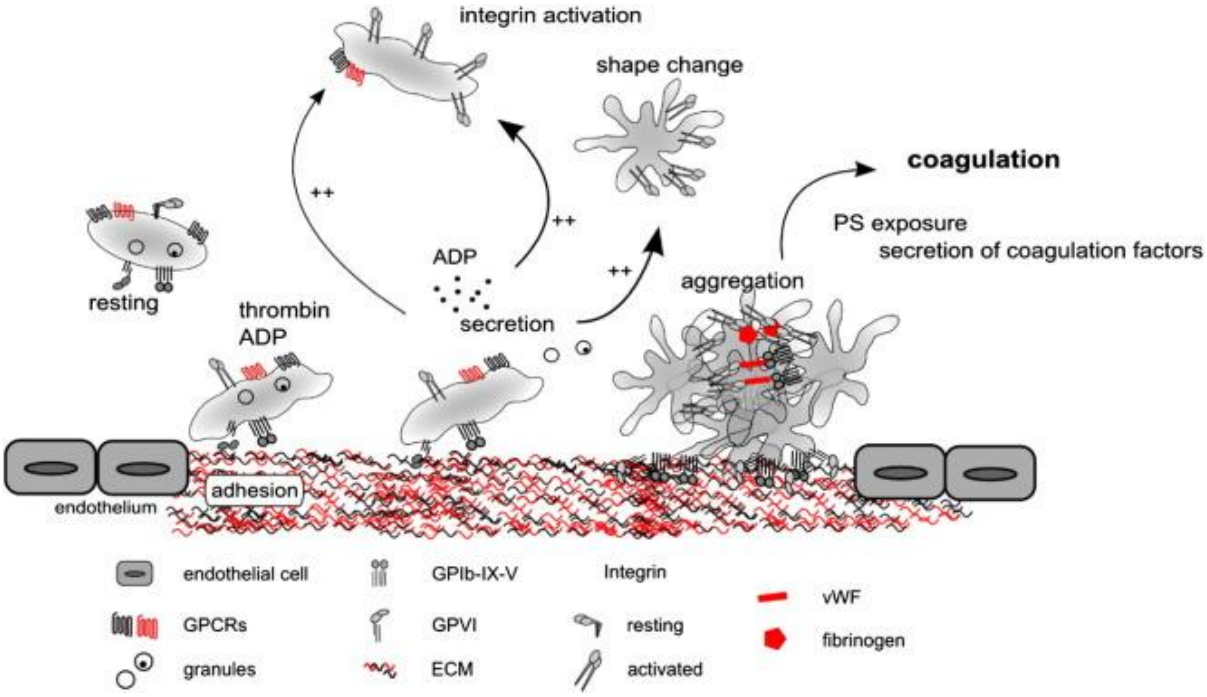
The pathophysiology of VTE can be considered in two parts; thrombus formation (Deep vein thrombosis or DVT), and subsequent embolisation of the thrombus.

Thrombus is defined as "a structured, solid mass composed of blood constituents that forms in the cardiovascular system"[2]. Formation of DVT in the postoperative patient is usually precipitated by the classic "Virchow's triad" of hypercoagulability (increased predisposition of the blood to coagulation, particularly as a result of systematic inflammatory response postoperatively), venous stasis (altered or reduced flow of blood through the vessel compared to normal), and local trauma (damage) to vessels, which activates the blood's coagulation cascade via both its extrinsic and intrinsic pathways.

Virchow's Triad & DVT formation

When intact, the endothelium (innermost lining) of the vessels works to prevent coagulation by both preventing platelets from contacting collagen and Von Willebrand factor which trigger them to aggregate and degranulate, and by itself producing prostacyclin and nitric oxide which prevent the platelets from adhering to the endothelium and aggregating. It also produces heparin like molecules and plasminogen activators which inhibit the coagulation cascade, and thrombomodulin on the endothelial surface binds to any locally formed thrombin with the resultant thrombin-thrombomodulin complex initiating the anticoagulant proteins C & S[2,3].

However, when the endothelium is damaged or dysfunctional as a result of trauma or inflammation (such as in the postoperative state), or there is stasis or slowed flow of blood though the vessel, platelets in the blood are exposed to collagen and Von Willebrand Factor and bind to these by their surface glycoprotein Ia and Ib receptors. Having bound to these, the adherent platelets undergo a shape change, aggregate and degranulate (exocytosis of the platelet's cytoplasmic granules), releasing adenosine diphosphate (ADP), thromboxane A2, and producing prostaglandin as well as expressing glycoprotein complex IIb-IIIA and multiple coagulation factors collectively referred to as platelet factor 3. This can be illustrated by the figure[4]:

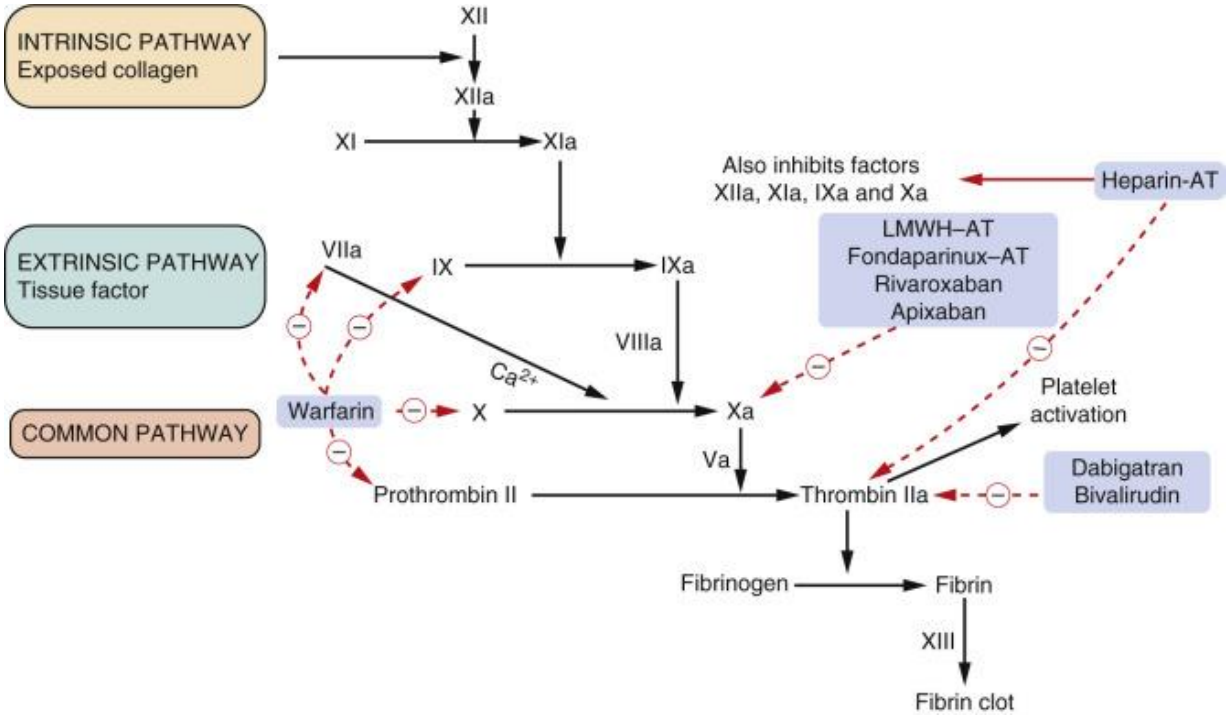


The ADP, thromboxane and prostaglandin contribute to the development of a "platelet plug" by stimulating further aggregation and adhesion of other platelets, creating a positive feedback loop. The release of prostaglandin also causes vasoconstriction of the vessel involved and hence further reduction in blood flow. The expression of glycoprotein IIb-IIIa acts as an additional receptor for fibrinogen and Von Willebrand Factor helping to form a firm haemostatic plug to the vessel wall[2,3].

Degranulation of platelets also releases Factor XII or Hageman factor, which combined with the platelet factor 3, initiates a cascade of the serial activation of factors XI (Antihaemophiliac factor C), IX (Antihaemophiliac factor B), and VIII (Antihaemophiliac factor A), and finally factor X (Thrombokinase), the intrinsic pathway of the coagulation cascade. Simultaneously the extrinsic pathway of the coagulation cascade is activated by the release of factor III (thromboplastin) from the damaged endothelium and perivascular tissues, activating factor VII (Proconvertin) and subsequently factor X[3].

Once factor X is activated both intrinsic and extrinsic pathways are identical. The combination of factor X with factor III and factor V (Proaccelerin) when platelet factor 3 and Calcium are also present results in the production of prothrombin activator which converts factor II (Prothrombin) into thrombin, an enzyme which converts the soluble plasma protein fibrinogen into insoluble fibrin[2,3] which creates a "framework" for clot development. Again, a positive feedback cycle resulting from the coagulation cascade enzymes results in the continued production of clot.

The following image[5] illustrates the coagulation cascade including points where anticoagulant medications interact with it.



While in normal physiological clotting this process is followed by tissue repair, remodelling and eventual fibrinolysis of the clot, the clotting process can become pathological when the thrombus continues to enlarge and propagate along the vessel, and or embolises from its site of formation.

Local Effects

Locally, pathological deep vein thrombosis (DVT) obstructs the flow of blood through the vein, resulting in increased venous hydrostatic pressure. This may be asymptomatic or present clinically with pain, heat and swelling in the affected extremity. Well's score[6] can be used to predict the relative probability of DVT based on history and clinical examination findings. When suspicion is high, diagnosis is able to be confirmed in several ways. In the modern clinical setting this is most commonly and least invasively done by use of ultrasound, however historically and in research settings the invasive but highly sensitive method of contrast venography has also been used.

Well's scoring system can be illustrated by:

CHARACTERISTIC	SCORE
Clinical signs or symptoms of DVT	3
PE is most likely or equally likely diagnosis	3
Heart rate >100	1.5
Immobility of 3 or more days OR surgery within the preceding 4 weeks	1.5
Previous objective diagnosis of PE/DVT	1.5
Haemoptysis	1
Malignancy with treatment within 6 months or palliative	1
SCORING 0 - 1 = Low risk 2 - 6 = Moderate risk > 6 = High risk	

Thromboembolism

Thromboembolism occurs when a mass of thrombus embolises, travelling within the venous system until it reaches a vessel with a lumen too small to permit its passage and occludes the vessel[2]. DVT developing in the systemic veins will travel first to the heart, and then if it is of small enough size to pass through the heart, into the pulmonary vasculature. The size of the embolus and hence the size of the occluded vessel determine the significance of the resultant effects of the embolus. Large emboli have the potential to cause death if the obstruction occurs in the heart or large vessels.

Presentation and management of VTE

Clinical presentation of VTE

Large pulmonary emboli which obstruct the heart or large pulmonary vessels obstruct cardiac output and consequently result in the sudden development of haemodynamic shock, rapidly progressing into cardiac arrest and death often occurring over a timeframe of only minutes from the embolic event[3]. Obstruction of moderate to larger sized pulmonary arteries but not resulting in sudden death causes a sudden increase in pulmonary vascular resistance and pulmonary artery pressure, with backpressure of blood into pulmonary artery capillaries. This results in hypoperfusion of the lung and ventilation perfusion (VQ) mismatch in the affected part of the lung, with resultant increase in alveolar dead space, hypoxia and hypercarbia, and possible pulmonary infarction.

Clinically, the classical presentation of pulmonary embolus is of a patient with pleuritic chest pain, breathlessness and desaturation. Tachypnoea and tachycardia occur as a result of attempted compensatory mechanisms. There may be respiratory acidosis, however alkalosis from compensatory tachypnoea is also possible. Increased right ventricular pressures and right heart strain as a result of increased pulmonary resistance may be evident on electrocardiogram (ECG) as the combination of S waves in lead I, Q waves in lead II and inverted T wave in lead III, although the most common ECG finding in patients with pulmonary embolus is the nonspecific finding of a sinus tachycardia. Hypoperfusion causing decreased surfactant production by alveolar type 2 cells can also contribute to atelectasis and pulmonary oedema, further exacerbating VQ mismatch[7]. In the case of smaller pulmonary emboli causing occlusion of minor pulmonary vessels the patient may still present with pleuritic chest pain and breathlessness to a lesser degree of severity, or in some cases may be asymptomatic.

Investigation and Confirmation of Diagnosis

The preferred investigation to confirm diagnosis of PE is computed tomography pulmonary angiography (CTPA)[8], where the clot is demonstrated by a filling defect within the pulmonary arteries which are opacified by contrast media. Use of CTPA may not be possible in patients whose initial presentation is too unstable for CT, those who have a an allergy to contrast media or in those who have significant renal failure making the risk of contrast induced nephropathy outweigh the benefit of the investigation. An alternative for patients who are not suitable to undergo CTPA is the Nuclear Medicine investigation of ventilation perfusion scintigraphy (VQ scan)[9,10] which utilises an inhaled radiopharmaceutical to detect areas of the lung which are ventilated but not perfused. Examples illustrating the images produced by each modality are shown below.

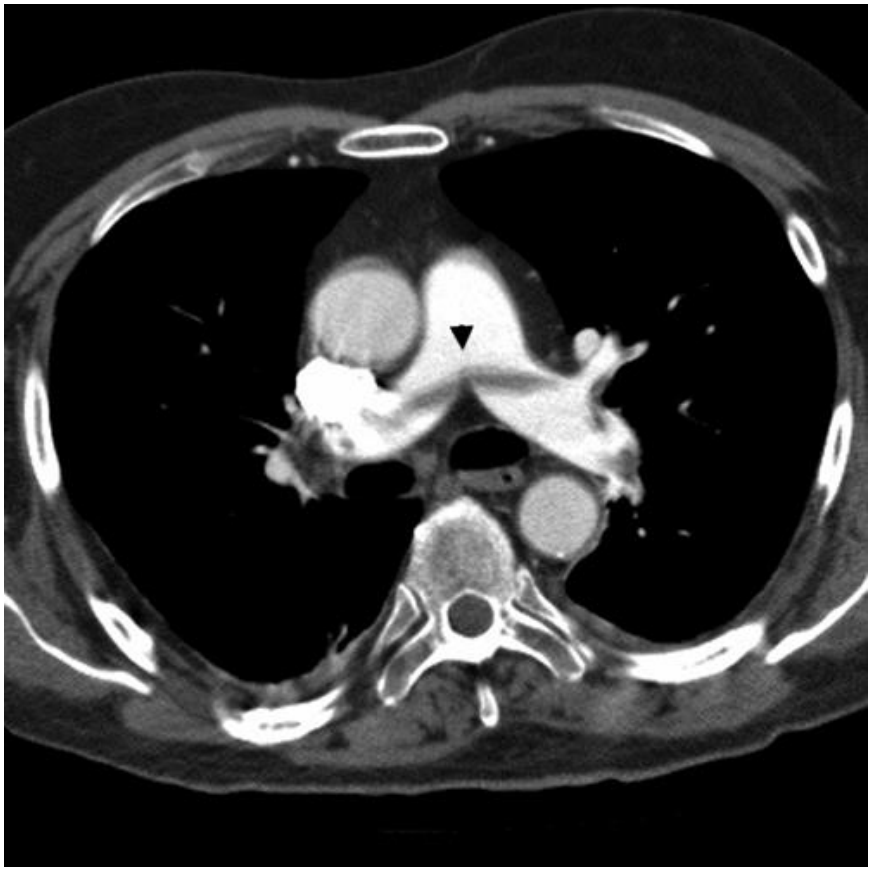


Image 3: CTPA image demonstrating filling defect in PE[8]

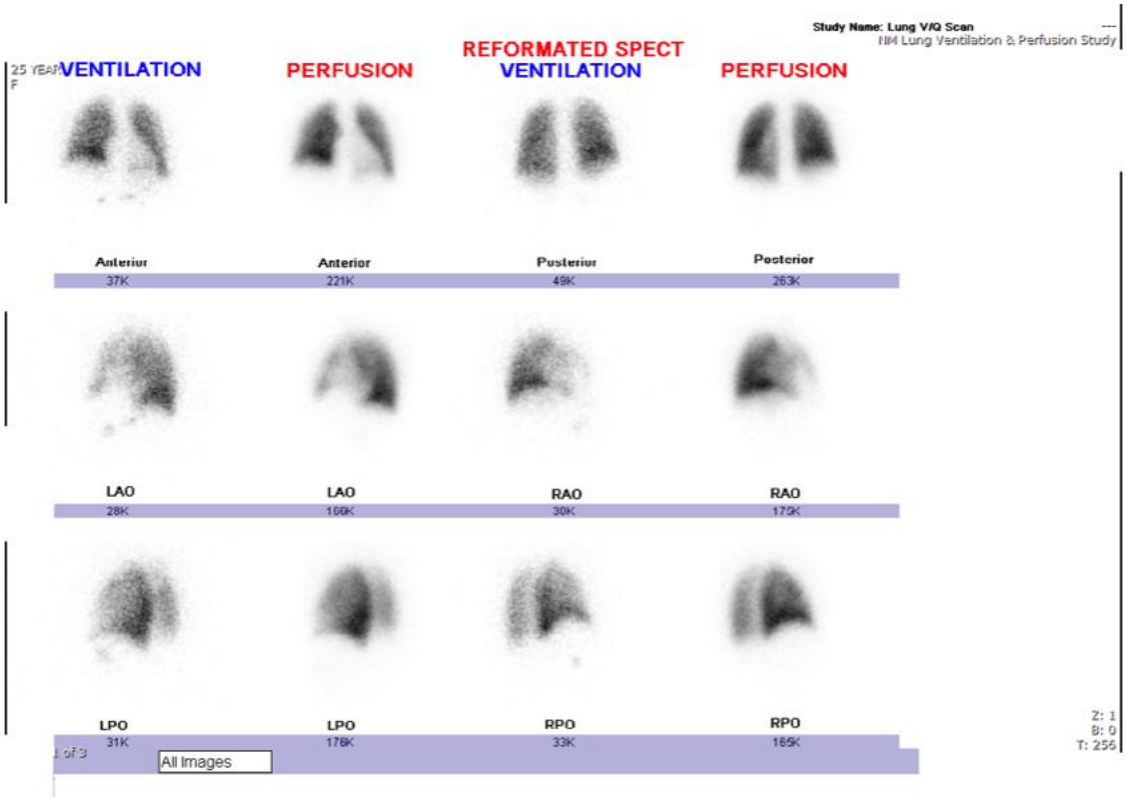


Image 4a: V/Q scan image demonstrating normal VQ scan [9]

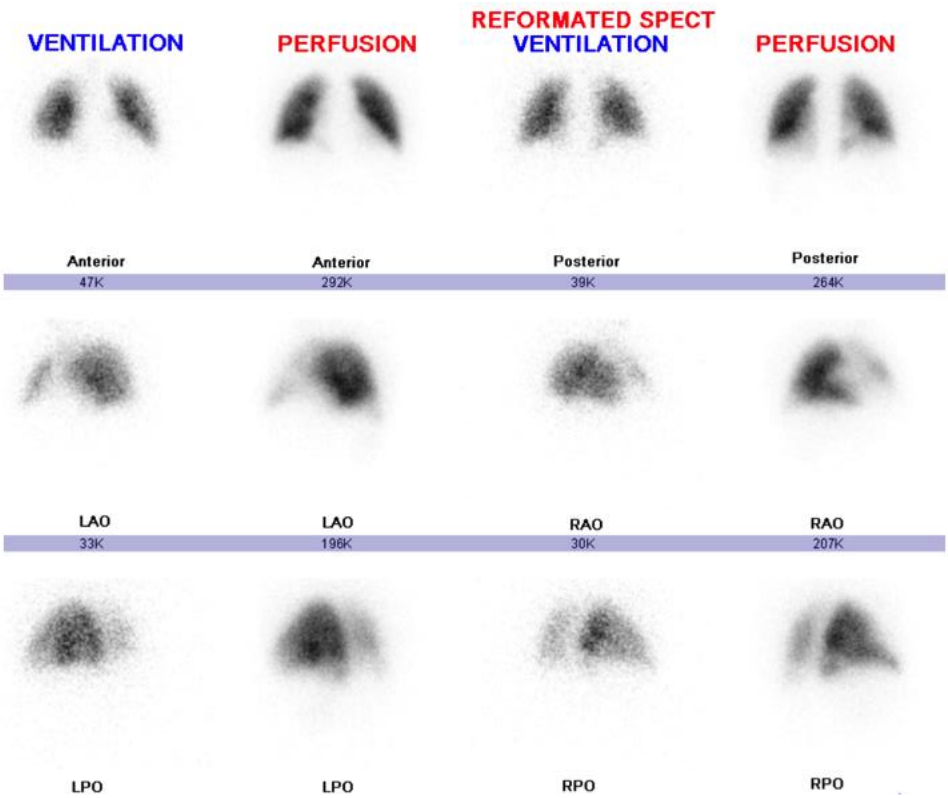


Image 4b: VQ scan image demonstrating ventilation perfusion mismatch in PE[10]

Treatment

Treatment options once a Pulmonary embolus has occurred include initial resuscitation (including with Cardiopulmonary resuscitation (CPR) if the patient is in extremis), supplemental oxygen and fluids, followed by anticoagulation and potential thrombolysis. Rarely, in the event of large emboli and a surviving patient, a thrombectomy may be performed. In more stable patients with smaller pulmonary emboli, treatment consists of anticoagulation and supportive care, in addition to treatment of any identified precipitating conditions. Therapeutic dose anticoagulation is usually continued for several months after the embolic event, and in some cases may be lifelong.

Risk Factors for VTE

Multiple factors can increase an individual's risk of VTE from baseline, usually by their effect on one of the components or Virchow's triad described above.
Of particular relevance to patients undergoing major open abdominal or pelvic surgery for malignancy, open approach[11] and malignancy[12] itself both independently carry increased risk of thrombosis formation.

Patient Position, Surgery and Venous Flow

Regarding operative factors, any abdominal or pelvic surgery is a significant trauma resulting in a systemic inflammatory response, with consequent release of inflammatory factors and increased coagulability of the blood. The surgical trauma itself includes a degree of direct endothelial damage to vessels intentionally or inadvertently ligated, removed or temporarily clamped as part of the procedure, as well as those affected by the placement of arterial or central venous lines for the purposes of close intraoperative monitoring. Anaesthesia and immobility during the procedure also causes in venous stasis. Stasis can be further exacerbated by specific patient positioning frequently employed

intraoperatively to aid exposure and access to the pathology being targeted. Common intraoperative positioning used in open abdominal and pelvic procedures include head down and lithotomy positions. These positions can further increase risk of VTE via reducing venous flow for example hip flexion during prolonged lithotomy compressing and kinking large pelvic veins.

While the use of insufflation and resultant temporary increase in abdominal pressures during laparoscopic or robotic procedures may also contribute to an increased risk DVT and VTE, in the majority of cases an open approach to the procedure results in both greater tissue trauma and higher postoperative pain levels[13]. Increased postoperative pain contributes to comparatively longer inpatient hospital stay and rehabilitation periods where there is ongoing reduced venous blood flow secondary to reduced mobility as compared to the patient's baseline activity. Finally, a patient's selection for an open approach to an abdominal or pelvic procedure may in many cases be related to a more advanced disease process or particularly complex prior surgical history that makes a minimally invasive approach unlikely to be feasible. Therefore the same characteristics that select a patient for an open approach, are also potentially associated with that patient having a more technically challenging and or longer duration procedure, which further increases VTE risk by longer intraoperative time of immobility, intraoperative temperature fluctuations and possible blood loss and transfusion requirement over the intraoperative course. In the postoperative period, patients with advanced disease who have undergone long, complex open procedures are at higher risk of other postoperative complications such as pelvic haematoma or seroma, which themselves are independently associated with an increased risk of DVT and VTE, for example by haematoma or seroma causing extrinsic compression of major pelvic veins leading to reduced venous return and stasis.

Thus, even if other patient factors are not considered, undergoing an open abdominal or pelvic surgical procedure alone significantly increases any patient's risk of VTE, with all components of Virchow's triad impacted.

Hypercoagulable State in malignancy

Solid or visceral malignancy of any type causes a pro-coagulable state. While the exact mechanism of this is complex and not yet fully understood, current factors thought to play a significant role include direct production of procoagulant, fibrinolytic and pro-aggregant agents by tumour cells, release of proinflammatory and proangiogenic cytokines, direct interactions via adhesion molecules between tumour cells and host vascular and blood cells and altered platelet, leucocyte and Tissue Factor (TF) counts in malignancy patients[14].

Patients with malignancy undergoing open abdominal or pelvic surgery may also have other non-modifiable risk factors for VTE including advanced age, limited baseline mobility, previous VTE or hereditary pro-thrombotic disorders such as factor V Leiden deficiency or Protein C&S deficiency. Modifiable risk factors include obesity, tobacco smoking and use of postmenopausal hormone replacement therapy or the oral contraceptive pill[15]. However, given the need for surgical treatment of malignancy to be performed in a timely fashion following diagnosis before further progression of disease, there may be only limited opportunity to significantly alter these factors. For example regarding obesity, the length of time required to achieve sufficient weight loss as to be beneficial would mean it is exceptionally unlikely any reduction of VTE risk by weight loss would not be outweighed by harm to the patient from delayed treatment of malignancy and consequent progression of disease.

Prophylaxis

The risk of VTE can be mitigated to some extent by providing prophylaxis (preventative treatment). VTE prophylaxis can be broadly grouped into mechanical prophylaxis and pharmacological prophylaxis.

Mechanical Prophylaxis:

Mechanical prophylaxis includes the use of graduated compression stockings (GCS), pneumatic compression devices and early postoperative mobility. Mechanical prophylaxis should be provided to all patients and include all measures unless there are specific contraindications to their use in that patient.

Graduated compression stockings exert graded compression on the limb, with the greatest compression provided at the ankle and progressive reduction in compressive force moving proximally. This theoretically results in increased venous pressure and therefore increased antegrade flow of blood with reduced venous reflux and stasis, as well as increased lymphatic drainage of the limb[16]. A previous Cochrane Review concluded that there is high quality evidence that GCS provide an effective reduction in risk of VTE in both general and orthopaedic surgery[17]. Contraindications to use of GCS are few, but include severe peripheral arterial disease or bypass grafting, severe peripheral neuropathy or other sensory impairment, and local skin or soft tissue conditions such as chronic ulcers, broken or extremely fragile skin, cellulitis, or conditions that prevent appropriate fitting of the stocking such as extreme deformity, massive peripheral oedema and or pulmonary oedema from congestive cardiac failure[16]. Care must be taken to ensure the stockings are worn correctly and there is no wrinkling of the stocking material causing localised constriction of the limb and risking pressure injuries.

Intermittent pneumatic compression devices (IPCDs) consist of inflatable sleeves fitted to the limb with a connected air pump that intermittently inflates the sleeve. Their mechanism of action is by external compression of the limb indirectly causing compression of the veins and so simulating the skeletal muscle pump of the calf muscles in mobilisation, increasing venous blood flow and reducing stasis[18]. Contraindications to their use include known pre-existing DVT or PE (as it is thought the force of the intermittent compressions may increase the risk of a DVT embolising), thrombophlebitis and local skin disease such as ulcers, wounds or cellulitis. A proportion of patients have been reported not to tolerate use of IPCDs due to finding the compression uncomfortable, or the noise of the air pump irritating.

Early postoperative mobilisation should be encouraged with the aim of the patient returning to their baseline preoperative mobility as quickly as possible postoperatively. This is arguably the most important component of mechanical VTE prophylaxis and is ideally approached with a multidisciplinary team. The multidisciplinary team includes the treating surgical team, ward nursing staff, and utilisation of specialised input from physiotherapists to assess and assist patients with safe mobility, and at times occupational therapists or prosthetists where mobility aids are required. Consultation with anaesthetic and pain physicians is also crucial in order to optimise analgesia and ensure postoperative pain is sufficiently controlled as to not unduly impair the patient's ability to participate in mobilisation.

Finally, optimising compliance with mechanical prophylaxis also requires commitment to effective patient education so the patient has awareness of VTE and its significance, and thus the importance of and reasons for each prophylactic strategy. Clear and consistent information including written information should ideally be provided to the patient both during preoperative planning and the postoperative period.

Pharmacological Prophylaxis

Pharmacological prophylaxis refers to the use of medication to reduce the blood's ability to clot via their effect on particular steps of the coagulation cascade described above. Commonly used anticoagulants include Aspirin, Warfarin, Direct Oral Anticoagulants and both unfractionated and low molecular weight heparins[19,20].

While all have been documented to have been used in VTE prophylaxis and therapeutic anticoagulation, heparins are the most commonly used agent in Australia, and are the recommended prophylactic agent in best practice guidelines including the current BJUI[19] recommendation, those previously produced by the American Urological Association[1], and the American College of Chest Physicians[20]. These guidelines specifically recommend low molecular weight (LMWH) or unfractionated heparin in patients who are at high risk of VTE. Consequently, for the purposes of this study we chose to focus on the use of heparin, in particular Enoxaparin (a low molecular weight heparin) in VTE prophylaxis.

Action of Heparin:

Heparins are acidic mucopolysaccharides that inhibit coagulation by potentiating the development of complexes between antithrombin and activated serine protease coagulation factors and factors IIa IXa, Xa and XIa, irreversibly inactivating these factors and thus preventing the conversion of prothrombin to thrombin and fibrinogen to fibrin. Unfractionated heparin also inhibits platelet function[21].

Enoxaparin is a low molecular weight heparin (as opposed to unfractionated) heparin, produced by depolymerisation of unfractionated heparin. Compared to unfractionated heparin it has a greater ability to inhibit factor Xa and reduced interaction with platelets as well as a greater bioavailability and a longer plasma half-life. These characteristics mean enoxaparin is considered an ideal agent for VTE prophylaxis as its half-life of approximately four hours after subcutaneous administration enables once daily administration. In addition there is a lower frequency of complications such as heparin induced thrombocytopaenia with Enoxaparin. In addition, an antidote, protamine, is available should its anticoagulant effect need to be reversed[23]. Specific individual factors that must be taken into consideration for enoxaparin use and dose adjustment include patient weight and renal function as it is renally excreted[22].

Consideration in use of Heparins:

However, as with all interventions, the benefit of prophylaxis must be weighed against the potential for adverse events. Known complications of pharmacological VTE prophylaxis include both major and minor haemorrhage, heparin induced thrombocytopaenia, elevation of serum aminotransferases, infection associated with haematoma at administration sites, hypersensitivity and local reactions[22]. With increased duration of prophylaxis there will be an increase in prophylaxis related adverse events, up to a point where this may outweigh the benefit of the prophylaxis. At what duration of prophylaxis this point is reached remains unclear. However, with the exception of major haemorrhage, infection and anaphylaxis, these complications likely pose a relatively smaller threat to patients than that associated with clinically detectable VTE. Furthermore, a patient diagnosed with VTE would be expected to be treated with more aggressive therapeutic dose anticoagulation than that given for prophylaxis for a longer treatment duration, thus exposing them to a higher risk of these complications than is associated with prophylaxis. Other minor disadvantages to its use include the need for parenteral administration as it is not absorbed from the gastrointestinal tract, which results in the risk of local administration site complications.

Duration of prophylaxis and relation to aims of project

Despite the consensus that risk of VTE extends for a significant period of time postoperatively, to date literature reviews have found insufficient evidence to determine an exact timeframe for this risk and consequently have not been able to make an evidence-based recommendation for optimum duration of postoperative prophylaxis[19].

In addition, there does not appear to be a consistent pattern of use of postoperative pharmacological VTE prophylaxis in abdomino-pelvic oncological surgery patients. This is possibly largely due to the generalised nature of current recommendations. Despite this, extended duration use appears to be becoming increasingly common. This may be explained by the fact that benefits of extended duration prophylaxis have been well documented in other specialties[20] and many practitioners therefore believe these could reasonably be expected also to apply to open abdomino-pelvic oncological surgery patients. However, it is questionable whether it is appropriate to apply evidence generated in other specialties to this population, as despite the observed similarities, equally there are a number of differences and so whether the populations are truly equivalent in relation to benefit and risks of prophylaxis is unknown.

Consequently, further investigation is warranted to define the optimum duration of postoperative pharmacological VTE prophylaxis with heparin following major abdomino-pelvic oncological surgery, with the goal being to determine the most effective reduction in population risk of VTE without disproportionately increasing the risk of heparin associated adverse events or cost of treatment. Identifying this and thus enabling an evidence-based recommendation to be made regarding recommended duration would enable all abdominal and pelvic oncological surgery patients to receive standardised best practice postoperative pharmacological VTE prophylaxis.

The primary aim of this work was therefore to contribute to potentially developing such an evidence based recommendation, by performing a systematic literature review and meta-analysis of existing literature, looking specifically at patients undergoing major open abdominal or pelvic surgery for malignancy and comparing the effectiveness and safety of postoperative inpatient versus extended venous thromboembolism (VTE) prophylaxis with heparin in this population. Subsequently a secondary aim is to use the findings of this literature review to evaluate the economic implications of this treatment by comparing cost of providing this prophylaxis to costs of treatment of VTE events in the absence of prophylaxis.

MAIN BODY CHAPTER 2: PUBLICATION 1 – PROTOCOL FOR A SYSTEMATIC REVIEW

Statement of Authorship

Title of Paper	Effectiveness and safety of inpatient versus extended venous thromboembolism (VTE) prophylaxis with heparin following major pelvic surgery for malignancy: protocol for a systematic review.
Publication Status	Published
Publication Details	Published in Journal of Systematic Reviews (Syst Rev. 2019 Oct 30;8(1):249. Doi: 10.1186/s13643-019-1179-1.)

Principal Author

Name of Principal Author (Candidate)	Bridget Caroline Heijkoop		
Contribution to the Paper	Authors; Dr Bridget Heijkoop wrote the study protocol, will perform initial data collection and review of identified articles, manage data records and write the systematic review document.		
Overall percentage (%)	90		
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	[redacted]	Date	21/05/2020

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 to 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.

Name of Co-Author	Ms Natalie Parker		
Contribution to the Paper	Ms Natalie Parker collated and managed the Queen Elizabeth Hospital database on extended VTE prophylaxis.		
Signature	[redacted]	Date	4/5/20

Name of Co-Author	Mr Dan Spernat		
Contribution to the Paper	Mr Dan Spernat acted as a co-supervisor of the project.		
Signature	[redacted]	Date	12/5/20

Name of Co-Author	Associate Professor George Kiroff
Contribution to the Paper	A/Prof George Kiroff acted as the primary supervisor of the project and was extensively involved in reviewing the manuscript and approving the final manuscript for submission.
Signature	Date 20/5/2020

TITLE

Effectiveness and Safety of Inpatient versus Extended Venous Thromboembolism (VTE) Prophylaxis with Heparin following Major Pelvic Surgery for Malignancy: Protocol for a Systematic Review.

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ABSTRACT

BACKGROUND
Venous Thromboembolism (VTE) is a common postoperative complication associated with significant morbidity and mortality. Use of prophylactic heparin postoperatively reduces this risk, and use of extended duration prophylaxis is becoming increasingly common. Malignancy and pelvic surgery both independently further increase the risk of postoperative VTE, and patients undergoing major pelvic surgery for malignancy are at particularly high risk of VTE. However, optimum duration of prophylaxis specifically in this population currently remains unclear.

METHODS
We will conduct a systematic review of literature in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[23] to evaluate current evidence of the effectiveness and safety of inpatient versus extended VTE prophylaxis with Heparin (all forms) following major pelvic surgery for malignancy. We will search PubMed, EMBASE, and the Cochrane Library. Regarding safety, Food and Drug Administration (FDA) and Therapeutic Goods Administration (TGA) websites will be searched, including all levels of evidence. Results will be the postoperative timeframe in which a VTE event can be considered to have been provoked by the surgery, and the number of patients needed to treat with both inpatient and extended prophylaxis to prevent a VTE event in this timeframe, comparing these to determine if there is a significant benefit from extended prophylaxis.

DISCUSSION
This systematic review will aim to identify the postoperative period in which patients undergoing major pelvic surgery for malignancy are at further increased risk of VTE as a result of their surgery, and the optimum duration of VTE prophylaxis with heparin to reduce this risk. Determining this will allow evidence-based recommendations to be made for optimum duration of heparin VTE prophylaxis post major pelvic surgery for malignancy, leading to improved standards of care that are consistent between different providers and institutions.

SYSTEMATIC REVIEW REGISTRATION:
In accordance with guidelines, our systematic review was submitted to PROSPERO for consideration of registration on 16/12/17 and was registered on 12/1/18 with the registration number CRD42018068961, it was last updated on 12/1/18.

KEYWORDS
Venous Thromboembolism, Prophylaxis, Postoperative, Heparin, Pelvic Surgery, Malignancy, safety

BACKGROUND

Venous thromboembolism (VTE) is a common postoperative complication associated with significant morbidity and mortality[1]. A major risk factor for VTE is type of surgery, with patients undergoing major oncological surgery or pelvic surgery being at significant risk[1]. These patients frequently also have additional non-modifiable risk factors for VTE including advanced age, limited mobility, previous VTE or hereditary pro-thrombotic disorders. However, these risks can be mitigated by providing mechanical and or pharmacological prophylaxis. Best practice guidelines including the current BJUI[19] recommendation and those previously produced by American Urological Association[1], recommend the use of low molecular weight (enoxaparin) or unfractionated heparin in patients who are at high risk of VTE.

However, despite consensus that the risk of VTE extends for a significant period postoperatively, to date literature reviews have found insufficient evidence to determine an exact timeframe for this, and consequently have not been able make an evidence-based recommendation for the optimum duration of prophylaxis[19]. In addition, there does not appear to be a consistent pattern of use of postoperative pharmacological VTE prophylaxis in pelvic oncological surgery patients.

As with all interventions, the benefit must be weighed against the potential for adverse events. Known complications of pharmacological DVT/VTE prophylaxis include both major and minor haemorrhage, thrombocytopaenia, elevation of serum aminotransferases, infection associated with haematoma, hypersensitivity reactions and local reactions[22]. With increased duration of prophylaxis there will be an increase in prophylaxis related adverse events, up to a point where these outweigh any ongoing benefit of the prophylaxis – again, at what duration of prophylaxis this point is reached remains unclear.

Consequently, further investigation is warranted and we aim to define the optimum duration of postoperative pharmacological VTE prophylaxis with heparin following major pelvic oncological surgery to provide the most effective reduction in population risk of VTE without disproportionately increasing the risk of heparin associated complications. Identifying this and making an evidence-based recommendation would enable all pelvic oncological surgery patients to receive standardised best practice postoperative pharmacological VTE prophylaxis.

METHODS/DESIGN

AIMS

The aim of this systematic review is to review the currently available literature to evaluate the effectiveness and safety of inpatient versus extended VTE prophylaxis with Heparin (all forms) following major pelvic surgery for malignancy answering the following questions:

1. Timeframe postoperatively in which a VTE event can reasonably be considered to have been provoked by the surgical procedure
2. Number needed to treat (NNT) with inpatient prophylaxis to prevent one VTE event within the timeframe established by 1.
3. NNT with extended prophylaxis to prevent one VTE event within the timeframe established by 1
4. Considering the results of 2 and 3, is there a significant benefit associated with extended prophylaxis in reducing risk of VTE events?
5. Considering result of 4, if extended prophylaxis is shown to significantly reduce VTE events in the postoperative period established in 1, does this benefit outweigh the associated risks of extended prophylaxis – ie is extended prophylaxis safe?

DESIGN - SEARCH STRATEGY & INFORMATION SOURCES

Literature search regarding both effectiveness and safety will be conducted by searching PubMed, EMBASE (2008-present), and Cochrane databases from inception to present. Regarding safety, Food and Drug Administration (FDA) and Therapeutic Goods Administration (TGA) websites will be reviewed in addition to targeted searches of Health Technology Assessment databases such as 'EuroSCAN' [24] to identify any further grey literature reporting of adverse events that may have been reported to these bodies but not published within a research paper and therefore not captured by the database search. In addition to the electronic database and regulatory website search described above we will review public registries of clinical trials and the reference lists of included literature and the published work of authors listed, with the aid of tools such as SCOPUS.

Search terms will include the medical subject headings (MeSH) and keywords combined by Boolean operators: Venous Thromboembolism OR VTE OR Deep vein thrombosis OR DVT AND Pelvic OR Malignancy OR Oncology AND Heparin OR Enoxaparin AND Prophylaxis. Refer to appendix 1 for search strategy.

DESIGN - ELIGIBILITY CRITERIA

1. We will include English language studies of NHMRC level of evidence I-V. The decision to include case reports (level V) and case series was made as it was felt these would be useful to identify adverse events.
2. Participants; participants will be the subjects of all included literature, including adult (18 years and older) patients of either gender undergoing pelvic surgery for malignancy
3. The intervention will be the use of extended pharmacological VTE prophylaxis (as opposed to in hospital pharmacological prophylaxis) with any form of heparin postoperatively, with the assumption made that all patients receiving pharmacological prophylaxis also received non-pharmacological VTE prophylaxis (eg compression stockings, sequential compression devices)
4. The comparator will be inpatient versus extended use of heparin VTE prophylaxis
5. Outcomes; endpoints considered will include
    a. VTE events
    b. Heparin associated complications; classified by Clavien-Dindo grade[25].
6. Studies published within the last ten years up to and included the date the literature search was completed will be included. The decision to exclude studies published more than ten years ago was made to ensure that included literature more closely reflects recent clinical practice and is therefore relatively representative of the current day patient population and care.
7. Setting will be inpatient and community patients receiving pharmacological VTE prophylaxis with heparin postoperatively

DESIGN - SELECTION PROCESS

Retrieved articles will be independently reviewed by primary author and peer reviewer and included or excluded by the pre-determined criteria described above.

Articles will first be shortlisted for inclusion or discarded based on their title. Of those shortlisted by title, the abstract will be reviewed and the papers returned to the shortlist or discarded by the relevance of the abstract. Those included or unclear based on the abstract will proceed to review of the entire article by both the primary and second author, who will independently document if they would include or discard the article.

Should there be a disagreement between the primary and secondary reviewer, the article will be additionally reviewed by the supervisors of the project and a reasonable effort made to contact the author for any clarification required on the included material.

Exclusion criteria will include non-English language papers as the team lacks the resources available to translate these, paediatric populations and animal studies. Non-English language papers with an

English abstract will be listed as potentially relevant studies awaiting assessment in the review to alert the reader of these papers' existence in a wider evidence base.

DESIGN - DATA COLLECTION PROCESS

A template form of data variables to be extracted will be produced, and reviewers will independently complete this for each article reviewed, and additionally transcribe the data points into separate excel spreadsheets. Each reviewer's assessment will then be compared and in the event of any discrepancies not able to be resolved on re-review the article will be reviewed by a supervisor, following which if the discrepancies remain unresolved reasonable attempts will be made to seek clarification from the author.
A template of this in table form is included as an Appendix to this document.

DESIGN - DATA ITEMS

Variables to source data for

- Timing of starting heparin postoperatively
- Total duration heparin prophylaxis; inpatient versus extended. This will be considered a dichotomous variable, with patients categorised into those receiving prophylaxis whilst a hospital inpatient or those receiving ongoing prophylaxis of any duration on discharge.
- VTE events
- Event that may be considered complications of prophylaxis and determine their Clavien Dindo grade[25]
- Type of surgery (primary or revision). If sufficient data is identified this may subsequently be used to conduct further analysis comparing outcomes of primary and revision procedures.
- Disease histology. If sufficient data is identified this may subsequently be used to conduct further analysis by each oncologic pathology.

Assumptions made

- Inpatient stay will be considered a single duration despite the fact that inpatient stay postoperatively may be of variable length as this remains of significant impact due to altered mobility/activity from baseline while in inpatient setting
- Concurrent use of mechanical prophylaxis; it will be assumed all patients received mechanical VTE prophylaxis in addition to pharmacological as the instances in which this is contraindicated are uncommon
- Assume all patients receive an appropriate dose of pharmacological prophylaxis for their individual condition (ie appropriate for body habitus, appropriate reduction in dose for impaired renal function). However, if it is possible from the included data to confirm an appropriate dose was used this will be confirmed.
- Potential VTE events not diagnosed on Ultrasound (US)/Computed tomography pulmonary angiography (CTPA)/V/Q Scan are of sufficiently insignificant impact on the individual's recovery as to be irrelevant to the outcomes of the study.

DESIGN - OUTCOMES PRIORITISATION

The primary outcome will be the number of clinically evident VTE events in patients treated with prophylactic heparin following major pelvic surgery for malignancy, subdivided into those treated only whilst inpatient immediately postoperatively and those treated with an extended course. Clinically evident VTE will be defined as that confirmed on investigation with US/CTPA. Any incidence of VTE not detected by these means will be interpreted as being sufficiently minor as to be clinically insignificant. In addition, any diagnoses of VTE made purely on the basis of history and examination findings without objective evidence of confirmed VTE on these modalities will be excluded as the clinical presentation of VTE is nonspecific and thus this may not represent a true VTE event.

Secondary outcomes will include both adverse events attributable to use of pharmacological VTE prophylaxis such as bleeding/haematoma/thrombocytopaenia/drug reaction, and in association with identified VTE events; length of stay/ICU admission/readmission to hospital following discharge.

DESIGN - RISK OF BIAS AND PLANNED ASSESSMENT OF META BIAS

Potential sources of bias in this review will be from pre-existing bias in reviewed articles, publication bias and potential of data censuring. Risk will be minimised by use of appropriate critical appraisal tools (e.g. AMSTAR2 for Systematic reviews[26] and Cochrane tool[27] for randomised controlled trials) to critically assess each article and consider exclusion of low scoring articles.

DESIGN - DATA SYNTHESIS

Statistical advice regarding the most appropriate method of analysis will be sought following literature search prior to data extraction. Should identified articles be of sufficient number and quality, data may be further broken down by cancer type.

DESIGN - HOW THE STRENGTH OF THE BODY OF EVIDENCE WILL BE ASSESSED

The strength of the body of evidence will be assessed using the GRADEpro tool[28].

DESIGN - STUDY RECORDS

Record of the details (Title, Author(s), Where published, Date of publication, Access date, Reasoning behind decision to include) of all included articles will be kept in an excel spreadsheet. Those relevant to effectiveness will be kept on a separate page of the spreadsheet to those relevant to safety, and those relevant to both effectiveness and safety duplicated across both pages.
The second author will keep an additional database of the articles they have reviewed and their reasoning for their recommendation that the article be included or discarded.
Details of articles initially identified on scoping search and subsequently excluded will be kept in a separate excel document which will also lists the reason for their exclusion.

DESIGN – PROCESS OF DEALING WITH AMENDMENTS TO PROTOCOL

A copy of the protocol will be saved and kept both without and with amendments, giving a new version number to the amended copy; thus versions at all stages of amendments remain available. Other contributors will be notified of amendment via email

DISCUSSION

As this protocol is for a systematic review of pre-existing literature, minimal operational issues are anticipated, with the primary difficulty anticipated being any situation where the full text of an identified article is not accessible. This will be managed on a case by case basis with the available text (e.g. abstract) of the article reviewed by both reviewers and the project supervisors to determine if it is suitable for inclusion or not. Should a consensus not be able to be reached the article will be included. We acknowledge limitations of this review including potential sources of bias described in methods and including only English language publications.

LIST OF ABBREVIATIONS

AUA: American Urological Association
BJUI: British Journal of Urology International
DVT: Deep Vein Thrombosis
MeSH: Medical Subject Headings
NNT: Number needed to treat
TGA: Therapeutic Goods Administration
VTE: Venous Thromboembolism

DECLARATIONS

ETHICS APPROVAL
Systematic review of pre-existing literature – exempt from ethical review.

CONSENT FOR PUBLICATION:
All authors are aware of this submission and consent to its submission for publication.

COMPETING INTERESTS:
None to declare.

FUNDING/SUPPORT
Financial: University fees are covered by the Research Training Program scheme.
Nonfinancial: ASERNIP-S provided advice and guidance on systematic review methods.
Assistance from The University of Adelaide librarians and statistics unit will be sought as required for data search, identification, extraction, collation and interpretation.

CONTRIBUTIONS
Authors; Dr Bridget Heijkoop wrote the study protocol, will perform initial data collection and review of identified articles, manage data records and write the systematic review document. A second reviewer will review articles identified as suitable for inclusion on initial review by Dr Bridget Heijkoop. Ms Natalie Parker collated and manages the Queen Elizabeth Hospital database on extended VTE prophylaxis. Associate Professor George Kiroff and Mr Daniel Spernat acted as supervisors of the project.

DATA AVAILABILITY
Data analysed during the study will be available from the corresponding author on request.

AKNOWLEDGEMENTS
The authors would like to thank ASERNIP-S, in particular Dr David Tivey and Mr Alun Cameron for their generosity in providing advice and guidance on conducting a systematic review of literature.

ADDITIONAL FILES

ADDITIONAL FILE 1. SEARCH STRATEGY

(((((((((aspirin) OR dalteparin) OR warfarin) OR low molecular weight heparin) OR enoxaparin) OR heparin)) OR ((((((heparin, low molecular weight[MeSH Terms]) OR aspirin[MeSH Terms]) OR warfarin[MeSH Terms]) OR dalteparin[MeSH Terms]) OR enoxaparin[MeSH Terms])))) AND ((((((((((((((((((cancer, uterine cervical[MeSH Terms] OR cervical cancer) OR urethral cancer[MeSH Terms]) OR urethral cancer) OR cancer, prostate[MeSH Terms]) OR prostate cancer) OR cancer, uterine[MeSH Terms]) OR uterine cancer) OR cancer, ovarian[MeSH Terms] OR ovarian cancer) OR colorectal cancer[MeSH Terms]) OR bowel cancer) OR cancer of the ureter[MeSH Terms]) OR ureteric cancer) OR bladder cancer) OR bladder cancer[MeSH Terms])) OR ((((“Abdominal Neoplasm”[Mesh]) OR abdominal neoplasm)) OR ((pelvic neoplasms) OR “Pelvic Neoplasms” [Mesh])))

History

Download history Clear history

Search	Add to builder	Query	Items found	Time
#66	Add	Search (((((((((aspirin) OR dalteparin) OR warfarin) OR low molecular weight heparin) OR enoxaparin) OR heparin)) OR ((((((heparin, low molecular weight[MeSH Terms]) OR aspirin[MeSH Terms]) OR warfarin[MeSH Terms]) OR dalteparin[MeSH Terms]) OR enoxaparin[MeSH Terms])))) AND ((((((((((((((((((cancer, uterine cervical[MeSH Terms]) OR cervical cancer) OR urethral cancer[MeSH Terms]) OR urethral cancer) OR cancer, prostate[MeSH Terms]) OR prostate cancer) OR cancer, uterine[MeSH Terms]) OR uterine cancer) OR cancer, ovarian[MeSH Terms]) OR ovarian cancer) OR colorectal cancer) OR cancer, colorectal[MeSH Terms]) OR bowel cancer) OR cancer of the ureter[MeSH Terms]) OR ureteric cancer) OR bladder cancer) OR bladder cancer[MeSH Terms])) OR ((((“Abdominal Neoplasms”[Mesh]) OR abdominal neoplasms)) OR ((pelvic neoplasms) OR “Pelvic Neoplasms”[Mesh]))))	3381	19:28:43

ADDITIONAL FILE 2: DATA COLLECTION TEMPLATE

Article	1	2	3
Title			
Author(s)			
Year of Publication			
Journal			
NHMRC Evidence Level			
Malignancy diagnosis/ese			
Procedure(s)			
Major intervention (Including dose/route/frequency/duration) - Number post exclusions			
Comparator (Including dose/route/frequency/duration) - Number post exclusion			
Outcomes - How were these defined - How were these measured			
Conclusions			
EFFICACY OUTCOMES			
Mortality rate secondary VTE			
Rate of VTE - Symptomatic - Asymptomatic - Total			
DVT:PE			
SAFETY OUTCOMES			

Bleeding events - Major - Minor - Total			
Number of transfusions			
Wound complications			
Other adverse events			
Readmissions			
Estimated intraoperative blood loss			

MAIN BODY CHAPTER 3: PUBLICATION 2 – SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

Statement of Authorship

Title of Paper	Extended or Inpatient Thromboprophylaxis with Heparins following major open pelvic surgery for malignancy - A systematic review of efficacy and safety
Publication Status	Published
Publication Details	Published in Perioperative Medicine 3/3/2020 DOI: PERI-D-19-00039R2 / 10.1186/s13741-020-0137-8

Principal Author

Name of Principal Author (Candidate)	Bridget Caroline Heijkoop
Contribution to the Paper	Bridget Heijkoop developed the protocol, conducted the literature review and wrote the manuscript.
Overall percentage (%)	90
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: 21/05/2020

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 to 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.

Name of Co-Author	Mr Sinan Nadi
Contribution to the Paper	Sinan Nadi acted as second reviewer of articles identified in literature review.
Signature	Date: 04-05-'20

Name of Co-Author	Mr Dan Spernat
Contribution to the Paper	Mr Dan Spernat acted as a co-supervisor of the project.
Signature	Date: 12/5/20

Name of Co-Author	Associate Professor George Kiroff
Contribution to the Paper	A/Prof George Kiroff acted as the primary supervisor of the project and was extensively involved in reviewing the manuscript and approving the final manuscript for submission.
Signature	Date 20/5/2020

TITLE:

Extended versus Inpatient Thromboprophylaxis with Heparins following Major Open Abdominopelvic Surgery for Malignancy - A Systematic Review of Efficacy and Safety

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3. Research and Evaluation, Incorporating ASERNIP-S, Royal Australasian College of Surgeons, Adelaide, Australia.

LIST OF ABBREVIATIONS:

AUA	-	American Urological Association
BJUI	-	British Journal of Urology (International)
CTPA	-	Computed Tomography Pulmonary Angiogram
CTP	-	Conventional Thromboprophylaxis
DVT	-	Deep Vein Thrombosis
ETP	-	Extended Thromboprophylaxis
ICU	-	Intensive Care Unit
LMWH	-	Low Molecular Weight Heparin
NHMRC	-	National Health and Medical Research Council
NNT	-	Number Needed to Treat
PE	-	Pulmonary Embolus
RCT	-	Randomised Controlled Trial
US	-	Ultrasound
V/Q	-	Ventilation/Perfusion
VTE	-	Venous Thromboembolism

DECLARATIONS:

Ethics approval and consent to participate: Not applicable

Consent for publications: Not applicable

Availability of data and materials: Data used and analysed in this review are available from the corresponding author on reasonable request.

Competing interests: All authors declare no conflict of interest to report.

Funding: Financial support to the value of $1000 (AUD) was provided via Student Support Funding from Adelaide Medical School Orbit Project 324-15119081. This was used to obtain expert advice in conducting statistical analysis of data included in the literature review.

Authors contributions: Bridget Heijkoop developed the protocol, conducted the literature review and wrote the manuscript. Sinan Nadi acted as second reviewer of articles identified in literature review. George Kiroff and Dan Spernat acted as supervisors of the project, with George Kiroff being the primary supervisor. All authors approved the final manuscript and order of authors before submission.

Acknowledgements: The authors wish to sincerely thank Mr David Tivey and Mr Ning Ma (Research and Evaluation, Incorporating ASERNIP-S, Royal Australasian College of Surgeons, Adelaide, Australia) for their invaluable advice and guidance in developing the protocol and search strategy and conducting literature review and analysis.

ABSTRACT:

BACKGROUND: Patients undergoing open abdomino-pelvic procedures for malignancy are at high risk of postoperative venous thromboembolism (VTE). This risk can be mitigated with prophylaxis, however optimum duration in this population remains unknown. Our objective was to conduct a systematic review of contemporary literature on use of heparin thromboprophylaxis following major open pelvic surgery for malignancy, comparing the efficacy and safety of extended duration to inpatient treatment.

METHODS: A study protocol describing search strategy, inclusion and exclusion criteria was developed and registered with PROSPERO. A literature review was conducted in accordance with the protocol.

RESULTS: Literature review identified only four studies directly comparing extended and inpatient duration prophylaxis, with a combined population of 3198 and 3135 patients for VTE rate and bleeding events respectively. Despite many studies reporting lower VTE rates in patients receiving extended prophylaxis, no statistically significant difference in rates of postoperative VTE ($p=0.18$) or bleeding complications ($p=0.43$) was identified between patients receiving extended duration prophylaxis and those receiving inpatient only prophylaxis.

CONCLUSION: On review of contemporary literature, no significant difference was found in rates of postoperative VTE or bleeding complications between patients receiving extended duration heparin VTE prophylaxis and those receiving inpatient prophylaxis after open abdominopelvic surgery for malignancy.
This raises the question of how extended duration prophylaxis has become common practice in this population, and whether this needs to be re-evaluated.

KEYWORDS:
Venous Thromboembolism
Malignancy
Surgery
Heparin
Prophylaxis

BACKGROUND:

Venous thromboembolism (VTE) is a common postoperative complication associated with significant morbidity and mortality[1]. A major risk factor for VTE is type of surgery, with patients undergoing major oncological surgery or pelvic surgery being at significant risk[19]. These patients frequently also have additional non-modifiable risk factors for VTE including advanced age, limited mobility, previous VTE or hereditary pro-thrombotic disorders. However, these risks can be mitigated by using prophylaxis. Best practice guidelines including the current British Journal of Urology (BJUI)[19]recommendation and those previously produced by American Urological Association (AUA)[1], recommend the use of low molecular weight heparin (enoxaparin) or unfractionated heparin in patients who are at high risk of VTE although they do not specify an exact quantified recommended duration of treatment.

However, despite consensus that the risk of VTE extends for a significant period postoperatively, to date literature reviews have found insufficient evidence to determine an exact timeframe for this, and consequently have not been able make an evidence-based recommendation for the optimum duration of prophylaxis[19]. In addition, there does not appear to be a consistent pattern of use of postoperative pharmacological VTE prophylaxis in pelvic oncological surgery patients.

As with all interventions, the benefit must be weighed against the potential for adverse events. Known complications of pharmacological DVT/VTE prophylaxis include both major and minor haemorrhage, thrombocytopenia, elevation of serum aminotransferases, infection associated with hematoma, hypersensitivity reactions and local reactions[22]. With increased duration of prophylaxis there will be an increase in prophylaxis related adverse events, up to a point where these outweigh any ongoing benefit of the prophylaxis – again, at what duration of prophylaxis this point is reached remains unclear. Furthermore, extending the duration of VTE prophylaxis beyond what is required adds an economic burden to the health care system.

Consequently, further investigation is warranted to define the optimum duration of postoperative pharmacological VTE prophylaxis with heparin following major pelvic oncological surgery to reduce the risk of VTE without disproportionately increasing the risk of heparin associated complications. Identifying this and making an evidence-based recommendation would enable all pelvic oncological surgery patients to receive standardized best practice postoperative pharmacological VTE prophylaxis.

In this article we conduct a meta-analysis of inpatient versus extended duration VTE prophylaxis in patients undergoing pelvic surgery for malignancy. Extended use was defined as any continuation of pharmacological VTE prophylaxis after discharge from the index hospital admission, with inpatient use defined as the use of pharmacological VTE prophylaxis for the majority of the index hospital inpatient admission.

METHODS: A study protocol describing search strategy, inclusion and exclusion criteria was developed and registered with PROSPERO (CRD42018068961).

In accordance with the protocol, literature search was conducted of PubMed, EMBASE, and Cochrane databases. Search terms included medical subject headings (MeSH) terms and keywords combined by Boolean operators: aspirin, dalteparin, enoxaparin, warfarin, heparin, low molecular weight heparin, abdominal neoplasm, pelvic neoplasm, prostate cancer, bladder cancer, ureteric cancer, urethral cancer, ovarian cancer, cervical cancer, uterine cancer.

Search results were screened by the primary author and initially shortlisted for inclusion or discarded based on the relevance of the title to the protocol. Of those shortlisted by title, the abstract was reviewed and the papers returned to the shortlist or discarded based on the relevance of the abstract.

Those included or unclear based on the abstract proceeded to review of the entire article by both the primary author and second peer reviewer, who independently documented if they would include or discard the article. Disagreement was resolved by discussion between the reviewers.

Studies identified were eligible for inclusion in the review if they met inclusion criteria of being English language studies of adult patients published within the last ten years at the time of literature search. All National Health and Medical Research Council (NHMRC) levels of evidence (I-V) were included as it was felt the inclusion of case series and case reports remained important as a means of capturing reporting of adverse events. Non-English language papers, paediatric populations, non-operative or exclusively laparoscopic surgical populations and animal studies were excluded. While other antithrombotic agents (warfarin, aspirin) were included in the initial search terms with the aim of capturing a broad range of literature on postoperative thromboprophylaxis, a decision was made to assess only papers regarding heparin thromboprophylaxis and those utilising other forms of thromboprophylaxis were excluded.

The intervention of interest was the use of extended pharmacological VTE prophylaxis with any form of heparin postoperatively following major open abdominal or pelvic surgery for malignancy, with the comparator being inpatient use of heparin pharmacological VTE prophylaxis in this population. Extended use was defined as any continuation of pharmacological VTE prophylaxis after discharge from the index hospital admission, with inpatient use defined as the use of pharmacological VTE prophylaxis for the majority of the index hospital inpatient admission. The primary outcome was the number of clinically evident VTE events objectively confirmed on investigation with ultrasound (US), computed tomography pulmonary angiography (CTPA) or nuclear ventilation/perfusion (V/Q) scan in patients treated with prophylactic heparin following major pelvic surgery for malignancy. Secondary outcomes included adverse events attributable to use of pharmacological VTE prophylaxis such as bleeding, haematoma, thrombocytopaenia, drug reaction, and in association with identified VTE events; length of stay, ICU admission or readmission to hospital following discharge.

Assumptions made included that all patients received an appropriate dose of pharmacological prophylaxis for their body habitus and pre-existing conditions such as renal impairment, and that patients receiving pharmacological prophylaxis also received appropriate non pharmacological VTE prophylaxis (such as compression stockings, sequential compression devices), and that potential VTE events not diagnosed on US, CTPA or V/Q scan are of sufficiently insignificant impact on the individual's recovery as to be irrelevant to the outcomes of the study. Finally, despite the inherently variable length of individual patients' inpatient admission, inpatient use of prophylaxis was considered as a single duration as the inpatient hospital setting was considered to have a significant impact on patient's VTE risk due to altered mobility from baseline. Likewise, while individual extended prophylaxis regimes varied in their exact duration, these were considered as a single group.

Following final identification of included articles and data extraction, 'Revman'[29] software was used to directly compare appropriate articles and produce Forest plots of these comparisons. Narrative review of remaining articles not appropriate for direct comparison was then performed.

RESULTS: Final database search using all fields OR Mesh terms for; aspirin, dalteparin, enoxaparin, warfarin, heparin, low molecular weight heparin AND All fields OR Mesh terms for; abdominal neoplasm, pelvic neoplasm, prostate cancer, bladder cancer, ureteric cancer, urethral cancer, ovarian cancer, cervical cancer, uterine cancer identified 3381 articles.

Of these 3381 articles, 1825 were excluded by age of publication, with a further 977 excluded on review of title and 540 excluded on review of abstract, leaving a total of 38 articles for full text review. The exclusion process is summarised in Figure 1.

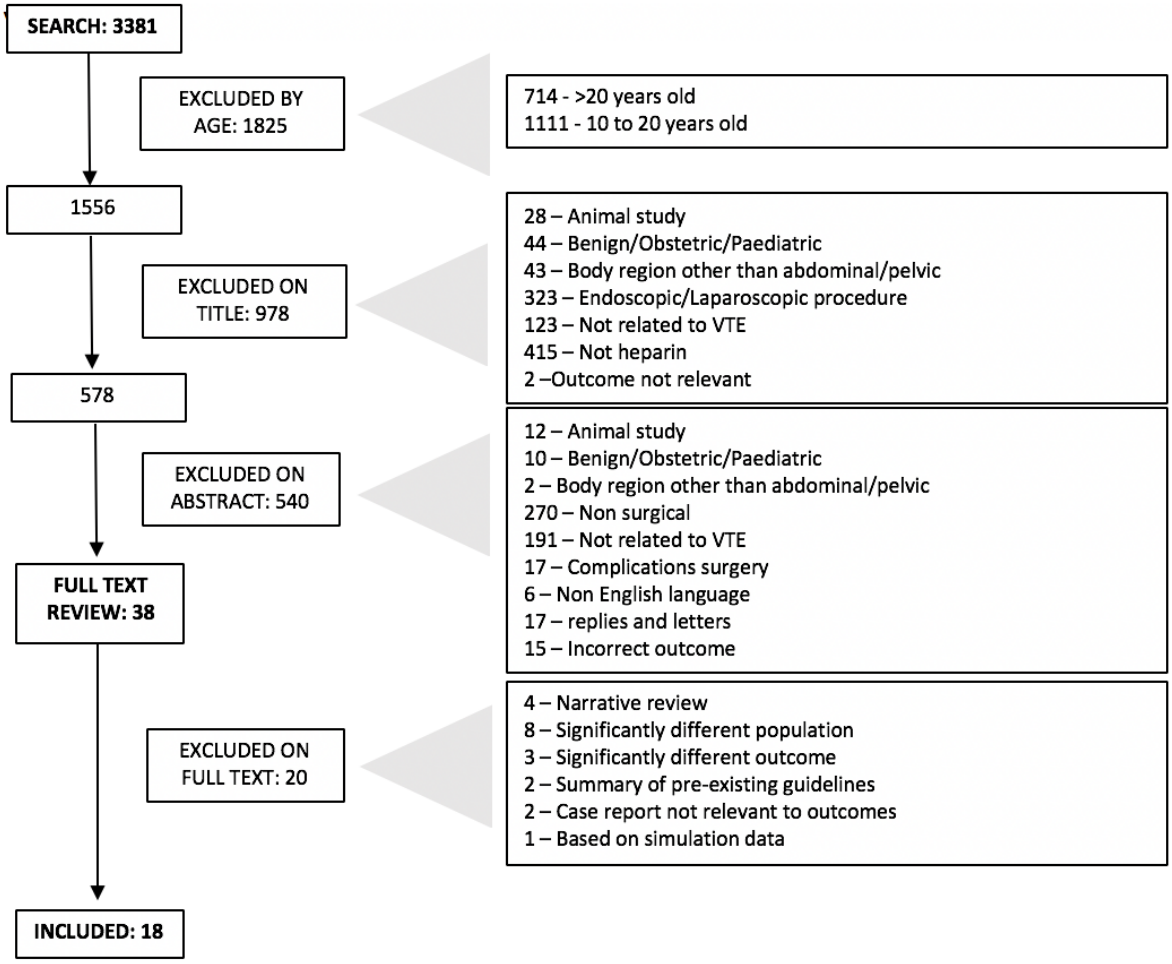

Figure 1: Flow diagram summarising exclusions on literature search.

Following full text review by both reviewers, a total of 18 articles met inclusion criteria. Of the 20 excluded on full text review, reasons for exclusion included narrative reviews (four), significant differences in population (eight) or outcome (three), as well as two articles which simply summarized pre-existing guidelines, two case reports not relevant to complications of anticoagulation and one article that was based on a simulation only.

Two pre-existing systematic reviews were identified – Fagaranasu et al[30] and Akl et al[31]. The characteristics of these can be summarized in Figure 2.

Figure 2: Summary of characteristics of two pre-existing reviews

	Fagaranasu et al. (SR1)	Akl et al. (SR2)
Title	Role of Extended Thromboprophylaxis after Abdominal and Pelvic Surgery in Cancer Patients: A Systematic Review and Meta-analysis	Extended perioperative thromboprophylaxis in patients with cancer, A systematic review
Journal	Ann Surg Oncol	Cellular Proteolysis and Oncology
Year	2016	2008

Country	Canada	United States of America
Funding	Did not comment	'Institutional support' + one author funded by a European Commission
Time period included	Inception of database – May 2015	Did not comment
Databases searched	- Cochrane Central Register of Controlled Trials - MEDLINE - EMBASE	- Cochrane Register of Controlled Trials (Jan 2007) - MEDLINE - EMBASE - ISI the Web of Science - CENTRAL
MeSH terms used	- Abdominal surgery - Pelvic surgery - Thromboprophylaxis	Not listed
Supplementary materials	- Abstracts from haematology oncology conferences - Clinical trial registries - Manual search of reference lists - Screening health technology assessments	- Hand searching of Conference proceedings - Review of reference lists - Related article feature in PubMed
Population	- Adult (>18 years) patients receiving thromboprophylaxis with Low Molecular. Weight Heparin after abdominal or pelvic cancer surgery	Adult patients with abdominal cancer undergoing abdominal surgery
Inclusion criteria	- Randomized clinical trial OR prospective observational cohort comparing extended thromboprophylaxis (2-6/52 postop) with conventional thromboprophylaxis (<2/52 postop) - Use of thromboprophylaxis with Low Molecular Weight Heparin - All VTE outcomes objectively diagnosed using US/CTPA/VQ scan - Included asymptomatic objectively diagnosed VTE - Study reported at least one of DVT, PE, mortality, major bleeding - Adult (>18) patients	- Randomized controlled trials assessing all-cause mortality, symptomatic DVT, Pulmonary Embolism, Major bleeding, Minor bleeding, Injection site hematoma and Heparin induced thrombocytopenia - Follow up rate equal to or greater than 80% for the outcome under consideration
Quality assessment tool	Newcastle-Ottawa scale	GRADE
Number of papers identified; included	2763 papers identified 32 full text review 7 eligible included studies (3 Randomized Controlled Trials 4 observational)	3986 papers identified 3 eligible included studies
Outcomes - Efficacy	1) All VTE: Extended Thromboprophylaxis significantly reduced incidence of all VTE compared to conventional thromboprophylaxis (2.6% v 5.6% Risk Ratio (RR) 0.44 Confidence Interval (CI)	1) Symptomatic DVT: none had analysable data 2) Asymptomatic DVT: only one study with sufficient follow up rate – statistically significant difference at four weeks postop

	0.28-0.70, Number needed to treat (NNT) 39) 2) Proximal DVT: Incidence significantly lower in Extended Thromboprophylaxis group (1.4% v 2.8% CI 0.23-0.91, NNT 71) 3) Distal DVT: results did not reach statistical significance 4) PE: No statistically significant difference between PE incidence in the two groups	3) PE: only reported in one study, insufficient follow up rate for criteria
Outcomes - safety	1) Major Bleeding: No statistically significant difference observed 2) All-Cause Mortality: Overall mortality similar 4.2% v 3.6% RR 0.79 CI 0.47-1.33 NNT 167	1) All-cause mortality: only reported in one study, with no statistically significant difference at three or twelve months. 2) Bleeding: only reported in one study – no statistically significant difference at four weeks or three months postoperatively for either major or minor bleeding
Conclusions	Extended Thromboprophylaxis significantly reduces the overall incidence of VTE and proximal DVT without increasing the risk of major bleeding.	There is limited and low-quality evidence that extended duration low molecular weight heparin for perioperative thromboprophylaxis reduces DVT in patients with cancer undergoing major abdominal or pelvic surgery. More and better-quality evidence is needed to justify extended regimens.
Acknowledged limitations of review	- Only 3 Randomized controlled trials identified - Heterogeneity from inclusion of different types of surgeries, two studies allowed inclusion laparoscopic interventions - Insufficient data on specific cancer types and stages; consequently, individualized recommendations cannot be derived from data - Open label nature of some included studies; associated bias in patient symptom reporting and physician suspicion of VTE	- Restriction of electronic search strategy to patients with cancer (potential missed studies with subgroups of cancer patients) - Limited number and low quality of included studies (included small sample size, high loss to follow up, focus on asymptomatic DVT)
Strengths of Review	- Comprehensive search - Inclusion all major prospective studies to date assessing ETP after major abdominal and pelvic cancer surgery - All VTE objectively diagnosed - Outcomes between studies reasonably similar - Low statistical heterogeneity	- Use of Cochrane collaboration methodology - Priori definition of outcomes - GRADE approach to evaluate quality of evidence

Of the 18 included articles, only four directly compared inpatient and extended duration VTE prophylaxis making them suitable for statistical analysis. These were Schomburg et al[32], Samama et al[33], Holwell et al[34] and Kakkar et al[35]. Furthermore, the only outcome consistently reported across all four of these studies was total VTE rate. Kakkar and Samama both reported DVT rate as a subgroup of VTE. Three (Kakkar, Samama and Schomburg) reported bleeding complications, however only Kakkar and Samama further reported subgroups of critical and fatal bleeding.

Regarding the primary outcome of VTE events, there was a non-significant risk reduction (risk ratio 1.55, CI 0.81-2.95) in total VTE rate. Moderate heterogeneity between the studies included in the assessment of total VTE rate was observed (I^2=59%). This is illustrated by Figure 3. No subgroups (DVT rate, PE rate) were assessed by more than two included articles.

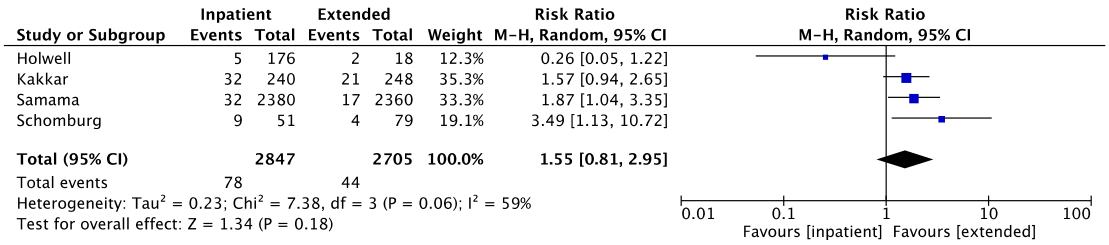

Figure 3: Forest plot illustrating direct comparison of total VTE rate

The only secondary outcome assessed across more than one of the direct comparison articles was the total rate of any bleeding complication, in Kakkar, Samama and Schomburg[32,33,35]. This result was also non-significant (P=0.43) and there was a larger degree of heterogeneity (I^2= 72%) seen between the results with only Samama[33] independently reaching statistical significance. This is illustrated in Figure 4.

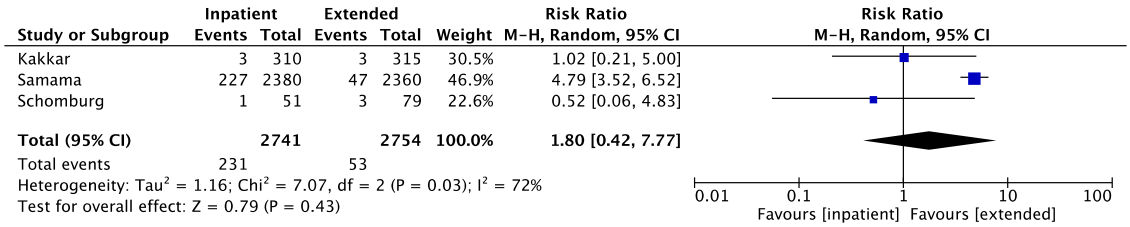

Figure 4: Forest plot illustrating direct comparison of bleeding events (any)

While additional outcomes including DVT rate, bleeding in a critical organ and fatal bleeding were covered by both the results in Kakkar and Samama, we did not feel it was appropriate to directly compare two papers only.

Of the remaining eleven included articles, eight reported outcomes relevant to the efficacy of heparin VTE prophylaxis while one reported outcomes relevant to the safety of heparin use as VTE prophylaxis in patients following open abdominal or pelvic surgery for malignancy. Two reported both efficacy and safety outcomes. None directly compared inpatient and extended duration prophylaxis.

Once again, the only efficacy outcome that was consistently reported across included studies was total VTE rate. Some studies did analyse subgroups of DVT versus PE rates and symptomatic versus asymptomatic VTE. Chandra et al[36], Sanderson et al[37], Mohn et al[38] and Varpe et al[39] all published cohort studies on the efficacy of inpatient heparin VTE prophylaxis following Colorectal procedures, with all reporting low VTE rates in these patients with a range between 0.6%[39] to 1.35%[38]. While these papers were comparable not only in their population (colorectal cancer patients) and length of follow up (one to three months), all were limited by a small sample size.

Klimowicz et al[40], Sun et al[41], Jeong et al[42], and Beyer et al[43] also all included a cohort of patients receiving inpatient heparin, with comparisons made to mechanical prophylaxis, no prophylaxis, as well as comparison to therapeutic enoxaparin in Schmitges[44] et al and warfarin anticoagulation by Sun et al[41].

Both Yang et al[45] and Sakon et al[46] reported the addition of inpatient pharmacological prophylaxis to reduce the risk of VTE compared to mechanical only prophylaxis (0.72% compared to 0.91% (Yang[45]) and 1.2% compared to 19.4% (Sakon[46])). The large difference in VTE rate reported in Sakon[46] could be attributed to its broad inclusion criteria for operative type – including any laparotomy with curative intent for a malignancy, whereas Yang included only colorectal cancer patients.
One study - Beyer et al[43] included subgroups of asymptomatic and symptomatic DVT, reporting extremely high rates of asymptomatic VTE at both day 8 (96.5%) and day 21 (88.7%) postoperatively.

Regarding safety, only Sakon et al[46], Jeong et al[42] and Schmitges et al[44] reported safety outcomes associated with postoperative heparin VTE prophylaxis. Sakon et al[46] and Jiong et al[42] compared inpatient heparin with mechanical only or no prophylaxis, while Schmitges et al[44], compared four weeks of therapeutic dose heparin (60+mg enoxaparin) with four weeks of prophylactic dose heparin (40mg enoxaparin subcutaneously daily).

Unsurprisingly Sakon[46] and Jiong[42] both report total bleeding events to be greater in patients receiving pharmacological prophylaxis (total bleeding complication rates of 9.17% and 13.4% in patients receiving heparin compared to 7.89% and 5.5% in those receiving mechanical and no prophylaxis). Sakon[46] also reported major bleeding events (defined as death, transfusion of more than two units of red cells, haemoglobin drop of more than 2g/dL, or retroperitoneal, intracranial or intraocular bleeding resulting in serious or life-threatening events) occur at a rate of 4.6% compared to 2.6% in those patients receiving mechanical prophylaxis with inpatient pneumatic compression alone.
Likewise, reported transfusion rates were lower when mechanical prophylaxis alone was used compared to those patients receiving additional pharmacological prophylaxis[42,43].

In summary, analysis of the included studies did <u>not</u> identify any statistically significant reduction in postoperative VTE risk associated with extended duration use of heparin VTE prophylaxis compared to inpatient only duration prophylaxis. Nor was any statistically significant difference in rates of bleeding complications identified between the two groups. However, multiple smaller cohort studies not suitable for inclusion in statistical analysis report lower rates of postoperative VTE in patients receiving extended duration pharmacological prophylaxis, albeit with an increased risk of bleeding complications and transfusion requirement.

<u>DISCUSSION:</u>
Overall, literature review of recently published papers (<10 years old) exposes a surprisingly low level of poor-quality evidence for extended pharmacological VTE prophylaxis.

Two pre-existing systematic reviews were identified, however only one study[47] is included in both.

These are interesting to compare to the outcome of our study in that their outcomes are almost directly contradictory – while Fagaranasu et al[30] concludes that "extended thromboembolism prophylaxis significantly reduces the overall incidence of VTE and proximal DVT without increasing the risk of major bleeding", Akl et al[31] is more consistent with our own results reporting "limited and low quality evidence that extended duration LMWH for perioperative thromboprophylaxis reduces DVT in patients with cancer undergoing major abdominal or pelvic surgery" concluding that "more and better quality evidence is needed to justify extended regimes". Criticisms of the Fagaranasu review which may explain its conflicting outcome include the comparison of laparoscopic and open studies (i.e. dissimilar populations) and invitation of bias by including observational studies as well as randomised controlled trials.

It is also interesting to note the number of narrative reviews that we excluded on full text review. It is possible this volume of narrative reviews reflects other prior attempts to perform systematic review and meta-analysis in this area, where the poor level of evidence available precluded systematic review from being conducted.

A limited number of papers were appropriate for direct comparison, and these results must be interpreted with caution due to the small number of studies included, small sample sizes in some studies, and significant degree of heterogeneity observed between included studies. In addition, the population of the Samama et al[33] study was much larger than that of the other included studies and so the combined results need to be interpreted with an awareness of the impact of this on the overall outcome.
Allowing for this, our analysis found no significant difference in postoperative VTE rates or postoperative bleeding complication in patients receiving extended duration prophylaxis compared to those receiving inpatient duration prophylaxis.

However, on narrative review of the remaining literature unsuitable for direct comparison, many studies did observe cohorts receiving extended duration pharmacological prophylaxis to have lower rates of postoperative VTE, and an increased rate of bleeding complications and number of blood transfusions.

Across all included studies, total rates of VTE events that were sufficiently symptomatic as to trigger investigation and objective confirmation of diagnosis by imaging were generally low. This may imply that clinically significant postoperative VTE is a rarer complication than many clinicians believe. Assuming this were true, extrapolation would suggest that while pharmacological prophylaxis with heparin may convey a benefit, this benefit is likely small and thus the number needed to treat (NNT) would be high, therefore leading to a high cost of prophylaxis at a population level despite the individual cost being low. Thus, Kakkar had only 2 patients in the extended group and 3 in the inpatient group that developed a PE[35]. Samama had 5 in the extended group and 10 in the inpatient group[33]. Combining the 2 extended populations one could conclude that extending VTE prophylaxis results in 6 fewer PE's for a total 2620 patients who received extended prophylaxis. Given the small number of studies and small sample sizes of the articles included in our direct comparison, it is possible that a benefit does exist, and the comparison was simply underpowered to confirm this. If this is true it is possible that the benefits of pharmacological VTE prophylaxis in reducing postoperative VTE may in fact be outweighed by the financial cost of treatment and or potential complications associated with its use. A cost benefit analysis was beyond the scope of the present study.

In contrast, when asymptomatic VTE was considered, this appears to have an extremely high prevalence postoperatively, with some studies reporting up to 96.5% on day 8 and 88.7% day 21 postoperatively[43]. If this is assumed to be true, with a prevalence this high it would appear unlikely it carries any truly significant implication on overall patient outcome, and raises the question if it is

possible asymptomatic DVT falls within the spectrum of normal physiology following a traumatic insult to the body such as major surgical intervention in the abdomen or pelvis.

This outcome, while unexpected does raise important questions. Firstly, use of pharmacological VTE prophylaxis is established practice worldwide, and while there is a lack of consistency between type and duration of prophylaxis used by individual providers and centres, extended duration is becoming extremely common. In failing to identify any significant reduction in VTE risk associated with extended duration prophylaxis, we must wonder how this became an established and widely accepted part of clinical practice without a truly strong evidence base.

While there is certainly evidence for its use in other specialties[47], it is uncertain to what extent it is appropriate to apply evidence from other specialties such as orthopaedics to patients undergoing pelvic surgery. While patient characteristics are likely to have commonalities across both specialties, vastly different operative characteristics and the presence or absence of malignancy in the patient result in a significant difference between the populations.

Limitations of our study included the small number of identified studies suitable for analysis and the small sample sizes of included articles. This could be improved by extending the time period used in the study's inclusion criteria to include articles older than ten years. In addition, due to the limited number of suitable articles identified, some included papers do include some data not exclusively from patients undergoing open surgery.

CONCLUSION: In conclusion, our study found no significant difference in postoperative VTE rates or bleeding complications in patients receiving extended duration heparin VTE prophylaxis compared to those receiving inpatient prophylaxis after open abdominopelvic surgery for malignancy. However, the available evidence was limited and of poor quality so this finding must be interpreted with caution.

This result raises the important question of how the use of extended duration prophylaxis in this population has become widespread, common practice without a truly strong evidence base proving a benefit. If this is truly the case, we question whether current recommendations regarding its use should be re-evaluated.

MAIN BODY CHAPTER 4: PUBLICATION 3 – COST ANALYSIS MANUSCRIPT

Statement of Authorship

Title of Paper	Extended Enoxsparin Thromboprophylaxis following Major Open Abdominopelvic surgery for malignancy – a cost analysis.
Publication Status	Written in Manuscript Style / Submitted for publication
Publication Details	

Principal Author

Name of Principal Author (Candidate)	Bridget Caroline Heijkoop		
Contribution to the Paper	Bridget Heijkoop developed the protocol, conducted the pre-existing literature review and performed the cost analysis based on prior results.		
Overall percentage (%)	90		
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	31/05/2020

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.

Name of Co-Author	Mr Dan Spernat		
Contribution to the Paper	Mr Dan Spernat acted as a co-supervisor of the project.		
Signature		Date	12/5/20

Name of Co-Author	Associate Professor George Kiroff
Contribution to the Paper	A/Prof George Kiroff acted as the primary supervisor of the project and was extensively involved in reviewing the manuscript and approving the final manuscript for submission.

Signature		Date	20/8/2020

TITLE:
Extended Enoxaparin Thromboprophylaxis following Major Open Abdominopelvic surgery for malignancy – A Cost Analysis.

RUNNING HEAD: Thromboprophylaxis – A cost analysis.

AUTHORS:
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ABSTRACT:

INTRODUCTION AND OBJECTIVES:
Extended Venous Thromboembolism (VTE) Prophylaxis is recommended as best practice following major open abdominopelvic surgery for malignancy. However, the financial implications of post-operative enoxaparin use in this setting have escaped scrutiny. We aim to compare the cost of providing this prophylaxis with that of predicted VTE events without prophylaxis.

MATERIALS/METHODS:
We previously published a literature review and meta-analysis comparing inpatient versus extended duration enoxaparin VTE prophylaxis in patients undergoing open abdominopelvic surgery for malignancy. In this paper we compare these results to literature estimates of the incidence of VTE, and the current cost of Enoxaparin on the Pharmaceutical benefits scheme.

RESULTS:
The risk of VTE after major surgery is estimated as between 0.8-6.2%, and cost of a standard 40 mg prophylactic dose of enoxaparin is $4.951. Therefore, the cost of preventing one Venous Thromboembolism can be estimated as being between $1116-$8522 using two weeks of prophylaxis, or between $17045-$23437 if four weeks of prophylaxis are used. The observed rate of VTE in the literature population was 1.63% despite this population having received extended prophylaxis.

CONCLUSIONS:
Our analysis suggests that providing extended duration postoperative VTE prophylaxis to patients following open abdominopelvic procedures for malignancy is financially justifiable, with a lower total cost than that of treating predicted VTE events in this population without prophylaxis. However, considering prior findings of no significant benefit in VTE reduction in patients of receiving extended duration over inpatient only prophylaxis, inpatient only duration prophylaxis may still be a more efficient use of resources.

KEY WORDS
Venous Thromboembolism
Prophylaxis
Surgery
Malignancy
Cost

MAIN TEXT:

INTRODUCTION AND OBJECTIVES:

Extended Venous Thromboembolism (VTE) prophylaxis following major open abdominopelvic surgery for malignancy is recommended as best practice[1,2]. However currently available guidelines do not quantify an exact recommended duration of prophylaxis, nor have the financial implications of post-operative prophylactic enoxaparin use been scrutinised in depth. We aim to compare the cost of providing this prophylaxis with that of VTE events without prophylaxis.

METHODS:

We previously designed and conducted a literature review and meta-analysis comparing inpatient versus extended duration VTE prophylaxis in patients undergoing major open abdominopelvic surgery for malignancy[49]. The results of this review were then compared with literature estimates of the incidence of VTE events in the absence of pharmacological prophylaxis and current cost of Enoxaparin on the Pharmaceutical Benefits Scheme (PBS)[50] in Australia. Using this data we calculated the cost of providing both two and four week duration extended duration prophylaxis to the overall population described within the literature, as well as the predicted/estimated cost of the VTE events observed in these populations.

Assumptions made in making these calculations include that all patients were compliant with treatment and received a standard prophylactic dose of enoxaparin, and did not receive any additional pharmacological thromboprophylactic agents or were otherwise anticoagulated.

Ethical approval was not required given no patients were directly involved in the study, with results based off literature review.

RESULTS:

The previous literature review identified a total of four articles directly comparing inpatient and extended duration VTE prophylaxis suitable for statistical analysis. Within these four articles a total population of 2705 patients received extended duration prophylaxis, with 44 VTE events observed in these 2705 patients despite them receiving prophylaxis. In the safety arms of the included studies, of 2754 patients being evaluated for bleeding complications associated with extended duration prophylaxis, 53 had a bleeding event potentially attributable to use of prophylaxis[49].

A standard prophylactic dose of enoxaparin prior to any adjustments for renal function or extremes of weight is 40mg injected subcutaneously once per day. The Pharmaceutical Benefits Scheme lists the dispensed price for maximum quantity of 40 mg enoxaparin as $99.02 for 20 syringes of 40 mg/0.4 ml enoxaparin sodium, so the cost of each 40 mg dose of enoxaparin is $4.951 ($99.02/20)[50]. Therefore providing 2 weeks of extended Venous Thromboembolism prophylaxis costs the healthcare system $69.314 ($4.951 x 14) per patient and 4 weeks of extended Venous Thromboembolism prophylaxis costs $138.628 ($4.951 x 28) per patient.

The risk of a Venous Thromboembolism event following major surgery is variably estimated between 0.8– 6.2%[51] which is equivalent to between 22 and 168 people in the overall literature population of 2705. With providing prophylaxis to the population of 2705 patients costing a total of $187 494.37 for two weeks or $374988.74 for four weeks, the cost of preventing one venous thromboembolism can be

estimated as between $8522 (187494.37/22) and $1116($187494.37/168) using two weeks prophylaxis or between $17044.9421 (374988.74/22) and $23436.7962 (374988.74/168) with four weeks prophylaxis. The calculations of this are summarised mathematically below

Predicted risk of VTE in study population (2705) = 22 to 168 people:
2705 x 0.8% = 21.64 (22)
2705 x 6.2% =167.71 (168)

Total cost of prophylaxis
a) 2 weeks: $69.314 x 2705 = $187 494.37
b) 4 weeks: $138.628 x 2705 = $374988.74

Therefore, to prevent one VTE:
a) With two weeks prophylaxis
$187494.37 ÷ 22 = $8522 AND $187494.37 ÷ 168 = $1116
b) With four weeks prophylaxis
$374988.72 ÷ 22 = $17044 AND $374988.72 ÷ 168 =$2232

Therefore, with the cost of a single VTE event estimated at $4090 USD[51] giving an adjusted cost accounting for inflation of $5987.14 USD in 2020, equivalent to $8222.97 AUD using 6/9/2020 exchange rates, the VTE rate would need to be at least 0.83% (8522/8222.97=1.03 and 1.03x0.8=0.83) to be equal or greater to the cost of providing extended prophylaxis for 2 weeks, or 1.66% (17044/8222.97=2.07and 2.07x0.8=1.66) to be equal or greater to the cost of providing extended prophylaxis for 4 weeks. These calculations are summarised mathematically below

a) Two weeks:
$8522 ÷ 8222.97 = 1.03
1.03 x 0.8 = 0.83

b) Four weeks:
$17044 ÷ 8222.97 = 2.07
2.07 x 0.8 = 1.66

The observed rate of VTE in the literature population was 44/2705 (1.63%)[49], with an estimated cost to healthcare services of $266 016.52, despite this population having received extended prophylaxis.

DISCUSSION:

In a healthcare environment with ultimately limited resources, there is ever increasing awareness of the need to consider the financial and economic impact of treatments at a population level in addition to their clinical indication for the individual. Ensuring the benefit of a treatment is not outweighed by the cost of providing it helps to ensure efficient use of resources to maximise the population benefit.

The initial introduction of VTE prophylaxis to select patient populations showed a clear benefit to these individuals resulting in rapid widespread uptake of its use and extrapolation to include other patient populations. Duration of use was later extended in recognition of the potential for VTE to be a delayed postoperative complication. However, guidelines remain nonspecific about the exact timeframe this risk and recommendation for prophylaxis persists, resulting in significant variability between individual providers and institutions. This is likely in part due to limited recent evidence specifically regarding extended duration prophylaxis use in specific and contemporary patient populations. In addition, many aspects of surgical technique and hospital admissions have changed since the initial research demonstrating efficacy of Enoxaparin prophylaxis.

Our finding that a VTE rate of 0.83% or 1.66% is required to achieve cost neutrality respectively for two and four weeks of prophylaxis supports the financial justifiability of extended VTE prophylaxis using either two or four weeks of enoxaparin, falling in the lower end of the range of predicted VTE rates without prophylaxis. In addition, the observed VTE rate of 1.63% within the literature population, despite this population's use of extended prophylaxis, falls not only within the predicted VTE rate without prophylaxis, but is greater than the VTE rate required for cost efficiency of two weeks prophylaxis and almost equal to that required for cost efficiency with four weeks prophylaxis. This not only further supports the financial justifiability of providing two weeks prophylaxis, but as this was observed in a population already receiving extended duration VTE prophylaxis, leads us to suspect the true VTE rate without prophylaxis to fall on the higher end of prior literature estimates, further increases the likelihood of four weeks duration prophylaxis also being financially justifiable.

However, our prior literature review did not identify any significant efficacy benefit in preventing VTE events to be associated with extended duration prophylaxis when compared with inpatient only duration prophylaxis in contemporary literature. Interpreting our findings on cost analysis in this context is challenging as while it appears provision of extended prophylaxis is justifiable with a lesser cost than that of managing predicted VTE events in this population without prophylaxis, if the overall reduction in VTE events by use of extended prophylaxis is insignificant compared to that with inpatient only prophylaxis, inpatient only duration would appear to be economically superior by incurring significantly less costs to provide an essentially equivalent benefit.

In applying these findings to a clinical context non-financial costs must also be considered. It is difficult to imagine healthcare providers being willing to place individual patients they manage at risk of a potentially catastrophic VTE event on the basis of providing a relatively intangible financial benefit to the greater population. Financial costs may also be perceived by individuals to be of insignificant importance when compared to the impact of decline in health and function on overall quality of life. Consequently, even with some evidence that inpatient duration prophylaxis provides a similar benefit in VTE reduction compared to extended duration for far lesser costs, while there remains no definite evidence of extended duration prophylaxis being directly harmful to the individual, it is likely providers will continue to provide extended duration prophylaxis to the individual patients in their care.

Limitations of this study include bias from using a patient population obtained via literature review, resulting in the inclusion of any pre-existing biases in the included papers. In particular the literature review identified only a small number of studies suitable for analysis, all but one of which had small

sample sizes, meaning the one paper with a larger sample size may have disproportionately skewed the results. This is difficult to eliminate without performing our own study and data collection on a novel population of patients which is outside the scope of this study. In addition, this analysis did not include analysis costs incurred from treatment of bleeding complications associated with use of VTE prophylaxis. However, our prior literature review again did not identify any significant difference in rate of bleeding complications between patients receiving inpatient duration prophylaxis compared to those receiving extended duration prophylaxis, making it unlikely this would result in a significant change to the outcome of cost analysis.

In future, it would be ideal to develop a multi-institutional, prospective database of patients receiving postoperative VTE prophylaxis documenting the duration of treatment, VTE and bleeding events and comprehensive details of treatments provided for these to enable further direct large-scale comparison of these events and their financial implications in the context of prophylaxis. This would however be resource intensive and time consuming making it again outside the scope of this study.

CONCLUSION:

In conclusion, our analysis suggests that providing extended duration postoperative VTE prophylaxis to patients following open abdominopelvic procedures for malignancy is financially justifiable, with a lower total cost than that of treating predicted VTE events in this population without prophylaxis. However, considering prior findings of no significant benefit in VTE reduction in patients of receiving extended duration over inpatient only prophylaxis, inpatient only duration prophylaxis may still be a more efficient use of resources.

MAIN TEXT CHAPTER 5: CONCLUSION

In conclusion, the project had three major findings.

Firstly, and perhaps the most significant finding, was the unexpected discovery that despite the fact that extended VTE prophylaxis with heparin is already an accepted and widely used treatment, there is only a small volume of contemporary literature (published within the last ten years) available directly investigating the impact of duration of VTE prophylaxis in patients undergoing abdominopelvic surgery for malignancy. In addition, what literature was available was of poor quality, limiting the confidence with which conclusions can be drawn from it and applied to clinical use.
If these limitations are accepted, the second major finding of the study was that we found no significant difference in either efficacy or safety of inpatient versus extended duration use of pharmacological VTE prophylaxis with heparins following major open abdominopelvic surgery for malignancy.
The third major finding was that when assessed on a purely financial basis we found provision of extended duration VTE prophylaxis using heparin to be likely justifiable, with a lesser cost than that of treating predicted VTE events in the absence of prophylaxis. This finding applied to both two week and four-week durations of use of extended prophylaxis.

Detailed discussion of these findings is included in each relevant publication and in accordance with The University of Adelaide theses specification guidelines these discussions will not be reworked here.

Problems encountered over the course of the project were primarily related to the unexpectedly small volume and poor quality of contemporary literature identified on systematic review. This meant it was not possible to answer all of the questions described in the protocol, and precluded subgroup analysis as was initially planned. While the initial decision to limit included papers to those published within the last ten years was made with the intent to ensure the literature populations were likely to closely resemble contemporary patient populations, it is likely that this decision significantly contributed to this problem by excluding larger and better-quality earlier studies. In addition, had a larger time period of publications been assessed, the inclusion of earlier publications may have benefited our study by potentially capturing a larger population of patients specifically undergoing open surgery given the use of laparoscopic, robotic and other minimally invasive techniques has increased over time, thus reducing the proportion of open cases being performed.

Immediate future directions for the project include publication of the final cost analysis paper pending the outcome of peer review. Further possible future directions could include addressing the problems described above by repeating the project with expansion of inclusion criteria to include earlier publications. An alternative, ideal solution to address this and definitively answer the question of optimum prophylaxis duration would be to develop a randomised controlled trial of inpatient versus varying extended duration VTE prophylaxis in a population of patients undergoing major open abdominopelvic surgery for malignancy. This would however likely be complex and extremely time consuming, requiring ethical approval, involvement of a large number of hospitals and clinicians in order to generate sufficient patient numbers to reach statistical significance, and potentially use of placebo extended prophylaxis (for example subcutaneous injection of sterile normal saline to mimic enoxaparin) in some patients to enable blinding. A more practical alternative could be the development of a national prospective database registry of patients undergoing VTE prophylaxis collecting data on operative procedure, type and duration of prophylaxis and incidence of VTE and bleeding events. This would again require ethical approval, cooperation of a large number of hospitals and clinicians, however could in future enable analysis of a large, population level cohort study and or analysis of subgroups within this population.

Overall, the major contributions of the project's findings to current knowledge are the discovery that the recent evidence for use of extended VTE prophylaxis in patients undergoing open abdominopelvic surgery for malignancy may not be as strong as it is perceived to be, and what recent evidence exists

does not demonstrate a significant difference in efficacy or safety of extended duration prophylaxis as compared to inpatient only duration. These findings should encourage both clinicians and researchers to not only to critically evaluate and re-examine their own practices and rationale in providing postoperative VTE prophylaxis, but also to continually critically reappraise all treatments and procedures, as simply being established practice or widely used does not necessarily guarantee there is a strong evidence base behind the use of a treatment.

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