

**IS an INTERMEDIATE DOSE of LMWH EFFECTIVE for
SECONDARY PREVENTION of RECURRENT VENOUS
THROMBOEMBOLISM in PREGNANT PATIENTS DIAGNOSED with
DEEP VEIN THROMBOSIS or PULMONARY EMBOLISM?
DESIGN of a PILOT STUDY**

Esteban Gándara

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment
of the requirements for the MSc in Epidemiology

Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa

© Esteban Gándara, Ottawa, Canada, 2012

30/09/2012

Abstract

Statement of the problem

The primary objective of this thesis was to determine the best study design to evaluate the safety and effectiveness of an intermediate dose of low molecular weight heparin for secondary prevention of pregnancy associated VTE (PAVTE). An RCT was deemed unfeasible, so the use of a single arm study with prior evaluation of feasibility with a pilot study is proposed.

Methods

A systematic review was conducted to evaluate the efficacy of current strategies used for secondary prevention of PAVTE. A survey was used to elicit the non-inferiority margin.

Results

The pooled proportion of recurrent VTE in patients treated with full dose LMWH was 0.012(95% CI 0.006 to 0.02) and the rate of major bleeding was 0.025(95% CI=0.01 to 0.041). The non-inferiority margin was elicited at 2.5%

Conclusions

Although an RCT should be conducted whenever possible, in certain scenarios they are unfeasible. Therefore, an alternative study design should perhaps be used to evaluate the safety and efficacy of therapeutic strategies.

“In seeking absolute truth we aim at the unattainable
and must be content with broken portions”
Sir William Osler (1849-1919)

Acknowledgments

I am extremely grateful to Dr. Marc Rodger, my primary thesis supervisor, for his mentorship and guidance, but most importantly for providing me the opportunity to grow as a researcher and excel not only a scientist but as a physician. He has been, and still is, an outstanding role model.

I am also indebted to Dr. Marc Carrier for his support as thesis co-supervisor, guidance and friendship over the last three years.

To the University of Ottawa and the Department of Medicine for their financial support during my fellowship.

Drs. C. Wiersba, D. Grassi, T. Insua, M. O'Flaherty, D. Bates, A. Kachalia and P. Wells for their guidance during my career.

To my family, and specially my father, for supporting me throughout all my studies at University and love, regardless of the distance.

Finally, very special thanks to Samantha LaRue for her love, support, patience during my working hours and for being the mother of my son Miles.

Contents

Abstract.....	ii
Statement of the problem.....	ii
Methods.....	ii
Results.....	ii
Conclusions.....	ii
Acknowledgments.....	iv
Contents.....	v
TABLES.....	viii
Figures.....	ix
1.0 Introduction.....	1
1.1 Scope of the Problem.....	1
1.2 Pathogenesis and risk factors of PAVTE.....	3
1.3 Clinical Features and diagnosis of PAVTE.....	5
1.4 Current approach to the treatment of PAVTE.....	7
1.5 Dosing and monitoring during treatment with LMWH.....	12
1.6 Rationale for the use of an intermediate dose for secondary prevention after the acute treatment period of pregnancy associated VTE.....	13
1.7 Guidelines and expert recommendations for PAVTE.....	16
1.9 Summary.....	20
2.0 Selection of the study design.....	22
2.1 Superiority, non-inferiority or placebo controlled?.....	22
2.2 Non-inferiority randomized controlled study.....	24
2.2.1 Non-inferiority study: Selection of the comparator.....	26
2.2.2 Non-inferiority study: Estimation of the non-inferiority margin and sample size calculations.....	28
2.3 Is a randomized controlled non-inferiority study feasible?.....	31
2.4 Alternative study design.....	35
2.4.1 Single arm study methodology.....	39
2.4.2 Limitations for the use of single arm studies.....	43
3.0 OVERALL AIMS OF THE THESIS.....	48
4.0 Systematic review.....	50
4.1 Rationale for the systematic review.....	50
4.2 PICOS Question.....	50
4.3 Methods.....	51
4.3.1 Literature Search.....	51
4.3.1.1 Literature search strategy.....	52
4.3.2 Study Selection.....	53
4.3.3 Outcome Measures.....	53
4.3.4 Data Extraction and Quality Assessment.....	55
4.3.5 Data Synthesis and Analysis.....	56
4.4 Results.....	57
4.4.1 Quality.....	61
4.4.2 Treatment strategies.....	61
Recurrent VTE during the acute treatment period (<30 days) with LMWH or UFH...64	
Full dose LMWH or UFH for secondary prevention.....	64

Prophylactic doses of LMWH or UFH for secondary prevention	66
Intermediate dose of LMWH or UFH for secondary prevention.....	67
4.4.3Osteoporosis and heparin induced thrombocytopenia in patients treated with LMWH or UFH.	69
4.4.3Fetal outcomes in patients treated with LMWH or UFH.....	69
4.4.4 Publication bias.....	70
4.5 Analysis of the results.....	70
4.6 Limitations.....	73
4.7 Conclusions.....	76
5.0 Survey.....	77
5.1 Rationale for the survey.....	77
5.2. Aims of the Survey.....	78
5.3. Methods.....	78
5.3.1 Design.....	78
5.3.2Survey Instrument.....	79
5.3.4 Survey delivery.....	82
5.3.5 Analysis.....	82
5.4 Results.....	83
5.4.1Elicitation of $-\Delta$	83
5.4.2 Current clinical practices.....	87
5.4.3 Clinical equipoise and potential participation in a future study.....	88
5.5 Analysis of the results.....	88
5.6 Limitations.....	91
5.7 Conclusions.....	94
6.0 Should a single arm study evaluating an intermediate dose of LMWH (given once a day without monitoring) for the secondary prevention of PAVTE be conducted?.....	95
7.0 Design of an single arm study for the evaluation of an intermediate dose of LMWH for secondary prevention of pregnancy associated VTE.....	96
8.0 Pilot study.....	100
8.1 Study design.....	100
8.3 Study population.....	101
8.3.1 Inclusion Criteria.....	102
8.3.2 Exclusion criteria.....	103
8.4 Study Intervention.....	104
8.5 Primary and secondary outcome measures.....	107
8.5.1 Recruitment rate and study feasibility.....	108
8.5.2 Efficacy and safety outcomes.....	108
1-Recurrent DVT.....	109
2-Recurrent PE.....	109
3-PE related mortality and all-cause mortality.....	110
4-Major bleeding.....	110
5-Obstetrical ante-partum Bleeding.....	111
6-Severe Post-partum Bleeding.....	111
7-Minor bleeding.....	111
8-Heparin Induced Thrombocytopenia.....	112
9-Osteoporotic Fractures.....	112
10-Miscarriage or stillbirth.....	112

11-Fetal malformation	113
8.6 Data collection and outcome surveillance	113
8.7 Management of Bias	115
8.8 Data analysis	116
8.9 Feasibility	117
8.9.1 Recruitment rate	117
8.9.2 Recruitment strategies	118
8.11 Safety	119
8.11 Anticipated results and conclusions	120
8.12 Study management	121
9.0 Conclusions	123
10.0 References	127
Appendix 3 Publication bias analysis	150
Appendix 2 Survey instrument	164

TABLES

Table 1 Common risk factors for the development of VTE	4
Table 2 Studies included by Greer et al (case reports are excluded)	20
Table 3 Studies supporting the efficacy of anticoagulation for the treatment of VTE	26
Table 4 Sample size calculations for a non-inferiority study	31
Table 5 Methodology of single arm studies conducted in the field of thrombosis.....	42
Table 6 Characteristics of the studies included	59
Table 7 Quality assessment by the Newcastle-Ottawa scale	60
Table 8 Treatment strategies.....	62
Table 9 Outcomes of patients treated with LMWH.....	63
Table 10 Outcomes of patients treated with UFH	63
Table 11 Summary of results	72
Table 12 Elicitation of $-\Delta$ by type of answer and scenario.....	86
Table 13. Estimation of the margin analyzed by respondent characteristics.....	86

Figures

Figure 1 Flow diagram.....	58
Figure 2 Recurrent VTE in patients treated with full doses of LMWH	64
Figure 3 Major bleeding patients treated with full doses of LMWH.....	65
Figure 4 Recurrent VTE in patients treated with prophylactic doses of LMWH.....	67
Figure 5 Recurrent VTE in patients treated with intermediate doses of LMWH.....	68
Figure 6 Major bleeding in patients treated with intermediate doses of LMWH.....	69
Figure 7 Absolute accepted increase in the rate of recurrent VTE if an intermediate dose of LMWH was associated with multiple dosing benefits and a clinically relevant reduction in bleeding.....	84
Figure 8 Absolute accepted increase in the rate of recurrent VTE if an intermediate dose of LMWH was associated with multiple dosing benefits and but does not reduce bleeding.....	85
Figure 9 Strategies used for secondary prevention in patients treated for DVT.....	87

1.0 Introduction

1.1 Scope of the Problem

Venous thromboembolism (VTE), manifesting as deep vein thrombosis (DVT) and/or pulmonary embolism (PE), is one of the most common cardiovascular diseases in industrialized countries, affecting 5% of the general population during their lifetime(1).

VTE is a serious and potentially fatal medical condition. Annually, as many as 300,000(2) people in the United States die from PE and the diagnosis is often not made until autopsy. That said, VTE is also, preventable and treatable(3). The risk of PE (either symptomatic or asymptomatic) in patients diagnosed with DVT is approximately fifty percent. If left untreated the mortality rate of PE ranges from 5% to 30%(4). Furthermore, VTE is associated with long-term consequences such as post-thrombotic syndrome (PTS) and recurrent VTE(5). Early treatment of VTE with anticoagulant drugs is a critical step in preventing further complications and/or recurrence(6).

For women the risk of VTE increases approximately 4 to 10 fold during pregnancy and 15 to 35 fold during the post-partum period(7;8). These estimates are supported by two recent population studies conducted in the United Kingdom (UK) (9) and the United States (US) (7). In the UK study, the rate of VTE was 19 (95% CI 18to20) per 100 000 person/years in non-pregnant women whereas the overall rate of pregnancy associated VTE (from here on referred to as PAVTE)was 107(95% CI 18to20) per 100 000 person/years [34 (95% CI 26to45) and 225 (95% CI 188to271) per 100000person/years during the ante-partum and post-partum periods respectively]. In the US study the rate of VTE in non-pregnant women was 46(95% CI 18to20) per 100 000 person years and 200 (95% CI 18to20)per 100 000 person/years during pregnancy [95(95% CI 18to20) and 511(95% CI 18to20) cases per 100000 during the ante-partum and post-partum periods respectively]. Liu et al(10) evaluated the incidence of PAVTE in Canada using administrative data collected from pregnant women admitted for VTE

between the years 1991 and 2006. The total incidence of DVT was 121 (95% CI 18to20) per 100,000 pregnancies, and the rate for PE was 54(95% CI 18to20) per 100,000 pregnancies. However these results should be interpreted carefully because only hospitalized patients were included in the study.

Therefore the actual rates of VTE could be significantly higher than what the authors calculated given that in Canada, persons with VTE are commonly treated as outpatients.

The risk of VTE during pregnancy is felt to remain relatively constant throughout each trimester and then doubles during the post-partum period(11). Ray et al(12) conducted a systematic review to evaluate the incidence of DVT during the different trimesters of pregnancy and the post-partum period(i.e. 6 weeks post-partum). They found that 21.9 % (95% CI 17.4to27.3) developed DVT in the first trimester, 33.7 % (95% CI 28.1to39.8) in the second trimester, and 47.6 % (95% CI 39.2to56.2) in the third trimester. Two recent population studies have challenged the findings of Ray et al(12). Sultan et al(9) reported the rate of VTE to be higher during the third trimester [78 (95% CI 57to105) per 100 000 person/years) and early post-partum period [421(95% CI 345to505)per 100 000 person/years], compared to the first trimester [7 (95% CI 2to21) per 100 000 person/years], the second trimester [11 (95% CI 4.4to25) per 100 000 person/years] or the late post-partum [35 (95% CI 18to67) per 100 000 person/years). Virkus et al(13) reported that the absolute risk of VTE increased from 41 (95% CI 3.2to5.2)per 100,000 pregnancy/years during weeks 1–11 up to 590(95% CI 46.1to76.4) per 100,000 pregnancy/years by the end of week 40. During the post-partum weeks 1-9 the rate of VTE was 600 (95% CI 47.2to76.4) per 100,000 pregnancy/years during and the decreased to 21(95% CI 1.1to4.2) per 100,000 pregnancy/years during the post-partum weeks 9–12.

As discussed above, PAVTE is a rare complication of normal pregnancy carrying potentially severe maternal adverse consequences. In developing countries, hemorrhage is the primary cause of maternal death(14) but in North America and Europe, the primary cause of maternal death is PAVTE(15-17).

PAVTE is thought to account for 1 to 1.5 maternal deaths per 100000 deliveries in the US and

Europe(7;15-17) representing 30% of all maternal deaths in the UK(16), 20% of all maternal in the US(7), and 50% of all maternal in Sweden(18). In Canada(10), it is estimated that 0.26 deaths occur per 100,000 pregnancies in patients diagnosed with pregnancy associated DVT that require admission, and 0.96 deaths per 100,000 pregnancies in patients diagnosed with PE. Contributing factors for death include: 1- cesarean section/surgery without thromboprophylaxis; 2- being overweight; 3- severe co-morbidities; 4-delays in seeking health-care; and 5-verbal miscommunication(18).

Population based suggests PAVTE associated mortality is decreasing(7). For example, in Sweden, there has been a fourfold increase in the rate of pregnancy associated PE from the 1970s to the end of 1990s, yet the case fatality rate has decreased from 4.5 to 0.6%(18) during the same time period. One explanation for the declining case fatality rate is over diagnosis leading to treatment of less severe VTE cases(19). Another explanation is the widespread use of more effective therapies (20) for treating PAVTE (21) such as LMWH.

1.2 Pathogenesis and risk factors of PAVTE

Venous thromboembolism arises from the interaction between multiple inherited and acquired known risk factors(22) . The risk of VTE increases with the number of risk factors present(23). In 1856, Virchow identified the physio-pathologic triad responsible for venous thrombosis(24): hypercoagulation, vascular damage, and venous stasis. Risk factors increase the risk of VTE by directly affecting one or more of the components of the Virchow triad. Table 1 shows the association of common risk factors(25) and the individual components of the Virchow triad.

VTE are usually divided in two categories: provoked or unprovoked. Provoked VTE is usually associated with transient risk factors such as: pregnancy, surgery, trauma, cancer or immobilization. Un-provoked VTE is usually associated with non-reversible risk factors such as: age, gender or thrombophilias. Correctly identifying the provoking factor leading to the development of VTE is fundamental for making therapeutic decisions regarding duration of treatment.

Compared to some other risk factors, such as surgery, where not all the components from Virchow’s triad play a role for the development of VTE(22;25) during pregnancy and the post-partum period all the components of the Virchow triad contribute to the increased risk for PAVTE(25) (Table 1).

Table 1 Common risk factors for the development of VTE

Risk Factor	Affected components of Virchow’s triad			Increased risk of VTE
	Hypercoagulation	Vascular damage	Venous stasis	
Increasing age	X			1000 fold
Surgery	X		X	6 fold
Cancer	X			5 fold
Trauma	X	X	X	5fold
Immobilization			X	8 fold
Thrombophilia#	X			2 to 10 fold
Hormone use	X			2 to 5 fold
Pregnancy	X	X	X	10 fold

#(antithrombin III deficiency, Protein C and Protein S deficiency, Factor V Leiden, Prothrombin 20210A)

Hypercoagulation is a normal physiological response to pregnancy caused by disequilibrium of blood coagulation factors(26;27). Fibrin generation is increased, fibrinolytic activity is decreased(28), levels of coagulation factors II, VII, VIII, and X are all increased, free protein S levels are decreased (28), and acquired resistance to activated protein C is common. Furthermore, during pregnancy there is an increase in markers of coagulation activation including prothrombin fragment F1+2 and D-dimer(29). Although changes in the coagulation system help reduce the risk of hemorrhage during childbirth and miscarriage, they may also increase the risk of VTE. After delivery, coagulation factors gradually return to their non-pregnant state, as evidenced by progressive normalization of markers of coagulation activation within six weeks of delivery(30;31).

Vascular damage of the iliac veins is usually caused by the mechanics of normal child delivery(32) or surgical delivery.

Venous stasis is also common during pregnancy. One of the proposed mechanisms for pregnancy associated venous stasis is hormone induced increase in venous capacitance leading to decreased

venous outflow(32). A reduction in venous flow velocity of approximately 50% occurs in the legs by 25 to 29 weeks of gestation and lasts until approximately 6 weeks after delivery, at which time it returns to non-pregnancy flow-velocity rates. Other factors associated with stasis are compression of the iliac veins by the uterus or the left iliac artery(12;33); and prolonged immobilization(34).

The risk of VTE during pregnancy is further increased by the presence of thrombophilias(35-37) and a prior history of VTE(38). Thrombophilias are disorders of the haemostatic system that can be congenital or acquired, and characterized by an increased risk for thrombosis(39). Congenital thrombophilias are present in at least 15% of the population and approximately 50% of PAVTE are associated with heritable thrombophilia(40). The risk for developing a VTE varies according to the type of thrombophilia(41).

A quarter of thromboembolic events associated with pregnancy are recurrent events (38;42) in women who have had an initial VTE provoked by either oral contraceptive use or a prior pregnancy (38;42). For pregnant women without a prior history of VTE, some recently identified risk factors during the ante-partum period are smoking, multiparity, immobilization, assisted reproductive technology, body mass index, and lower than average weight gain(43).

1.3 Clinical Features and diagnosis of PAVTE

Deep vein thrombosis is a blood clot that forms in a deep vein(39). A deep vein usually accompanies the arteries, enclosed in a sheath that wraps both the vein and the associated artery. DVT usually occurs in the lower leg or thigh but can also occur in other parts of the body (i.e. arms or abdominal organs).

Serious complications of DVT are PE or severe ischemia of the leg.

PE occurs when a(39) blood clot in a deep vein breaks off and travels through the bloodstream into the lungs and blocks blood flow to a portion of the lung. PE is a very serious condition that can damage the lungs, the heart, and even cause death.

Deep vein thrombosis typically originates from untreated calf thrombi that extend into the deep veins, usually within a week of their formation(44). The incidence of DVT isolated to the iliac vein is thought to be higher among pregnant women than among non-pregnant women (46). Isolated iliac vein thrombosis may present with abdominal pain, back pain, or swelling of the entire leg (46). During pregnancy women are more likely to be diagnosed with DVT (with 85% of the cases occurring in the left leg) (7;40) than PE(8;45;46). During the post-partum period, this trend reverses and PE becomes more prevalent than DVT(7;40;46). The risk of PE (either symptomatic or asymptomatic) in patients diagnosed with DVT is approximately 50%(47). The most common presenting signs of DVT are swelling, redness, and pain in the calf or inner thigh. Those presenting with PE typically report shortness of breath, chest pain, and hemoptysis(48). Rarely, VTE can result in cardiac arrest, shock, or vascular compromise of the leg (i.e., phlegmasia cerulea dolens)(48).

To complicate diagnostic matters, many of the classic signs and symptoms of DVT and PE such as leg swelling, tachycardia, tachypnea, and dyspnea, mirror symptoms of normal pregnancy(49). Although VTE is found in less than 10% of the suspected cases during pregnancy (compared with approximately 25% in studies of non-pregnant patients)(50), timely, objective testing is paramount given the potential consequences of a missed diagnosis (e.g., death)(51).

Studies evaluating strategies for the diagnosis of DVT and PE have excluded pregnant women(52). Diagnostic imaging remains the cornerstone of diagnosis of PAVTE as non-invasive tests (e.g.-dimer)are, generally, considered not as reliable for this population(34). Selection of imaging techniques of the lungs must take into account the level of radiation exposure to the mother and the fetus(33). CT scan carries the lowest fetal radiation exposure but increases the level of radiation exposure to the mother (potentially leading to an increased risk of breast cancer). On the other hand ventilation/perfusion lung (V/Q) scans are safer for the mother but increases the level of fetal exposure to radiation(33;34). Still, the estimated radiation exposure to the unborn child with V/Q scans is up to

0.58 cGy, a level well below the below the maximum safety limit of 5 cGy specified by the National Commission on Radiation Protection(33).

Compression ultrasonography of the legs is a reasonable initial diagnostic approach to avoid radiation exposure in pregnant women with suspected PE or in patients with suspected DVT(33;34). If compression ultrasonography of the legs is negative, in-patients with suspected PE, women should have a V/Q scan or CT scan; in patients with suspected DVT an MRI aiming to evaluate the iliac veins or sequential compression ultrasound are required(33;34).

1.4 Current approach to the treatment of PAVTE

After being diagnosed with DVT or PE, treatment with anticoagulant drugs is necessary. Heparin was originally used for the treatment of VTE during the 1930s(53) while the combination of heparin and vitamin K antagonist has been the standard of care since the 1960's(54). The treatment is usually divided in two stages: 1- the acute treatment period (0-30 days); and 2-secondary prevention. In both pregnant and non-pregnant patients therapy during the acute treatment period requires immediate anticoagulation with IV unfractionated heparin (UFH) or full dose low molecular weight heparin (LMWH) to prevent recurrent VTE.

Anticoagulants (i.e. LMWH or UFH in combination with vitamin K antagonists) are the most effective and commonly used medical interventions for treating DVT and PE (39). They decrease the blood's ability to clot thereby stopping existing blood clots from progressing and preventing new(or recurrent VTE) from forming; however, they do not dissolve existing blood clots(39). They can be taken as a pill, an injection under the skin, or an injection into a vein.

Recurrent VTE is a new thrombotic event (manifested either as DVT or PE) occurring either during treatment with anticoagulants, after stopping treatment for a short period of time or after therapy is completed(55). During the first 3 months of treatment up to 5% of the patients treated with anticoagulants will experience a recurrent event with a case fatality rate [defined as the proportion of

all recurrent VTE (fatal and nonfatal) resulting in death]of 11%(55). For the purpose of the thesis, recurrent VTE will be defined as those events occurring during treatment with anticoagulants. Patients presenting with PE are more likely to develop a fatal recurrent PE, and non-fatal recurrent DVT or PE than patients presenting with DVT during the first 90 days of anticoagulation(55;56). Other clinical factors independently associated with an increased risk of fatal PE during treatment are immobilization for neurological disease, age >75 years, cancer(56) or the presence of lupus anticoagulant antibodies. The most severe side effect of anticoagulants is major bleeding. Major bleeding is usually defined as(57;58): clinically overt bleeding associated with transfusion of at least 2 units of packed red blood cells; bleeding into a critical organ (such as the brain); or death. The case fatality rate of major bleeding is 10%.

Unfractionated heparin is a naturally-occurring glycosaminoglycan that inactivates activated clotting factors (thrombin, factor Xa) by potentiating the effect of anti-thrombin(endogenous coagulation inhibitor). Unfractionated heparin has been used for the treatment of VTE since the 1930s(53).

Unfractionated heparin is administered either by intravenous infusion which has an immediate effect and short plasma half-life (30 minutes-2 hours); or by subcutaneous injection which has a delayed effect (2 hours) but prolonged half-life (10 hours). Treatment with full-dose UFH must be monitored with blood coagulation assays(59)at least once a day and the dose must be adjusted to achieve the target therapeutic range [within which the risk of bleeding or recurrent thrombosis is reduced(60)] . In general those who are treated with UFH for VTE require admission to the hospital for 5 to 10 days to receive intravenous therapy(61).

Low molecular weight heparins are derived from UFH by chemical or enzymatic depolymerization. LMWHs are about one third the molecular weight of UFH and have pharmacokinetic advantages over UFH. After subcutaneous injection, the bioavailability of LMWHs is about 90%(62). Low molecular weight heparins produces a more predictable anticoagulant response than UFH(63). The elimination

half-life of LMWHs (3 to 6 h after subcutaneous injection) is dose independent and anti-Xa levels peak 3 to 5 h after dosing(63). Given that LMWHs are eliminated by the kidneys, one limitation is a prolonged biological half-life in patients with renal insufficiency(64).

Low molecular weight heparins typically are administered in weight-adjusted doses for therapeutic purposes(3). For non-pregnant patients taking LMWH, laboratory monitoring of the anticoagulation effect based on anti-Xa levels is not normally necessary(3).

In non-pregnant patients, LMWH or UFH is given for at least 5 days alongside vitamin K antagonists(3). Heparins are discontinued when a therapeutic international normalized ratio for vitamin K antagonists is achieved on two consecutive days. Vitamin K antagonists are continued afterwards as secondary prevention. The combination of heparin and Vitamin K antagonists is a highly effective way to prevent recurrent VTE, reducing the risk to 3% while on treatment. Nevertheless, continuous use of anticoagulants is associated with a constant risk of major bleeding (47), an outcome with a high case fatality rate (proportion of all major bleeding events causing or associated with death).

In non-pregnant patients the duration of secondary prevention is determined by the presence of transient risk factors(5). For those diagnosed with a DVT or a PE after a surgery or prolonged immobilization are usually treated for three months, whereas those with idiopathic (unprovoked) VTE require treatment for at least 6 months(5).

In those treated with vitamin K antagonists for secondary prevention the risk of recurrent VTE and/or bleeding is associated with the amount of time spent on therapeutic range.

The ideal treatment strategy for PAVTE balances four imperatives: 1-Reduce the rate of recurrent VTE (fatal and non-fatal); 2-Decrease the bleeding risk associated with anticoagulation (including the ante-partum, pre-partum and post-partum periods); 3-Reduce drug adverse effects to the mother and fetus and 4- be based on evidence generated by high quality clinical studies ideally conducted in pregnant women.

As discussed above from the 1960s to date(65), heparin and vitamin K antagonists have been the standard treatments for non-pregnancy related VTE. But, vitamin K antagonists are associated with increased risk of fetal malformations and are thus contraindicated during pregnancy(59).

Malformations associated with the use of vitamin K antagonists include(34): facial hypoplasia, stippled condral calcification, short proximal limbs and short phalanges. A recent meta-analysis by Chan and et al(66) found that exposure to vitamin K antagonists during pregnancy was associated with a 6.4% incidence of fetal malformations . Furthermore, Vitamin K antagonists increase the risk of fetal and neonatal bleeding(66)for the duration of pregnancy. Although vitamin K antagonists are generally considered safe during the second and third trimesters of pregnancy, careful examination of school-aged children who have been exposed to vitamin K antagonists after the second trimester have shown a two fold increase in the risk of minor neurologic defects and/or an intelligence quotient of 80 or less(67-69).

Given the risks that vitamin K antagonists [and other anticoagulants - e.g., fondaparinux which has been found in blood samples from the umbilical cord(70)] pose to the fetus, recent guidelines recommend continuing treatment after the acute period with UFH or LMWH(61;71-73) (preferably the latter) in patients diagnosed with DVT or PE, as these medications are safe for the fetus because they do not cross the placental barrier. Ginsberg et al, provided re-assurance regarding the safety of UFH for the fetus showing that the rate of fetal malformations among women treated with UFH was no different that among pregnant women not exposed to UFH. Low molecular weight heparin also appears to be safe for the fetus(74). Exposure to massive doses of LMWH does not have any teratogenic effects in pregnant rats(75), and no anti-Xa activity was detected in the umbilical cord from women who were exposed to LMWH(76).

Acute VTE in pregnant women should be treated with full-dose LMWH or UFH for one month.

Options for secondary prevention include continuing the full therapeutic dose or reducing to an

intermediate dose. Pregnant women normally require anticoagulant drugs for the duration of pregnancy and for at least six weeks post-delivery to reduce the chances of recurrent VTE associated with the physiologic changes of pregnancy(61). In 2012, new guidelines from the American College of Chest Physicians (ACCP) suggested that it sufficient to treat throughout pregnancy and the post-partum period for a minimum total duration of 3 months(71). The ACCP supported their recommendations using evidence from the non-pregnant populations(77).

Notwithstanding the paucity of supportive data from controlled trials(78) or even large prospective observational studies(35) conducted in pregnant patients, LMWH remains the most recommended(21;61;79;80) and used(81;82) drug for treatment of pregnancy associated VTE. Recommendations for using LMWH are primarily based on results from large trials in non-pregnant patients showing that are at least as safe and as effective when compared with UFH(21) and observational studies conducted in pregnant patients suggesting that the rate of recurrent VTE is 1.15% in those treated with LMWH(35).

LMWH have better bioavailability, longer plasma-half-life, a predictable dose response, a superior safety profile, and require less monitoring when compared to UFH in non-pregnant patients (35;83;84). A recent a meta-analysis suggested that in non-pregnant patients LMWH is superior to UFH for reducing recurrent VTE (OR 0.57; 95% CI 0.44 to 0.75), associated with a reduction in major bleeding (OR 0.50; 95% CI 0.29 to 0.85) and all-cause mortality (OR 0.77; 95% CI 0.63to0.93).

The benefits of LMWH over UFH for long-term prevention of VTE beyond the potential reduction of recurrent VTE appear to be: 1- a reduced incidence of bleeding(21); 2- less cases of heparin induced thrombocytopenia(85); and 3- a lower incidence of heparin induced osteoporosis(86;87). Moreover, patients treated with LMWH need less monitoring(88) and can be safely treated as outpatients(89).

In general most of the authors agree that UFH(33;34;90-93) should only be used in women with PAVTE with a contraindication for the use LMWH (mostly those with chronic renal failure with a

creatinine clearance < 30 mL/min), when LMWH is not available, or when immediate reversal is needed.

To summarize, most authors and guidelines agree that LMWH is the drug of choice for the management of PAVTE during the acute and secondary prevention period for the following reasons: 1- being more effective in reducing recurrent VTE (fatal and non-fatal) in non-pregnant patients than UFH; 2- Decreasing the bleeding risk, osteoporosis and heparin induced thrombocytopenia associated with UFH; and 3- Is not dangerous for the fetus. Still, its use is not supported by high quality clinical studies conducted in pregnant women.

1.5 Dosing and monitoring during treatment with LMWH

In non-pregnant patients treated for acute VTE the dose of LMWH can be given once a day or by twice a day dosing. When patients are treated with twice a day dosing regimen, the total daily amount of LMWH is divided in two equal doses that are given twelve hours apart from each other. In non-pregnant women the ACCP suggests once a day over twice a day dosing administration; and discourage the use of anti-Xa monitoring to measure the anticoagulant effect of LMWH. This recommendation places value on improving patient comfort, and indirectly leads to a reduction in cost of care. Still, the ideal LMWH dosing strategy and the role of monitoring during pregnancy remains a matter of debate(33;34;90-93). As pregnancy progresses certain normal physiologic changes associated with normal gestation, could potentially reduce the efficacy of LMWH.

During pregnancy, there is an expansion of intravascular(94) and extra-vascular (mostly in the breasts, uterus and the lower extremities) water content which in turn increases the volume of distribution of LMWH(62). Low molecular weight heparin is excreted by the kidneys and its elimination depends on the glomerular filtration rate. During pregnancy the glomerular filtration rate increases by 50%(94) until the last week of pregnancy(59;95). During pregnancy, differences in the pharmacokinetics of LMWH have been observed, with an overall reduction in anti-Xa activity(94;96).

In summary, it could be predicted that the use of LMWH during pregnancy would be associated with a reduce C_{max} (peak concentration) and a shorter half-life(62), potentially affecting the efficacy to prevent recurrent VTE. Given the later certain authors recommend to either adjust the dose according to changes in body weight (34;64;88); twice a day dosing over once a day to overcome increased excretion, or to monitor LMWH using anti-Xa (97)levels. Conversely, a minority of other studies suggest that only a small group of patients require changes in doses based on anti-levels (98), that twice a day dosing might not be enough to achieve therapeutic anti-levels(99) and that all these measures taken to overcome the physiologic changes of pregnancy do not appear to improve the clinical outcome of patients(100).

The evidence supporting dose adjustments based on anti-Xa levels outside pregnancy is weak(62). There is lack of standardization regarding the timing of measurement and target levels(82;101). Lastly, anti-Xa monitoring increases cost of care and discomfort for the patients.

Uncertainty regarding the best dosing strategy and the use monitoring is reflected daily clinical practice (82;101). Voke et al(82) reported the treatment strategies in the UK for 126 patients diagnosed with PAVTE. They found that 66% of patients were treated with once a day full doses of LMWH and 79% were monitored with anti-Xa levels. Knight et al(46) evaluated the treatment strategies of pregnancy associated PE in the UK. They found that nearly 50% of the patients were treated with LMWH once a day. The findings of both studies suggest that half of the physicians treated patients with PAVTE against the recommendations of the RCOG guidelines(79). In the last version of their guidelines the RCOG recommended the use of full dose LMWH twice a day and the use of anti-Xa levels monitoring only for special situations.

1.6 Rationale for the use of an intermediate dose for secondary prevention after the acute treatment period of pregnancy associated VTE

Despite the physiologic and pharmacokinetic changes seen among those pregnant patients receiving LMWH, some experts(33;90) recommend an intermediate dose of LMWH for secondary prevention in

order to potentially reduce the risk of major bleeding, osteoporosis, facilitate treatment and reduce cost of care for pregnant patients. The definition of what is an intermediate dose has varied significantly between studies but in general it ranges from a 50 to 75% of the dose used during the acute treatment period.

Benefits for using an intermediate dose for secondary prevention are documented in randomized control studies comparing low doses of LMWH to vitamin K antagonists for the secondary prevention of idiopathic, provoked, or cancer associated VTE(102-109) . The updated version of the ACCP guidelines issued in 2012 addressed the potential benefits of using an intermediate dose of LMWH for secondary prevention of PAVTE(71). The authors agreed that an intermediate dose could potentially lower the risk of bleeding and osteoporosis but found no evidence to support or refute the use of this strategy during pregnancy.

Opponents of a dose reduction for PAVTE have claimed that that the use of an intermediate dose in pregnant patients is likely associated with lower efficacy(34). Changes in renal function that occur during pregnancy(34) and the volume of distribution of the drug alongside the absence of direct evidence serve to bolster the argument against intermediate doses(79).

At least 5 randomized control studies(102-109) (481 patients) outside pregnancy and one meta-analyses(110) have shown that patients treated for more than 3 months with a reduced dose of LMWH for secondary prevention after the acute treatment period had similar rates of recurrent VTE to those treated with oral vitamin K antagonists (although there was a trend towards an increased risk of recurrent VTE in patients treated with prophylactic doses). Lower doses were associated with a reduction in major bleeding (OR 0.2; p-value 0.02)(111).

In a landmark randomized control study by Lee et al(102), a strategy using an intermediate dose given once a day after the acute treatment period in cancer associated VTE lead to a reduction in the rate of recurrent VTE when compared to vitamin K antagonists in patients treated for cancer associated VTE.

The probability of recurrent thromboembolism during the six months of treatment was 17% in those treated with vitamin K antagonists and 9 % in those treated with dalteparin. No significant differences in rates of major bleeding were found between those treated with dalteparin or vitamin K antagonists (6 percent and 4 percent, respectively) (102). Patients with cancer are believed to be at 4-fold higher risk for recurrent VTE than those patients with idiopathic or secondary VTE (including pregnant patients). Only two studies evaluating the efficacy of an intermediate dose for the secondary prevention of PAVTE were included in a systematic review conducted by Greer et al. Ulander et al(112) compared the effectiveness and safety of a reduced dose of dalteparin for secondary prevention in a prospective observational study. After confirmation of DVT by ultrasonography, 10 women were treated with UFH and 21 women with dalteparin for seven days and thereafter, all women were given full doses of LMWH for an extra two weeks. The dose was then decreased after 21 days and given once a day with anti-Xa monitoring, until delivery. One patient experienced a recurrent event (the result of a protocol violation wherein she was only treated with a week of full dose LMWH). One limitation of the study is that four patients continued with full dose treatment due to persistent symptoms.

Daskalakis et al(113) prospectively evaluated 18 patients treated with intermediate fix doses of nadroparin (double the usual prophylactic dose used for surgery) after 2 weeks of full dose treatment with UFH. None of them suffered a recurrent VTE. Neither study was adequately powered to detect to detect relevant differences in recurrent VTE

To conclude, the use of intermediate doses of LMWH is a safe and effective strategy for the secondary of non-pregnancy associated VTE. Preliminary evidence from two small observational studies supports the evaluation of this strategy in pregnant patients to reduce the risk the major bleeding and cost of care, while increasing the comfort for the patient.

1.7 Guidelines and expert recommendations for PAVTE

Most of the current guidelines are based on data derived from observational studies of pregnant patients(112;114;115) and randomized controlled trials conducted in non-pregnant patients(102-109). The treatment of PAVTE was recently reviewed in four guidelines(21;61;79;80), four systematic reviews(21;35;116;117) and at least six expert narrative reviews(33;34;90-93).

The American College of Chest Physicians (ACCP) guidelines are considered the 'gold standard' in VTE prevention, diagnosis and management(118;119).

The guidelines were updated in 2012(71), and included the following: 1- *“For pregnant women with acute VTE, we recommend therapy with adjusted-dose subcutaneous LMWH over adjusted-dose UFH (Grade 1B)”*; 2- *“If LMWH is used for treatment of acute VTE in pregnancy, a weight-adjusted dosing regimen should be used.”*; and 3- *“Given the absence of large studies using clinical end points that demonstrate an optimal therapeutic anti-Xa LMWH range or that dose adjustments increase the safety or efficacy of therapy, the lack of accuracy and reliability of the measurement, the lack of correlation with risk of bleeding and recurrence, and the cost of the assay, routine monitoring with anti-Xa levels is difficult to justify.”*

Guidelines from the UK Royal College of Gynecologists and Obstetricians, published in 2007 and reviewed in 2010(79), recommend that women with antenatal VTE could be managed with subcutaneous LMWH injections administered twice a day for the remainder of the pregnancy. Anti-Xa monitoring was recommended in cases of extreme body weight (greater than 120 kg or less than 50 kg) or renal impairment. The authors discussed the possible benefits of a reduced dose strategy, but given the paucity of research pertaining to this population, they continue to recommend therapeutic doses based on patient weight (for example, enoxaparin 1 mg/kg q 12-hourly; dalteparin 100 units/kg twice a day up; tinzaparin 175 units/kg daily) throughout pregnancy. The guidelines favor LMWH over UFH because the former is associated with a lower rate of major bleeding.

The Society of Obstetric Medicine of Australia and New Zealand and the Australasian Society of Thrombosis and Haemostasis(80) issued their recommendations for the management of PAVTE in 2011. They recommended using LMWH over UFH and administering a full dose either once a day or twice a day, with anti-Xa monitoring reserved only for special situations.

The American College of Physicians and the American society of Family physicians(73) issued their VTE management recommendations alongside a systematic review conducted by Segal et al(21) that included 14 studies and 195 patients treated with UFH or LWWH until the year 2003(21). They concluded that there was inadequate evidence to derive definitive recommendations for managing VTE in pregnancy.

The first systematic review evaluating the use of LMWH during pregnancy was conducted by Sanson et al(120) in 1999. They identified 18 patients treated with LMWH for pregnancy associated VTE.

None of them suffered a recurrent event.

The most cited systematic review evaluating the use of LMWH during pregnancy was conducted by Greer et al in 2005(35). They included 15 studies; six of them were case reports evaluating 174 patients. The reported rate of recurrent VTE was 1.15% (95% CI, 0.14%-4.09%). There were no maternal deaths and the rate of significant bleeding (defined as blood loss greater than 500 ml) was 1.72% (95% CI, 0.36%-5.00%). Table 2 presents the quality of the studies included in his systematic review and the outcomes reported in each study (excluding case reports).

On close examination of the data evaluated by Greer et al(35), the number of recurrent events in the study from Lepercq et al(114), was higher than the one reported by Greer et al(74). Greer et al claim that only one case of recurrent VTE occurred in a patient treated with full dose enoxaparin for acute VTE, but did not include four events occurring when the dose of enoxaparin was reduced to a 40 mg once a day, after 90 days of treatment. Lepercq et al(114) clearly stated in their results that “Among these eight recurrent VTE events, one occurred in a woman who took 20mg/day, six in women who

took 40mg/day and one DVT despite 2mg/kg /day... Nevertheless, all reported VTE events before delivery occurred despite thromboprophylaxis with enoxaparin 40mg/day in women who had a first DVT during the current pregnancy”.

Yaakob et al(78) conducted a systematic review for the Cochrane Library evaluating the efficacy of different anticoagulation regimens for the treatment of pregnancy related DVT. The authors included only randomized controlled trials or quasi-experimental studies. They arrived at the following conclusion: “At this stage we are unable to recommend the adoption of LMWH as a standard clinical practice during pregnancy”. Compared to other systematic reviews(21;35), this group only identified three potential studies(98;121;122). Also, they did not mention or comment on the findings from prior systematic reviews(21;35) in their discussion.

Experts’ opinions in narrative reviews generally agree with guidelines supporting the use of LMWH over UFH but differ when it comes to strategies for secondary prevention of PAVTE using LMWH:

- i. Rodger (2010): Favored LMWH over UFH and suggested full dose LMWH for the acute period +/- anti-Xa monitoring, followed by the use of an intermediate dose without monitoring, for the duration of pregnancy
- ii. Greer (2006)(91): Favored LMWH over UFH and suggested full dose given twice a day without monitoring, for the duration of pregnancy
- iii. Middeldorp (2011)(34): Favored LMWH over UFH and suggested full dose LMWH once a day, or twice a day based on anti-Xa monitoring, for the duration of pregnancy
- iv. Marik (2010)(93): Favored LMWH over UFH and suggested full dose LMWH once a day, without monitoring, for the duration of pregnancy
- v. Ayra (2011)(92): Favored LMWH over UFH and suggested full dose LMWH once a day, with monitoring for the duration of pregnancy

- vi. Bauersachs (2009)(90): Favored LMWH over UFH and suggested full dose LMWH once a day or twice a day for the acute period, followed by full or intermediate doses twice a day(monitoring reserved for special situations).

In summary, experts(33;34;90-93) and guidelines favor the use of LMWH over UFH for treating PAVTE despite the absence of high quality evidence supporting those recommendations. Moreover, they do not provide uniform guidance regarding best dosing strategies for secondary prevention (> than 30 days). Lack of high quality evidence and unified criteria for the management of PAVTE leaves the practicing physician to decide the best treatment approach out of at least five different(33;34;90-93) strategies for secondary prevention. As described above proposed strategies for secondary prevention are full or intermediate doses of LMWH, given once or twice, with or without anti-Xa monitoring.

Table 2 Studies included by Greer et al (case reports are excluded)

	Design	Year	N	Inclusion Criteria	Secondary prevention	Twice daily	Monitoring	Recurrent VTE (%)
Daskalakis(115)	Case series	1997	18	No	Intermediate		No	0
Ellison(123)	Retrospective Cohort	2000	10	NR	Full	No	Yes	0
Jacobsen(124)	Prospective cohort	2003	20	Yes	Full	Yes	Yes	0
Lepercq(114)	Retrospective Cohort	2001	46	Yes	Prophylaxis	No	NR	11
Rey(125)	Prospective Cohort	2000	20	Yes	Full	Yes	Yes	0
Rodie(98)	Prospective Cohort	2002	33	No	Full	Yes	Yes	0
Ulander(112)	Prospective Cohort	2002	31	No	Intermediate	No	Yes	3

1.9 Summary

Physicians treating PAVTE face multiple challenges. First, high quality evidence for the support of any strategy used during secondary prevention of PAVTE is lacking. Second, an approach based on the physiologic changes associated with pregnancy, although reasonable, exposes the patient to higher doses of LMWH for longer periods of time, perhaps increasing the risk of major bleeding, increasing the discomfort associated with treatment and the cost of care. Third, the use of an intermediate dose of LMWH (given once a day and without monitoring), which is an effective alternative to full dose anticoagulation for secondary prevention in non-pregnant patients, could help physicians to reduce adverse events associated with anticoagulation, simplify treatment and reduce cost of care.

In conclusion, although a favorable risk-benefit balance associated with an intermediate dose of LMWH for the secondary prevention of VTE has been documented in the non-pregnant population there has yet to be a well design study validating a favorable risk-benefit balance for this strategy in pregnant patients.

RESEARCH QUESTION

Is an intermediate dose of LMWH (given once a day and without anti-Xa monitoring) safe and effective for secondary prevention of VTE in pregnant patients diagnosed with DVT or PE?

THESIS QUESTION

Is it feasible to conduct a single arm study using a reduced dose of LMWH for the secondary prevention of VTE in pregnant patients?

2.0 Selection of the study design

In the hierarchy of research designs, randomized controlled trials are considered the highest grade evidence, whereas observational studies are viewed as having less validity because they reportedly overestimate treatment effects(126).

The ideal study design to evaluate the safety and efficacy of an intermediate dose of LMWH (given once a day without anti-Xa monitoring), is a randomized controlled study against the standard of care. As will be discussed later, a randomized controlled study for this particular intervention would be likely impossible and an alternative study design is needed.

2.1 Superiority, non-inferiority or placebo controlled?

In the absence of prior randomized placebo controlled studies evaluating the efficacy of LMWH for the secondary prevention of PAVTE, should one be conducted? The answer is no, the declaration of Helsinki stipulates that when an effective treatment exists the use of placebo is unethical and should not be conducted(127). This is the case for studies evaluating the efficacy of anticoagulation for patients diagnosed with VTE. The only randomized placebo controlled study was conducted in the 1960s by Barrit and Jordan(54), showing a significant reduction of recurrent VTE (23 vs. 0%) and mortality in patients of the treatment group receiving anticoagulation (but not specifically LMWH)(25 vs. 0% rate of recurrent VTE, and a statistically significant reduction in mortality). Proof of efficacy of anticoagulation was also shown in a small randomized studies comparing UFH/Vitamin K antagonists vs. Vitamin K antagonists alone(128); or UFH/Vitamin K antagonists vs. low doses of UFH(129) in patients who are immobilized. The only study challenging the benefit of anticoagulation was conducted by Nielsen et al(130). The authors claimed that anticoagulation was no better than anti-inflammatory drugs for the treatment of objectively diagnosed DVT in patients who were actively mobile. Still, given

the accepted efficacy of anticoagulation a randomized placebo-controlled study would be considered unethical.

A superiority study evaluating the efficacy of a reduced dose strategy to prevent recurrent VTE would face severe limitations. First, although the systematic review suggests that a reduced dose regimen appears to have similar efficacy to a full dose regimen this assumption is based on small observational studies which could have been subject to bias (as will be discussed later). Second, intermediate doses of LMWH are not expected to have greater efficacy than full doses. A recent meta-analysis suggested that using very low doses of LMWH (e.g. prophylactic doses) increases the chances of recurrent VTE(110). Furthermore, given that physiologic changes during pregnancy are associated with increased excretion of LMWH(97), this assumption would be implausible from a pharmacological standpoint. On the other hand, a superiority study comparing a reduced dose of LMWH against full doses of LMWH for secondary prevention could aim to prove that an intermediate dose is associated with a reduction in major bleeding. Major bleeding is a serious complication of anticoagulation that carries a high mortality rate (10% case fatality rate)(55). A superiority study aiming to show a clinically relevant reduction of forty percent in the rate of major bleeding (set for a power of 0.8 and a two sided alpha level 0.5) would require 3476 participants in each arm without adjusting for the rate of loss to follow up. This study would also face some an ethical limitation: The main objective of anticoagulant treatment is to reduce recurrent VTE(59;61;71). Currently there is no high quality evidence to support the efficacy of a reduced dose strategy for the secondary prevention of recurrent VTE in pregnant associated VTE(33;90) potentially exposing patients to a less effective treatment.

Ergo, the ideal study design to evaluate the proposed intervention would be a randomized controlled non-inferiority study, comparing standard full dose therapy against an intermediate for secondary prevention (started 30 days after the initial treatment given once a day without anti-Xa monitoring).

2.2 Non-inferiority randomized controlled study

Assuming, that the active control would have been superior to a placebo, if a placebo-controlled study was conducted, a non-inferiority study states as a null hypothesis that the new drug is inferior by some margin and tests this statistically(127;131-137).

H0: $C - T > M$ (T is more inferior to C than M); null hypothesis

H1: $C - T < M$ (T is less inferior to C than M); alternative hypothesis

[C represents the control, T represents the new intervention and M defines the non-inferiority margin (from here on referred to as $-\Delta$)]. If the 95% C.I. upper bound of the new drug is smaller than the non-inferiority margin, the null hypothesis of inferiority is rejected(127;131-137).

The first question to be answered in order to demonstrate non-inferiority is if there evidence of ‘assay sensitivity’(138;139). The ability of a study to distinguish between active and inactive treatments is termed assay sensitivity. To demonstrate or establish assay sensitivity in the non-inferiority trial we must have assurance that the active control would have been superior to a placebo if a placebo was employed(127). If assay sensitivity cannot be proven the study cannot demonstrate effectiveness of the new drug over placebo(139).

To demonstrate assay sensitivity three conditions are needed(138):

- i. Historical evidence of sensitivity to drug effects (HESDE). HESDE is assumed when appropriately design studies in a specified population have consistently shown the effect of a drug over placebo. The use of anticoagulation for the treatment of VTE is one of the areas where HESDE has been proven, albeit with certain limitations. The main limitation in the area of anticoagulants is that the only study showing efficacy of anticoagulation with heparin against placebo was conducted more than 50 years ago (123), in non-pregnant patients and without an objective diagnosis of VTE (123). Additional proof of the efficacy of IV UFH in treatment of acute VTE was provided by Brandjes et al(128) who performed a randomized double-blind study comparing UFH with Vitamin K antagonists against VIT K

antagonist alone. The study was terminated early given the high rate of recurrent VTE in patients not receiving UFH. Nevertheless, given the current knowledge regarding the high mortality rate (around 35%) associated with untreated VTE (4), it would be unethical to conduct a placebo study. HESDE of the comparator could be assumed from historical data and indirect evidence of studies using "less effective therapy" in the non-pregnant population as shown in table 3.

- ii. Constancy assumption. Assumptions of HESDE apply only when the prior studies were conducted in a similar population, using similar inclusion criteria and endpoints (or constancy assumption), as any changes in the prior criteria could alter the effect size of the active control. In the studies included in table 3 pregnant patients were systematically excluded and patients were treated with a combination of UFH/Vitamin K antagonists. Most of the studies evaluating non-inferiority of new oral anticoagulant agents(140-142) have used prior data of patients treated with UFH and Vitamin K antagonists, assuming that the constancy assumption holds(127). The treatment of VTE had not changed until the 1990s when LMWH was introduced into clinical practice, showing superiority over UFH in multiple randomized controlled trials (143). Furthermore, the introduction of CT scanners as a diagnostic method for PE has been(19) associated with changes consistent with over diagnosis: i.e., rising incidence, minimal change in mortality, and lower case fatality rate. Authors have suggested that the benefit of treating less severe forms of the disease should be reevaluated(144) as short-term prognosis for recurrent thromboembolism may be lower than the risk of adverse events with anticoagulation(145). Based on those two facts, the constancy assumption would not hold as the total effect of anticoagulation would be lower than previously assumed, leading studies to require more conservative $-\Delta$ than previously used.

iii. Quality of the prior studies. Even if HESDE exist, the design of prior could lead to an over estimation of the effect of the control. Factors affecting the quality of the prior studies are lack of diagnostic criteria for inclusion, poor quality of measurements or selection of more susceptible populations. As an example the study by Barrit et al included(65) patients without an objective diagnosis of PE. Patients received not only UFH but were mandated to remain immobilized during treatment, which is proposed risk factor for death and recurrent VTE(56). The adjudication of outcomes was based on subjective criteria, and physicians were not blinded to the treatment group. All these factors would affect assay sensitivity.

Table 3 Studies supporting the efficacy of anticoagulation for the treatment of VTE

	Barrit (54)	Hull (129)	Holmgren (146)	Lagerstedt (147)	Hull (148)	Brandjes (149)	Raschke (150)	Levine (151)	Schulman (152)
Year	1960	1979	1985	1985	1986	1992	1995	1995	1995
N	37	68	135	51	105	120	73	214	897
PE included	Yes	No	No	No	No	No	Yes	No	Yes
Comparator	Placebo	UFH 5000 BID	Warfarin x 4 weeks	Placebo	IV UFH no weight adjusted	Placebo	IV UFH no weight adjusted	Warfarin X 4weeks	Warfarin X 6 weeks
Recurrent VTE Intervention vs. control (%)	0/57	0/17	4.5/8.7	0/25	5.2/19.3	3.3/16.7	5/25	0.9/5.9	0.9/5.9

In conclusion, assay sensitivity has been assumed for multiple studies evaluating new anticoagulants drugs in the non-pregnant population. The extrapolation of assay sensitivity to the pregnant population, although logical, would be undermined as most of the studies comparing anticoagulation against placebo excluded pregnant patients and had methodological limitations.

2.2.1 Non-inferiority study: Selection of the comparator

The second question to be defined is: Against what strategy should the use of intermediate dose of LMWH for the secondary prevention of PAVTE be tested for non-inferiority? The selection of the right comparator is fundamental to avoid biocreep(127;136;137). Biocreep is the phenomenon that occurs

when an inferior treatment becomes the active control for future non-inferiority studies, leading eventually to use a control that is no better than placebo(127). To avoid biocreep the control should always be the best comparator.

Since most guidelines and experts agree that full dose LMWH for the duration of pregnancy is the standard of care, ergo it should be the selected comparator for the study. What dosing strategy or the use of monitoring remains a matter of debate.

In general, studies comparing differences between strategies using once a day or twice a day doses of LMWH are small randomized controlled trials (153) in the non-pregnant population and observational studies in the pregnant population(154). Of the five randomized(155-159)controlled trials in non-pregnant patients, none were adequately powered to show any relevant differences in recurrent VTE.

Most of the authors(33) who support once a day dosing for patients treated for PAVTE cite three studies as proof of similar efficacy between the two dosing strategies. Only the concurrent control study by Narin et al(154) was specifically designed to answer this question. Moreover, it was not a randomized controlled study. Narin reported no differences in outcomes between both treatment groups but the sample size was too small (total sample 35 patients) to identify any relevant differences.

The other two studies reported(46;82)the outcomes for patients with PAVTE treated either once a day or twice a day with LMWH however, these studies were not specifically designed to address this question.

In the survey conducted by Voke et al(82), 24% of patients initially treated with once a day dosing were then switched to twice a day dosing. An explanation for this finding might be the high prevalence of anti-Xa monitoring in this particular study. Still, none of the patients treated with once a day dosing suffered a recurrent event.

Knight et al (46)specifically evaluated treatment strategies for pregnancy associated PE in a registry. They reported that 49% of the patients were treated with once a day dosing yet when the analysis is

limited to drugs that can be given either once a day or twice a day (dalteparin or enoxaparin), only 39% of the patients were treated with once a day doses.

Although discouraged by current guidelines(71;79), anti-Xa monitoring is common in clinical practice(74;82). As shown in the systematic review by Greer et al, the use of anti-Xa monitoring to guide LMWH dosing was documented in the majority of studies(74). Voke et al reported that more than 76% of the patients treated with LMWH were monitored with anti-Xa levels(82).

The above evidence clearly suggests that in the absence of well-designed randomized controlled trials, and to avoid biocreep(127;137), the comparator should be the most likely to be the most effective strategy used in clinical practice. Therefore if a randomized study was to be conducted, an intermediate dose of LMWH given once a day and without anti-Xa monitoring for secondary prevention of PAVTE should be compared against full dose LMWH given twice a day and with anti-Xa monitoring. An advantage of using full doses as a comparator is that it would represent the current standard of care accepted by a majority of physicians and clinical guidelines. The use of full doses of LMWH given twice a day guided by anti-Xa monitoring for secondary prevention would provide the perspective of current practices outside guidelines, although it could be argued that evidence supporting this approach is lacking.

2.2.2 Non-inferiority study: Estimation of the non-inferiority margin and sample size calculations

The third question is: What is the $-\Delta$? The determination of the margin is the most critical step to evaluate non-inferiority(136). The margin quantifies the worst-case loss in efficacy that is clinically acceptable while considering the advantages of a new treatment. The methodology used for its estimation is not standardized(160;161). The International Conference on Harmonization(162) guidance advises that the determination of the margin should be: 1) specified a priori before the study initiation, 2) based on both clinical judgment and statistical reasoning, and 3) reflect the uncertainty of the available clinical evidence. However, what constitutes a clinically acceptable difference is

ultimately a matter of judgment and might vary widely for physician, investigator and outcomes used (e.g. hard vs. soft) (136).

The definition of $-\Delta$ is based on two values (M_1 and M_2)(133), which need to be chosen before the non-inferiority study is performed. M_1 is defined as the entire effect of the active control, assumed to be present in the non-inferiority study, corresponding to the lower bound of the 95% confidence interval for control–treatment. The choice of M_1 should be based on the following premises(133):

- i. Treatment effect estimated using historical evidence of sensitivity to drug effects with active control drug, using a meta-analysis. In the case of the proposed study, the treatment effect should be assumed from extrapolations from a single small randomized controlled study, conducted 50 years ago(54), in a different population without an objective diagnosis of the disease; from small randomized studies conducted in non-pregnant patients with a diagnoses of DVT receiving less effective treatments(129) or shorter duration of treatment(152); or historical data from observational studies not evaluating the role of placebo.
- ii. Using historical evidence of assay sensitivity as the basis of M_1 for the non-inferiority study is only appropriate if the constancy assumption holds.

When M_1 cannot be calculated one solution is to simply use what is believed to be a conservative estimate of the effect of the active control over placebo(135). The FDA guidance(133;162)clearly states that there should be a good estimate of the historical spontaneous cure rate or outcome without treatment for this approach to be used. For example, if the spontaneous cure rate of a disease is 10-20% and the cure rate with an active control is 70-80%, these are substantially different and an acceptable margin, generally chosen conservatively, can probably be identified for M_1 (133;162). As discussed above, there is clear (although limited) evidence that anticoagulation with UFH is more efficacious than placebo(54), than less effective therapies(128;129);and that LMWH are more effective than UFH in large randomized controlled trials in the non-pregnant population(143).

The clinically acceptable loss of this effect can then be determined for M_2 . M_2 is defined as the largest clinically acceptable difference of the test drug compared with the active control(132;136;137). The derivation is to be based on the largest loss of effect that would be clinically acceptable; therefore, quantifying how much of the effect of the active control needs to be preserved. Generally it can never exceed M_1 (127;131-137). By knowing M_2 the value of $-\Delta$ can be calculated.

M_2 preserves some predetermined fraction of the estimated active control effect, for example, 50 or 75%. The food drug administration generally recommends a conservation of the clinical efficacy of 50% in studies evaluating intervention in cancer and cardiovascular diseases(133;162).

One recommended approach to elicit $-\Delta$ is the use of the Delphi method, where experts (or sometimes even patients) provide their input(131). This method has been criticized for its lack of scientific validity(131).

Sample size calculations for non-inferiority studies are based on the following formula(127;137):

$$Pr [(\hat{\theta}_T - \hat{\theta}_C) - 1.96 SE (\hat{\theta}_T - \hat{\theta}_C) > -\theta_T - \theta_C = \gamma] \geq \text{Desired power}$$

For the prior formula the sample size must be large enough so that the probability (Pr) is sufficiently high that the lower bound of the 95% CI (1.96 SE) for the estimated difference between the treated group (θ_T) and the control group (θ_C) is greater than the margin, $-\Delta$, when the true difference between the groups, $\theta_T - \theta_C$, is γ (137). The sample size for a non-inferiority trial is usually calculated under the assumption that the experimental agent and control treatment have equal effects.

If a non-inferiority study was to be conducted in pregnant patients diagnosed with VTE aiming to show that an intermediate dose (given once a day and without monitoring) is not inferior to full doses (given twice a day and monitored with anti-Xa levels) it would require 3045 participants. The assumptions for the calculation of the sample size needed were: 1- that the rate of recurrent VTE during secondary prevention of PAVTE with full doses of LWMH given twice a day and monitored with anti-Xa levels is 1.15%; 2- M_1 was 4.5% based on the systematic review by Greer et al including observational studies,

as there no prior randomized studies in the pregnant population; and $3-M_2$ was assumed using a conservative OR of 2.3 corresponding to a $-\Delta$ of 2.6%, which is similar to recent non-inferiority studies evaluating new oral anticoagulant agents in non-pregnant patients, and would lead to at least a conservation of the efficacy of more than 50%. Based on these assumptions, 3045 participants (accounting for a 15% loss to follow up) would provide a power of 90% to demonstrate that the reduced dose is non-inferior to standard therapy, at a one-sided alpha level of 0.025, excluding an OR of 2.9 with a preservation of the fraction greater than 50%. The selection of a single sided test was based on the biological implausibility that a reduced dose of LMWH will be more effective than full doses to prevent recurrent VTE. More conservative approaches to determining $-\Delta$, would lead to larger sample sizes as shown in Table 4.

Table 4 Sample size calculations for a non-inferiority study

Test significance level	0.025	0.025
Baseline rate	0.012	0.012
One or two sided	1	1
$-\Delta$	0.015	0.021
OR	1.5	2.1
Power	Sample *	Sample *
80	6000	1400
90	8500	2000
95	10000	2200

**Sample for one arm not including loss to follow up*

2.3 Is a randomized controlled non-inferiority study feasible?

A non-inferiority study should be conducted when a new treatment has some benefits over the standard treatment and physicians would be willing to sacrifice some degree of efficacy for those benefits. The advantages could be ease of use, dosing schedule, or most importantly, an improved safety profile. Patients affected by PAVTE represent a challenging population to conduct randomized controlled trials. As an example, consider use of LMWH for PAVTE compared to UFH for PAVTE. Despite LMWH being widely recommended by experts and LMWH's benefits over UFH shown in well design

randomized controlled trials in non-pregnant patients, no RCTs have been conducted to evaluate LMWH compared to UFH for the treatment of PAVTE. Notably, in the era of the systematic review of LMWH use in pregnancy by Greer et al, more than ten thousand non-pregnant patients were included in twelve randomized controlled comparing UFH vs. LMWH for the acute treatment of VTE. In comparison, only 124 patients with PAVTE treated with LMWH were included in 7 published observational studies.

One relevant factor that limits participation of pregnant women in randomized controlled trials is that pregnant women need to weigh the risks and benefits of participation not only for herself, but also for the baby(163). Pregnant patients with PAVTE cannot be exposed to vitamin K antagonist (see section 1.4) due to the potential risk of fetal malformation, Beyond the safety limitations, other factors limit the feasibility of conducting randomized controlled trials in patients with PAVTE. These factors are the incidence of the PAVTE, the number of outcome events in PAVTE patients and the difficulty in enrolling pregnant patients in injectable drug trials (Cite Gates in refman and burrows in refman).

Jacobsen(164) et al in their study evaluating the efficacy of dalteparin for the treatment of PAVTE provide a relevant reference to elucidate the potential limitations of a randomized controlled study. The investigators invited all the hospitals in Denmark to participate (population ~5 million). The study only enrolled 21 patients over the course of 12-months (estimated to be 1/3 of the new cases of PAVTE during the same period of time).

A non-inferiority randomized controlled trial trying to demonstrate that an intermediate dose of LMWH is non-inferior to full dose LMWH for the secondary prevention of PAVTE would require at least 3000 participants to exclude that an OR of 2.1 or a loss in efficacy greater than 1.25%, assuming a baseline rate of events of 1.15% (power of 90% and a single alpha of 0.025).

The incidence of ante-partum PAVTE is too low to enroll enough participants in a large multi-center randomized controlled trial. A perspective on the number of potential subjects to be enrolled in Canada

can be derived from the 2005 census. In 2005, 447,485 women were pregnant in Canada (including miscarriages). Assuming that 1.5 pregnant women out of 1000 would develop a VTE and that one third of those would occur during the ante-partum period, the total number of PAVTE event would be 894 with only 223 of those occurring during the ante-partum period per year. Assuming that: 1- the real rate of recurrent VTE with either treatment arm is 1%; 2- we could conduct a study including 200 centers in Canada (that take care of at least 10000 pregnant women every year each year; 3- each center enrolled five patients per year (or all eligible cases); it would take at more than four years to complete the study.

Despite all the limitations described above, large well design randomized multicenter studies have been conducted successfully in pregnant patients for different medical conditions with similar expected number of outcomes or prevalence of the disease. The Magnesium sulphate for Prevention of Eclampsia (a disease which complicates 2 to 8% of all pregnancies with an expected 1% of the patients suffering the outcome of interest) was a randomized placebo controlled study aiming to enrol 14000 patients in 175 centers to demonstrate a reduction in events greater than 50%. The study was successfully completed within 3 years, using a 15% smaller sample size as the rate of primary events was higher than expected in both groups. Furthermore, successful and well design randomised controlled trials have been conducted in patients with eclampsia enrolling a total 2558 patients. Eclampsia has a similar prevalence to PAVTE (0.03 to 0.7% prevalence depending on the country and economic setting), but it is associated rate of events close to 10%.

Even though successful RCTs have been conducted in pregnant patients for conditions with similar prevalence of the disease or expected number of outcomes; recruiting pregnant patients for randomised controlled trials, especially for studies for the prevention of PAVTE, appears to be challenging (164). The use of injectable medications, and the hassles associated with the treatment, for the duration of pregnancy or for long periods of time during pregnancy appears to discourage patients to participate. In

our study the use of a double blind design would expose all patients to twice daily injections and multiple anti-Xa measurements (Assuming that full dose LMWH given twice daily with anti-Xa was the selected comparator). It is understandable that given the discomforts associated with the study patients will be unwilling to participate.

Other specific participant factors associated with low recruitment rate are: 1-Women and parents may overestimate the risks involved in trial participation and overestimate the benefits of untested interventions;2- Potential risks for the baby dominate over potential risks for the mother when deciding to participate; 3-The process of recruiting mothers and babies into trials often impacts the decision to participate; 4-Communication skills of recruiters are important to potential research participants; 5-The timing and method of approach may impact a woman's decision to participate; 6- Practical concerns about the trial medications/treatments; and 7- Women and parents may not understand specific aspects of the trial design such as randomisation, blinding and the use of placebos.

Proposed strategies from the Women and Babies Health and Wellbeing: Action Through Trial workshops(163) to increase recruitment into studies enrolling pregnant patients are:1- provide information that is important to participants (not researchers); 2- use a personalised approach in terms of method and timing of approach and request for consent to participate; 3- make it easy to participate by making trial protocol not too onerous;4- use different methods for reaching participants including pamphlets, telephone and mass media; 5-increase transparency of information provided about treatment and research to help potential participants understand the need for a trial; and 6- Assure potential participants that there will be no compromise in care if they choose not to participate. These recommendations have not yet been validated in prospective studies.

For all the reasons discussed above, it should be concluded that a non-inferiority randomized controlled trial is extremely unlikely to be feasible. Given the significant limitations in achieving the needed

sample size and that an alternative study design to evaluate the safety and efficacy of an intermediate dose of LMWH for the secondary prevention of PAVTE is needed.

2.4 Alternative study design

From the discussion above, it seems that despite the potential multi-center and multi-year nature of study evaluating the efficacy of an intermediate dose of LMWH for the secondary prevention of pregnancy associated VTE, the number of patients forecasted to be eligible and enrolled in a study evaluating the use of an intermediate dose of LMWH for the secondary prevention PAVTE, is clearly insufficient to render a randomized controlled trial feasible. Finally, the cost of such a large trial would also be prohibitive for peer review grant agencies.

Given the anticipated recruitment constraints, the low prevalence of the disease, and low rate of the outcome of interest use an alternative study design to evaluate the proposed intervention was sought.

Alternative study designs include 1) Observational studies or 2) Non-randomized studies.

Observational studies such as cohorts or case-control have been used to assess efficacy of therapeutic strategies(165). By using rigorous methodology observational studies can provide estimates similar to those of randomized controlled trials (126;166;167), although the literature is fraught with cautionary examples supporting the notion that observational studies should be carefully used to assess efficacy [i.e. hormone replacement therapy for the prevention of cardiovascular events in women(168)].

Among the many bias affecting observational studies, confounding by indication has been cited as the most relevant bias(169). Proposed solutions for the use of observational studies assessing efficacy include identifying “zero-time” for patients’ eligibility and status, using specific inclusion and exclusion criteria, adjusting for susceptibility (confounding) factors, using the statistical methods of randomized controlled trials; and analysis using propensity scores, matching or regression(126;168;169). Regression methods use logistic regression models for short-term outcomes or a proportional hazards model for longer term outcomes, using the outcome as a dependent variable.

The type of treatment is used as an independent variable along with factors suspected or known to be related to adverse outcomes(170). Propensity analysis matches patients in an observational study with regard to characteristics that are associated with the choice of treatment. Typically, this is done by developing a logistic regression model that has choice of treatment as a binary dependent variable and the characteristics associated with treatment choice as the independent variables(168;170). Then, subjects with similar probabilities of receiving the same treatment can be identified and directly compared.

The efficacy of an intermediate dose of LMWH for secondary prevention of PAVTE could be evaluated using a simple prospective observational cohort of all patients treated with LMWH for pregnancy associated VTE. In this study design all patients treated would be enrolled using similar inclusion criteria to those used in a randomized controlled study and the results analyzed with a propensity scores to reduce confounding by indication(168).

This alternative could produce a similar effect size to those of randomized controlled trials but the results would be more generalizable given the increased external validity(168). A cohort study may also be used to provide an indirect comparison of multiple treatment strategies to select the best treatment strategy for the secondary prevention of pregnancy associated VTE. Given the wide variation in practice and recommendations for the use of LMWH during secondary prevention of PAVTE(20;33;34;90;93), an observational study would face bias that would be difficult to account for and reduce the validity of the results. For example, some of the potential strategies using LMWH for secondary prevention after the acute treatment period are:

- i. LMWH full dose given once a day monitored by anti-Xa levels
- ii. LMWH full dose given once a day not monitored by anti-Xa levels
- iii. LMWH full dose given twice a day monitored by anti-Xa levels
- iv. LMWH full dose given twice a day not monitored by anti-Xa levels

- v. Intermediate dose LMWH dose given once a day monitored by anti-Xa levels
- vi. Intermediate dose LMWH dose given once a day not monitored by anti-Xa levels
- vii. Intermediate dose LMWH dose given twice a day monitored by anti-Xa levels
- viii. Intermediate dose LMWH dose given twice a day not monitored by anti-Xa levels
- ix. Prophylactic doses after 90 days of treatment with full doses of LMWH.

Finally crossover during secondary prevention is common, as shown by Voke et al(82), and would have a severe impact in the interpretation of the results. Nearly 20% of patients treated with full dose LMWH experienced a change on their dosing strategy (once a day from twice or vice versa) after the initiation of the secondary prevention phase.

In light of all the issues discussed, a non-randomized experimental study could be a more appropriate design for the evaluation of an intermediate dose of LMWH for the secondary prevention of PAVTE. Non randomized studies are usually considered quasi-experimental(126) because they lack randomization. Non randomized studies are frequently used when it is not logistically feasible or not ethical to conduct a randomized controlled trial(171).Quasi-experimental designs are typically represented by three different groups(165): Single arm without control (or using historical data), before and after, and non-randomized concurrent control.

Before and after studies are usually conducted for the evaluation of the quality of medical interventions. With this study design the outcomes are measured before the intervention is implemented and compared with outcomes measured afterward. Accuracy of the estimates are highly dependent on the selection of the prior controls(171;172) and temporal trends(173). Temporal trends are relevant in the assessment of outcomes as many outcomes change over time, regardless of whether an intervention has been applied. Evaluation of temporal trends requires lengthy evaluations of the efficacy of prior care before comparisons with new interventions can be made(173).

Non-randomized concurrent control studies, although sometimes are preferred as they do not require randomization (and increase enrollment rate), also have limitations(171). The main one being unexpected differences between the two study groups making them not comparable. Furthermore, they also require large sample sizes to detect small differences as would be expected in our proposed study. For their discussed limitations both concurrent control studies and before-after studies are not suitable designs for the evaluation of an intermediate dose of LMWH for secondary prevention of pregnancy associated VTE. A single arm study would likely be the appropriate study design

Single arm studies

Single arm (169;174) studies are not commonly used to assess therapeutic interventions, beyond phase II studies in cancer, diseases with a low prevalence or special populations (i.e. children); but they have been widely employed for the evaluation of diagnostic strategies (175-180) and medical devices. They provide relevant clinical information such as the rate of recurrent VTE at 90 days, after a negative diagnostic test without the need for a direct comparison(181) and they have been cited as proof of efficacy for the use of different diagnostic strategies(177;182) in recent clinical guidelines(72;183). The main difference between a single arm study and a cohort is that in the single arm the intention is experimental rather than observational(174;184).

The food and drug administration typically recommends the use of randomized controlled trials; as such studies provide the highest level of clinical evidence and patient comparability. However, in accordance with the “least burdensome” provisions specified in the FDA Modernization Act of 1997(185), data from alternative study designs, such as single-arm studies, provided the data are scientifically sound and free of bias, is now accepted as proof of efficacy.

Single arm studies have been previously used to successfully change the diagnostic management of VTE(176-180) and medical devices(185;186). Single arm adapt principles of randomized controlled trials (187) to the design of observational studies by: determining a patient's eligibility and baseline

features; using inclusion and exclusion criteria; and using similar statistical methods (e.g., intention-to-treat analysis).

The main advantage of single arm studies is that they can reduce the number of participants needed to achieve statistical power by 50% or more, depending on the methodology used for the sample size calculations(188). Sample size is usually based on what is considered “gold standard rate or data from historical controls” and an upper margin using prior reported rates or expert consensus(175-180).

Single arm studies are useful when the following conditions exists(171;189): 1-Without an intervention an effect is not likely to occur.; 2-The effect of the intervention is large;3-No prior study has evaluated the intervention correctly; 4-the population is homogenous; and 5-appropriate patients are rare.

For the proposed study evaluating the use of intermediate dose of LMWH for the secondary prevention of VTE all those conditions are met. First, as shown in figure 1, in non-pregnant patients’ historical data from small placebo controlled studies or studies comparing “least effective strategies”, anticoagulation is effective for the prevention of recurrent VTE. Second, anticoagulation the use of anticoagulation is assumed to results in a significant reduction of severe outcomes such as death of recurrent VTE. Third, to date only two small studies(113;190) have evaluated the intervention. Fourth, it is expected that the population is going to be homogenous. Fifth, the incidence of PAVTE is rare.

2.4.1 Single arm study methodology

In single arm studies the effectiveness of the intervention is compared, in general, against historical data but they are not primarily intended to be comparative(191-193). Nonetheless, they do involve an implicit comparison of the new agent with the standard agent or medical device based on prior data(174;191-193).

The selection of the data supporting the efficacy of the comparator is one of the most critical steps for the design of this type of study(194). Estimations of effects based on low quality historical data or the assumptions of large estimates for the new intervention have been blamed for an over estimation of the

efficacy in phase II single arm studies when posterior phase III randomized controlled trials are conducted(195).

Two approaches have been proposed for the selection of controls:

- i. Non-concurrent controls: the control arm was treated prior to the beginning of the enrollment of patients in the treatment arm or the control arm is constituted by patients in a previously finished study.
- ii. Information about controls is extracted from outside the study via synthesis of previously conducted studies or accumulated clinical experience.

In general the use of non-concurrent controls requires compliance with the Pocock conditions. The Pocock condition(172) states that a concurrent control study can only be conducted if all of the following are met:

- i. *Control group received the precisely defined treatment in a recent study.* As it will be shown in the systematic review and survey this condition would not be met if physicians use multiple strategies for secondary prevention
- ii. *Criteria for eligibility, workup and evaluations must be the same in both groups.* Most of the studies included in the systematic review did not use the same criteria for inclusion, and furthermore, did not use standardized methods for the assessment of the outcome
- iii. *Prognostic factors are completely known and the same in both groups.*
- iv. *No unexplained indications lead one to expect different results.* Patients with PE are more likely to be treated with more aggressive strategies than those with DVT; given the perceived risk in those with PE

- v. *If there are differences in prognostic factors, they are not sufficient to explain any observed difference in outcomes.* Current trends show probable over diagnosis (or treatment of less severe forms of the disease) affecting the prevalence of outcomes.
- vi. The previous study must have been performed largely in the same institution and by the same investigators. The use of controls extracted for the literature is not recommended because, in general, they do not comply with the five prior conditions.

In a single arm study without controls the comparison is usually made using data collected from the patients enrolled into the study and information collected via synthesis of prior studies and/or clinical judgment. A numerical value is currently the most common form for the extracted comparator and has been referred as objective performance criterion (OPC), goal or target value for studies evaluating medical devices and/or diagnostic strategies. It has been recommended that statistical reasoning is applied for the selection of the value although sometimes it can establish by clinical judgment.

The information extracted from the literature, regarding the efficacy of prior interventions, needs to be representative of the target population of the study. Reported limiting factors are: limited availability of high quality historical data, participant variability and assurance of generalizability across time and patient populations(196).

The approach to the selection of controls or the margin to claim efficacy or non-inferiority has varied significantly in the VTE and anticoagulant literature. Some approaches used have been best clinical judgment(182;197), reports of prior studies(198;199) or systematic reviews(177;200) (as shown in table 5). In general studies approaching the determination of the margin using systematic reviews(177;200) required bigger sample size compared to the best clinical judgment (182;197) or historical data (198;199) approach to evaluate the same intervention.

Table 5 Methodology of single arm studies conducted in the field of thrombosis

Author	Setting	Inclusion criteria	Intervention	Participants received same intervention	Calculation of margin and baseline rate	Hypothesis	Outcome	Sample size
Pengo(200)	Stopping warfarin for surgical procedure	Yes	LMWH bridging	No, stratified by risk	Based on systematic review	1% increase in 95% confidence level	Thrombotic event and major bleeding	1262
Kovacs(197)	Stopping warfarin for surgical procedure	Yes	LMWH bridging	Yes	NR	Tight 95% CI for main outcomes	Thrombotic event and major bleeding	200
Malabo(199)	Stopping warfarin for surgical procedure	Yes	LMWH bridging	No, stratified by risk	Prior literature	Bleeding not exceeding a 4.5%	Bleeding; thrombosis	300
Perrier(198)	Suspected PE	Yes	D-dimer/US/CT	Yes	Same margin as prior studies	Not higher than 4%	Objective recurrent VTE	956
Van Belle(177)	Suspected PE	Yes	D-dimer/US/CT	Yes	Systematic review	Upper bound of 95% CI does not exceed 3%	Objective recurrent VTE	3306
Wells(182)	Suspected PE	Yes	D-Dimer/US/VQ scan	Yes	Clinical judgment	95% CI does not exceed 1%	Objective recurrent VTE	930

Typically, the null and alternative hypotheses take the one-sided formulation(188;196):

$$‘H_0: \theta \leq C_0; H_1: \theta > C_0’$$

θ is the parameter of interest associated with the primary endpoint considered. For the purpose of power or sample size calculation, θ is assumed to be C_1 . The values C_0 and C_1 are based on the information extracted from the literature with C_1 representing the expected performance of the intervention and C_0 represents the target value to exclude.

Hypothesis testing is based on the Z distribution, using the following formula(188):

$$Z = \frac{p - \pi}{\sqrt{\pi(1 - \pi)/n}}$$

P corresponds to the observed proportion, π is the hypothesized proportion and n is the number of participants enrolled. Just like the T-test, the Z-test divides the difference between the observed and the

expected proportions by the standard error. In general, it is recommended that the approach is based on a one-sided test(201), although a two sided test could be used when there are expected benefits for the intervention.

Recently, experts(201-203) and the FDA(185)have advocated for the use Objective Performance Criteria (OPC) or Objective Performance Criteria Goals (OPG), against which new interventions can be tested in single arm studies when randomized studies are difficult to conduct (i.e. mechanical valves or medical devices)(186). An OPC/OPG design is design to evaluate a new intervention against a set value based on pre-specified criteria(201). To be granted approval by the FDA, manufacturers of heart valves, have to demonstrate “that the observed rates for the study valve are significantly less than 2 times the OPC”(186) with their new product. In this case the OPC is calculated by rate of systemic embolism for all the valves approved by the FDA. Sample sizes are usually calculated using a one-sided hypothesis test, with an alpha 0.05 and a power of 0.80(186;201;202).

To avoid conducting single arm studies that would not show any benefit, “futility studies” have been proposed(195). In futility studies, the null hypothesis states that the experimental therapy is sufficiently promising, whereas the alternative hypothesis states that the experimental therapy lacks the pre-specified superiority(204), reversing the logic behind the null and alternative hypotheses in the traditional efficacy design. The main advantage of this study design is that the required sample size is reduced by five to ten folds. Three key elements serve to achieve this. 1) The one-sided nature of the hypotheses; 2) larger values of alpha, e.g., 0.10 (1-tailed); and 3) the use of only a single arm(195;204).

2.4.2 Limitations for the use of single arm studies

Single arm studies are not primarily intended to be comparative, but they do involve an implicit comparison of the tested intervention with the standard agent or medical device based on prior published data or clinical judgement/impression. Their main limitation is that in a situation where there

is considerable uncertainty or lack of agreement about the event rates from historical data, the absence of a controlled arm makes the results difficult to interpret.

The results of observational studies, or in this case a single-arm study, do not appear to need confirmation from randomized controlled trials when:

- 1- "All or none" criterion is met(205). For example jumping out of an airplane with a parachute does not require a controlled arm to prove that use of parachutes reduces mortality(206). In our scenario of PAVTE therapy one could assume that full dose LMWH is 100% effective in the reduction of recurrent VTE, but we could hypothetically imagine that it was also associated with a severe side effect (e.g. 50% of fetal malformations). In such a scenario a single arm study could be designed that would have the 90% power with a single sided alpha of 0.25, to exclude an increase 1% in the rate of recurrent VTE, without the need of exposing patients to a risk of fetal malformation. The sample size of such a design would be 381 participants. Most observers and interpreters of this literature would no doubt prefer this study design to an RCT.
- 2- When the effects of the intervention are large(205). Rate ratios > 10 are highly likely to reflect real treatment effects, even if confounding factors are associated, because such extremes are unlikely to occur without the intervention. In 1936, Colebrook et al., (207) proved that treatment with sulphas reduced puerperal mortality by a more than 10% (baseline rate of events was 22%), regardless of the natural trend seen by improving patient care.

Beyond these two extremes situations, the results of observational studies require special attention, and, whenever possible, confirmation in well design randomized studies.

In any experimental or observational study variables apart from the therapy being evaluated, such as characteristics of patients included in the study or natural history of the disease can contribute to outcome even rates. Factors limiting the interpretation of results from single arm studies include the (165;171)Hawthorne effect, regression to the mean, the assumption of a predictable clinical course, selection bias, confounding and increase type I error.

In general, it has been accepted that single arm studies appear to be more susceptible to systematic errors than randomized controlled trials leading to an increase in Type I error rates for studies evaluating interventions(184). Single-arm studies are designed, in general, assuming the historical response rate is a known constant, whereas in practice the response rate is never precisely known (and susceptible to changes over time/setting such as the standard of care or the severity of disease). The use of historical controls appears to produce an overestimation of the effect mostly driven by an overestimation of the outcomes in this group, which is not usually seen in the control arms of randomized controlled studies the number of outcomes in the controlled group appears to be lower. Sacks et al(208), analyzed the results of randomized controlled studies against historical controls in a systematic review conducted in 1981 showing that the use of historical controls lead to an overestimation of the effects (79% of historical controls claim a benefit of the studied intervention vs. a 20% in randomized controlled trials). Recent statistical modeling supported this notion showing that phase II single-arm studies were more likely than phase II randomized controlled studies to incorrectly suggest benefit of interventions that were refuted on phase III studies(209-211). On the other hand, the increase in accuracy from randomized controlled studies was at the expense of sample sizes 2 to four times larger(211). A recent systematic review(212) compared the results of a highly cited(213)randomized controlled trial against a observational studies for the use of patent foramen closure devices, the estimates of observational studies for the efficacy of the device were more profound with observational studies than in. Interestingly, the systematic review showed no differences in the estimates for the efficacy of anticoagulation in observational studies or in the randomized controlled study. This systematic review was limited by the quality of the randomized controlled trial which was underpowered, and stopped early for difficulty in enrollment(212).

The Hawthorne effect suggests that study subjects' behavior or study results are altered by the subjects' awareness that they are being studied or that they received additional attention, especially when

subjects are not blinded to randomization or when they participate in studies with observational components(214).The Hawthorne effect would not be expected in the proposed study population as the outcomes are hard outcomes based on objective criteria and not subjective ones, where the perception of the patient about his improvement could be biased by the simple fact that they are receiving an intervention.

Regression towards the mean occurs whenever we select an extreme group based on one variable and then measure another variable for that group(215). Regression towards the mean is likely to affect studies aimed to show differences in continuous outcomes measured only once. Those with extreme values are more likely to have second results closer to normality affecting the interpretation of results (or falsely claiming benefits).

Presence of a predictable course of the disease is needed to interpret single arm results(165). If there is wide variability in the course of the disease the separation between the effect of the disease treatment and the effect of the intervention is difficult to assess. For the interpretation a single arm study evaluating the effectiveness of the an intermediate dose of LMWH for the secondary prevention of pregnancy associated VTE, the clinical course of the disease would be interpreted from studies evaluating less than effective therapies after a month of treatment with anticoagulation.

Single-arm trials based using data from historical control subjects are also limited by selection bias and confounding(191).

Selection bias refers to the selection of subjects based on certain characteristic that are directly associated with the outcome of interest (i.e. healthy patients are more likely to be treated with surgery and older sicker patients with medical treatment, falsely leading to the assumption that patient who have received surgery have better outcomes). Similarly to observational studies the use of regression or propensity scores has been proposed to adjust for bias in single arm studies(203). Another strategy to limit selection bias is known as ‘weighted margin’(191;201). The idea of weighted approach is to express C_0 as the weighted average of two other constants, (C_{01} and C_{02}), representing two mutually

exclusive patient populations. The weights w_1 and w_2 are the proportion of patients enrolled in the two treatment groups, and the margin is analyzed based on a different proportion for the two groups. The problem with the above approach is that it would result in an inappropriate formulation of the null and the alternative hypotheses(191); and that if the value is not defined a priori would not provide sufficient protection for bias in patient enrolment.

Confounding refers to the phenomenon that current study participants may have a different (better or worse) outcome than historical control subjects because of factors not related to the intervention. For example data from studies of patients with PE has suggested that the introduction of CT scanners has led to an apparent reduction in mortality secondary to an over diagnosis of the diseases. Confounding could lead to believe that the studied intervention is associated to be associated with better outcomes, when most likely these were influenced by changes in diagnostic techniques.

In conclusion, well design randomized controlled trials provide the best quality of evidence for the comparison of treatment strategies. Single arm studies could be used to evaluate therapeutic intervention with the need of a lower sample size when randomized controlled studies are unfeasible or unethical. Researchers should be aware of the limitations of the limitation of the study design and ensure that they base their assumptions on the best quality of evidence possible and plan strategies to reduce bias.

3.0 OVERALL AIMS OF THE THESIS

Based on the prior discussion a single arm study appears to be the appropriate study design to evaluate the effectiveness of an intermediate dose of LMWH for the secondary prevention of pregnancy associated VTE. Prior to initiating a single arm study, several factors needed to be determined: 1) an accurate estimate of the main outcome event rate and $-\Delta$; 2) an accurate estimate of sample size needed; and 3) evaluation of study feasibility (enrollment rate).

THESIS OBJECTIVES

- i. Calculation of the rate of recurrent VTE during secondary prevention of pregnant patients treated with full dose LMWH for VTE-Systematic review of the existing literature
 - a. Determine the rate of recurrent VTE events (and 95% CI) during secondary prevention of PAVTE in patients treated with full dose LWMH
 - b. Determine the rate of major bleeding events (and 95% CI) during secondary prevention of PAVTE in patients treated with full dose LWMH
- ii. Calculation of the non-inferiority margin - Survey
 - a. Main objective: Elicitation of $-\Delta$ to assess efficacy
 - b. Secondary objectives: Evaluation of the clinical equipoise, current practices and potential participation in the study
- iii. Design of a Pilot study-The aim of a pilot study is to collect all the necessary clinical and epidemiological information prior to embarking on a full multi-center study. The pilot study will address potential issues that could arise during the main cohort study. The objectives of the pilot are:
 - a. Main objective:
 - b. Obtain a precise estimate of the potential recruitment rate per participating center
 - c. Secondary objectives:

- d. Obtain precise estimates of the primary outcome event rate for the main study (recurrent VTE) and safety outcome (major bleeding)
- e. Estimate the percentage of eligible candidates to enroll
- f. Estimate the percentage of patients who will complete follow up

4.0 Systematic review

4.1 Rationale for the systematic review

As discussed above four systematic reviews have evaluated the efficacy of LMWH for the management of PAVTE (21;74;85;117). Two of them included studies conducted up to 2005 (21;74) and one included those up to 2009 (117). Three of them evaluated the efficacy of LMWH alone (74;117). Two of them concluded that the quality of evidence was low to provide an accurate estimate of the efficacy of LMWH (one aimed to include only randomized controlled trials) (21;85;117). Greer et al. (74) provided an estimate of recurrent VTE of 1.15% with an upper bound of 4.1% pooling estimates from studies including three different strategies (full, intermediate and prophylactic). Furthermore, their estimates were calculated from observational studies including case reports, and the data from one of the studies included could have been misinterpreted as not all the recurrent VTE were included (74).

In light of the aforementioned limitations, it was sought to conduct an updated systematic review and meta-analysis with individual estimates of efficacy and safety of full, intermediate and prophylactic doses of LMWH. The objective was to provide the best estimate of effectiveness for different treatment strategies used for secondary prevention of pregnancy associated VTE.

4.2 PICOS Question

Populations: Pregnant patients diagnosed with acute PAVTE

Intervention: Treatment strategies with LMWH or UFH

Comparator: Treatment strategies with LMWH or UFH

Main Outcomes: Recurrent VTE and major bleeding

Studies: Interventional studies and/or observational studies (case reports or series were excluded)

The main goal of the systematic review was to calculate the rate of recurrent VTE during secondary prevention (after 30 days of treatment) of pregnancy associated VTE. Event rates were calculated, if

possible, according to the drug chosen for initial treatment (LMWH vs. UFH), duration of initial treatment, dosing (once a day vs. twice a day), dose reduction (full dose vs. intermediate dose vs. prophylactic dose) and monitoring of anti-Xa levels.

Major bleeding (ante-partum or post-partum) was evaluated as the main safety outcome according to the drug chosen for initial treatment (LMWH vs. UFH), duration of initial treatment, dosing (once a day vs. twice a day), dose reduction (full dose vs. intermediate dose vs. prophylactic dose) and monitoring of anti-Xa levels.

Secondary outcomes included: incidence of maternal death, heparin induced thrombocytopenia, heparin induced osteoporosis, fetal malformation, and miscarriage or stillbirth.

4.3 Methods

4.3.1 Literature Search

A systematic review of electronic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE was conducted to assess the efficacy, safety and current dosing regimens of LMWH or UFH used for the treatment of VTE in pregnant patients. The search was supplemented by hand search of relevant articles, abstract books from international meetings and published reviews.

Studies were included if they reported the use of heparin for the treatment of PAVTE and included more than four cases. Studies in English, French and Spanish were included and screened by the investigators personally; authors of relevant publications in other languages were contacted in an effort to retrieve all the relevant data. The search was not limited by age groups. The timeframe of the search was from Jan 1980 to March 2011.

The search was designed in conjunction with Alexandra Davis from the library services at the Ottawa Hospital. Complete references of all articles were collected into a RefWorks database and duplicates were removed using RefWorks software.

4.3.1.1 Literature search strategy

Medline

1 heparin, low-molecular-weight/ or (LMWH\$ or lmwh).tw.
2 dalteparin/ or (dalteparin or fragmin).af.
3 enoxaparin/ or (enoxaparin or lovenox or clexane).af.
4 nadroparin/ or (nadroparin or fraxiparine).af.
5 (fondaparinux or arixtra or tinzaparin or innohep or ardeparin or normiflo or reviparin or bemiparin).af.
6 or/1-5
7 Venous Thrombosis/ or VTE/ or vte.tw.
8 Thromboembolism/ or (thromboembolism or thromboembolic or thromboprophylaxis).tw.
9 (deep vein thrombosis\$ or deep venous thrombosis\$ or data).tw.
10 Pulmonary Embolism/ or pulmonary emboli\$.tw.
11 or/7-10
12 exp Pregnancy/ or (pregnancy or pregnant or gestation).tw.
13 (childbirth or child birth).tw.
14 pregnancy outcome/
15 Pregnancy Complications, Cardiovascular/
16 or/12-15
17 6 and 11 and 16
18 Epidemiologic studies/
19 exp case control studies/ or exp cohort studies/
20 case reports.pt.
21 Case control.tw
22 (cohort adj (study or studies)).tw
23 Cohort analy\$.tw.
24 (Follow up adj (study or studies)).tw.
25 (observational adj (study or studies)).tw.
26 (Longitudinal or retrospective or cross sectional).tw.
27 Cross-sectional studies/
28 randomized controlled trial.pt.
29 controlled clinical trial.pt
30 randomized.ab.
31 placebo.ab.
32 clinical trials as topic.sh.

33 randomly.ab.
34 trial.ti
35 (systematic adj1 (review\$ or overview)).tw.
36 or/18-35
37 17 and 36
38 limit 37 to yr="1980 - Current"
EMBASE <1980 to 2011 Week 12>
1 LMWH/ or (LMWH\$ or lmwh).tw.
2 (dalteparin or fragmin or enoxaparin or lovenox or clexane or nadroparin or fraxiparine or fondaparinux or tinzaparin or ardeparin or reviparin or bemiparin).af.
3 1 or 2
4 vein thrombosis/ or VTE/ or vte.tw.
5 deep vein thrombosis/ or (vein thrombos\$ or venous thrombos\$ or dvt).tw.
6 lung embolism/ or pulmonary emboli\$.tw.
7 thromboembolism/ or (thromboembolism or thromboembolic or thromboprophylaxis).tw.
8 or/4-7
9 exp pregnancy/
10 (pregnancy or pregnant or gestation).tw.
11 childbirth/ or (childbirth or child birth).tw.
12 pregnancy outcome/
13 pregnancy complication/
14 or/9-13
15 3 and 8 and 14
16 Clinical study/
17 case control study/
18 family study/
19 Longitudinal study/
20 Retrospective study/
21 Prospective study/
22 Cohort analysis/
23 (Cohort adj (study or studies)).mp.
24 (Case control adj (study or studies)).tw.
25 (follow up adj (study or studies)).tw.
26 (epidemiologic\$ adj (study or studies)).tw.

27 (cross sectional adj (study or studies)).tw.
28 case report/
29 random\$.tw.
30 placebo\$.mp.
31 double-blind\$.tw.
32 clinical trial\$.tw.
33 Randomized controlled trial/
34 Randomization/
35 exp Meta Analysis/
36 ((metaadjanaly\$) or metaanalys\$.tw.
37 (systematic adj1 (review\$ or overview\$)).tw.
38 search\$.tw.
39 or/16-38
40 15 and 39
41 limit 41 to yr="1980 - Current"
42 from 41 keep 1-506 (506)

Cochrane Database of Systematic Reviews 2005 to March 2011 Database: CCTR, CDSR, DARE

1 heparin, low-molecular-weight/ or (LMWH\$ or lmwh).tw.
2 dalteparin/ or (dalteparin or fragmin).af.
3 enoxaparin/ or (enoxaparin or lovenox or clexane).af.
4 nadroparin/ or (nadroparin or fraxiparine).af.
5 (tinzaparin or innohep or ardeparin or normiflo or reviparin or bemiparin).af.
6 or/1-5
7 Venous Thrombosis/ or VTE/ or vte.tw. (763)
8 Thromboembolism/ or (thromboembolism or thromboembolic or thromboprophylaxis).tw.
9 (vein thrombos\$ or venous thrombos\$ or dvt).tw.
10 Pulmonary Embolism/ or pulmonary emboli\$.tw.
11 or/7-10
12 exp Pregnancy/ or (pregnancy or pregnant or gestation).tw.
13 (childbirth or child birth).tw.
14 pregnancy outcome/
15 Pregnancy Complications, Cardiovascular/
16 or/124

4.3.2 Study Selection

All abstracts were screened using a standardized data collection form to aid the literature search. All potentially relevant articles were reviewed in full length to ensure that they satisfied 5 criteria: 1) enrollment of pregnant patients with symptomatic DVT or PE; 2) qualifying recurrent events were symptomatic and objectively confirmed; 3) patients received initial treatment for at least 5 days with UFH (intravenous, adjusted-dose, or weight-based subcutaneous) or LMWH (intravenous or weight-based subcutaneous); 4) patients received treatment until delivery; and 5) the primary efficacy outcome was reported.

Studies were excluded if they included patients treated with IVC filters, thrombolytic drugs and/or interventional procedures, such as surgery or catheter fragmentation/extraction, for the treatment of pregnancy associated DVT or PE. Patients who developed PAVTE during the post-partum period were also excluded from the analysis.

4.3.3 Outcome Measures

The primary outcome measure was recurrent VTE. This primary outcome was evaluated according to the treatment strategy used for secondary VTE prevention (i.e. full, intermediate or prophylactic; given once a day or twice a day; and with or without anti-Xa monitoring). Recurrent VTE was defined, whenever possible, as a new perfusion defect in a ventilation–perfusion scan, a new intra-luminal filling defect detected on computed tomography, ultrasound or venography; or a high clinical suspicion of fatal PE, as defined by the investigators of the individual studies.

The following were the definitions for the outcomes of interest:

A. Fatal recurrent VTE and all-cause mortality

Cause of death classified as being due to PE, or as sudden death or unexplained sudden cardio-respiratory deterioration.

B. Recurrent DVT

- i. Compression ultrasound revealing a new area of non-compressibility of a venous segment above the trifurcation of the popliteal vein was considered diagnostic of a recurrent DVT.
- ii. Venography demonstrating a new intraluminal filling defects in the DVT above the trifurcation of the popliteal vein.

C. Recurrent PE

- i. V/Q scan showed a new mismatched segmental or greater perfusion defect.
- ii. Spiral CT demonstrated a new intraluminal-filling defect in a segmental or greater
- iii. Pulmonary angiography demonstrating a new intraluminal filling defect or a cutoff of a vessel > 2.5 mm in diameter.
- iv. New PE found at autopsy was considered diagnostic of recurrent VTE.

D. Major bleeding

- i. Major bleeding was the primary safety outcome and was defined as symptomatic intracranial hemorrhage, a retroperitoneal hemorrhage, an intraocular hemorrhage leading to significant vision loss, a decrease in hemoglobin of at least 3.0 g/dL [with each blood transfusion unit counting for 1.0 g/dL of Hbg], bleeding requiring transfusion of two or more units of red blood cells or equivalent of whole blood(216), clinically overt bleeding that is fatal or as defined as major bleeding by the study investigator. Bleeding was categorized as:
 - a. Ante-partum: Occurring after the initiation of treatment with heparin and until delivery
 - b. Post-partum: Any major bleeding occurring after delivery and classified by the study investigator as associated with anticoagulation; traditionally defined as a blood loss greater than 500cc in patients who delivered vaginally, and greater

than 1000cc in patients who underwent C-section(217)

E. Heparin Induced Thrombocytopenia

- i. All patients who developed non-mild thrombocytopenia (platelets less than 115 or 50% decrease from baseline) and confirmatory assays suggestive of heparin induced thrombocytopenia; AND
- ii. An alternative anticoagulant was commenced as per standard of care (e.g. danaparoid or lepirudin)

F. Osteoporotic Fractures

A bone fracture associated with the use of LMWH, as determined by the study investigator

G. Miscarriage or stillbirth

- i. Miscarriage was defined as the loss of an embryo or fetus before the 20th week of pregnancy and associated with the use of LMWH, as determined by the study investigator.
- ii. Stillbirth was defined as the delivery of a fetus that has died before birth after 20 weeks of pregnancy and associated with the use of LMWH, as determined by the study investigator.

H. Fetal malformation

A physical defect present in a baby at birth that is permanent and determined by the study investigator to be associated with LMWH treatment.

4.3.4 Data Extraction and Quality Assessment

Two reviewers (MC and EG) independently assessed the eligibility of all the articles identified in the initial search strategy for inclusion in the study. The review was conducted using a standardized data collection form to independently extract data. A third reviewer adjudicated all discrepancies (MR).

The methodological quality of the studies was assessed according to the type of study: 1) using the

Risk of Bias Assessment Tool from the Cochrane Handbook for randomized trials(218); 2) and/or the Newcastle–Ottawa Quality Assessment scale(219) for observational studies.

4.3.5 Data Synthesis and Analysis

To estimate the weighted rates and 95% CIs for the review's primary outcomes, individual study estimates were converted to rates. The rates were transformed using the Freeman–Tukey arcsine square root transformation before pooling the case-recurrent rates (220). DerSimonian–Laird random-effects models were used to pool the transformed rates whenever possible (221-223), unless stated otherwise, because they incorporate an estimate of the between-study variance in the calculations and they tend to give wider, more conservative, confidence intervals than fixed effects. After pooling the resulting estimates and their 95% CIs, limits were back-transformed to pooled proportions. Outcomes were allocated according to the intention-to-treat principle. Sensitivity analysis was planned in advance based on study characteristics: prospective vs. retrospective, DVT vs. PE, and type of provoking factor. Given the expected difference in the duration of treatment after pooling the resulting estimates and their 95% CIs limits and if possible to back-transform the rates per patient-month of follow-up. If outcomes could only be calculated as proportions, the pooled proportion was calculated as the back-transformation of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian-Laird (1986) weights for the random effects model. Transformation of proportions into a quantity using the Freeman-Tukey variant of the arcsine square root method is suitable for the usual fixed and random effects summaries(221-223). A Q test was used to address for heterogeneity with a significance set at $p < 0.05$ and the I^2 statistic was used to quantify heterogeneity among the pooled estimates across studies(224). An I^2 value less than 25% was considered low-level heterogeneity, 25% to 50% as moderate-level, and greater than 50% as high-level(225). Publication bias (226) was only addressed for analysis including more than 10 studies using the method of Egger.

4.4 Results

The initial search identified 1047 articles in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE, after duplications were excluded from each database. Four extra studies were identified outside the literature search. One study was retrieved from the American Society of Haematology Abstract book(227), the second was suggested by an author contacted to retrieve information(228), the third by one of my thesis supervisors (MR)(229), and the fourth was identified from a narrative review(34).

Of the 1051 potentially relevant articles identified by our search, 50 were retrieved for full text analysis. Of the studies retrieved in full text, 22 were excluded. Of those excluded after full text review, two were duplicates or updates of prior studies(190;230), five reported on less than four patients(231-235), data could not be extracted in four studies(236-239), one excluded pregnancies(240), four were reports on primary prophylaxis(122;241-243), two were deemed not relevant(244;245), two included patients who were surgically treated(246;247), one full text was reported as abstract(248), and one was a long term follow up(249).Seven authors were contacted by electronic mail (82;229;230;250-253) to retrieve additional information. Four of the authors provided further information on drugs and major outcomes (recurrent VTE and bleeding). One author did not respond and two initially agreed to provide information but did not respond to further communications. In Table 6 the characteristics of the studies included in the systematic review is presented

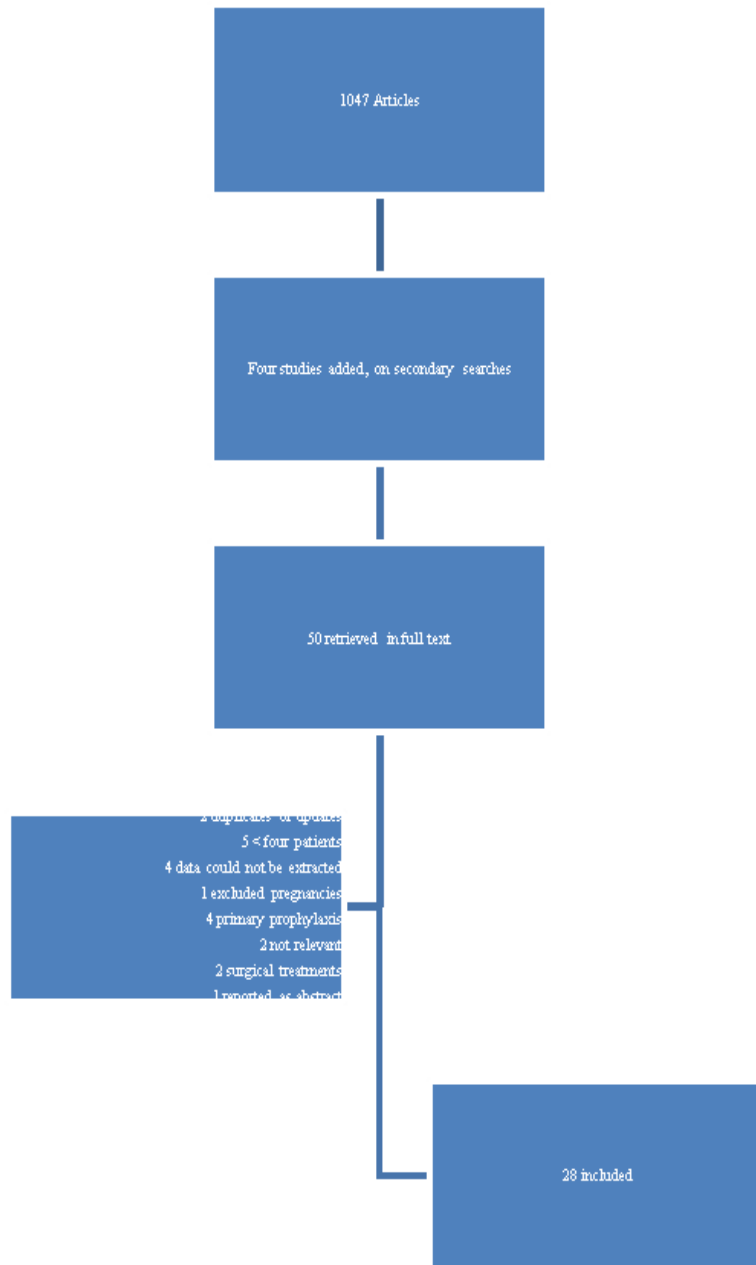


Figure 1 Flow diagram

Table 6 Characteristics of the studies included

Author	Year	Type	Prospective	Country	Centers		Inclusion criteria	Mean age	Prior VTE (%)	Thrombophilia (%)
					(N)	(N)				
Aburahma	1995	Cohort	Yes	USA	1	15	Objectively diagnosed VTE	NR	NR	NR
Andersen	2010	Cohort	No	Denmark	1	6	Any use of LMWH	NR	NR	NR
Bergqvist	1983	Cohort	Yes	Sweden	1	16	NR	26	NR	NR
Blanco-Molina	2010	Registry	Yes	NR	NR	173	Objectively diagnosed VTE	30	5.6	24
Clark	2009	Cohort	No	US	1	15	Any treatment with Heparin	NR	NR	NR
Daskalakis	1997	Cohort	NR	Greece	1	18	Objectively diagnosed DVT	NR	30	22
Deiter	1985	Cohort	Yes	USA	1	4	Objectively diagnosed DVT	NR	NR	NR
Deruelle	2006	Cohort	No	France	1	7	Treatment with LMWH			
Dulitzki	1996	Cohort	No	Israel	1	6	Use of Enoxaparin	NR	NR	NR
Ellison	2000	Cohort	No	UK	1	10	Use of Enoxaparin	NR	NR	33
Fionnuala	2008	Cohort	No	Ireland	2	26	Use of full dose Tinzaparin	NR	NR	NR
Ginsberg	1989	Cohort	No	Canada	1	43	Treatment with UFH	NR	NR	NR
Jacobsen	2003	Cohort	Yes	Norway	NR	20	Objectively diagnosed VTE	31	10	40
Knight	2008	Case Control	NA	UK	NR	134	Objectively diagnosed PE	NR	4	4
Lepercq	2001	Cohort	No	France	55	49	Any use of LMWH	NR	NR	NR
Lykke	2008	Cohort	No	Denmark	1	22	Objectively diagnosed DVT, managed with Tinzaparin	30	NR	NR
Malcom	2002	Cohort	No	Canada	1	23	Objectively diagnosed VTE	30	42	NR
Mitic	2010	Cohort	Yes	Serbia	2	72	Objectively diagnosed VTE	NR	NR	62.5
Myers	2008	Cohort	No	UK	1	42	Objectively diagnosed VTE	NR	14	24
Narin	2008	Cohort	Yes	Turkey	1	35	Objectively diagnosed VTE	29	9	18
Nelson-Piercy	2011	Registry	No	Multiple	28	254	Confirmed use of Tinzaparin	30.1	14.2	12.6
O'Connor	2011	Cohort	No	US	2	34	Objectively diagnosed VTE	NR	NR	NR
Rey	2000	Cohort	Yes	Canada	2	5	Use of Dalteparin	29	NR	NR
Rodie	2002	Cohort	Yes	UK	3	21	Objectively diagnosed VTE	NR	NR	NR
Rowan	2002	Registry	Yes	New Zealand	1	13	Use of Enoxaparin	NR	NR	NR
Smith	2004	Cohort	Yes	UK	NR	12	Complex	NR	NR	NR
Ulander	2002	Cohort	Yes	Finland	1	35	Acute DVT	31	1	20
Voke	2007	Survey	No	UK and Ireland	25	134	Complete survey report	32	12	18

NR not reported; NA not applicable

Table 7 Quality assessment by the Newcastle-Ottawa scale

Author	Representative cohort	Ascertainment of exposure	Outcome of was not present at start of study	Assessment of outcome	Was follow-up long enough	Adequate Follow up
Aburahma	*	*			*	*
Andersen				*	*	*
Bergqvist	*		*		*	*
Blanco-Molina	*	*	*	*	*	*
Clark		*			*	*
Daskalakis	*	*	*		*	*
Deiter	*	*			*	*
Deruelle	*				*	*
Dulitzki	*		*		*	*
Ellison	*				*	*
Fionnuala					*	*
Ginsberg		*		*	*	*
Jacobsen	*	*	*		*	*
Knight	*	*			*	*
Leperc				*	*	*
Lykke	*	*			*	*
Malcom	*	*			*	*
Mitic	*		*		*	*
Myers	*	*			*	*
Nelson-Piercy		*		*	*	*
O'Connor	*	*			*	*
Rey	*		*		*	*
Rodie	*	*	*		*	*
Rowan			*		*	*
Smith	*	*	*		*	*
Ulander	*	*	*		*	*
Voke	*	*	*		*	*

4.4.1 Quality

None of the studies included was a randomized controlled trial. Three studies were surveys(82), one was a case-control(81), one a registry(254), and twenty three were cohorts(82;100;114;115;250-253;255-269). Thirteen of the cohort studies were conducted prospectively. Fourteen of the studies included were conducted exclusively in patients with an objective diagnosis of VTE(46;82;115;154;250;251;253;255-257;263-265;267;269;270)while the rest were conducted in patients who were exposed to heparin for the treatment of VTE or prophylaxis. One study enrolled patients with PE alone (46), and six included only patients with DVT(100;115;232;255;257;264;269). Two studies did not report on the drug used for treatment (253;254). Quality of analysis is presented on Table 7.

4.4.2 Treatment strategies

The studies included 1107 patients who were treated with LMWH(46;82;100;114;115;154;227;232;250;251;253;256;258-261;263-270)and 115 patients treated who were treated with UFH(251;252;255;257;262;270;271).

Three main strategies were used for secondary prevention: Full dose (46;82;154;227;232;251;253;256;258;260;261;263;264;266;267;270), intermediate dose (100;115;250;258;259;265;269) and prophylactic doses (268;272). Low molecular weight heparin strategies varied significantly with respect to dosing (BID vs. OD), dose used for secondary prevention, and anti-Xa level monitoring. Six studies used intermediate doses after the acute initial period(100;115;250;258;259;265;269) and two studies used fix prophylactic doses(268;272) .

In patients treated with UFH one study used prophylactic doses (273) and one used intermediate doses(257). In all studies using full dose or intermediate doses, anti-Xa monitoring was also used. Table 8 describes the different strategies used, a summary of events for each study separated by LMWH or UFH are presented in Tables9 and 10; and Table 11 presents a summary of the analysis.

Table 8 Treatment strategies

Author	Initial Treatment	Route	Dosing	Duration (days)	Secondary prophylaxis	Dose	Route	Dosing	Monitoring %
Aburahma	UFH	IV/SC	Continuous/BID	90	UFH	Prophylactic	SC	BID	No
Andersen	NR	NR	NR	NR	NR	NR	NR	NR	No
Bergqvist	UFH	IV	QID	<7	UFH	Full	SC	BID	No
Blanco-Molina*	Any LMWH/UFH	NR	NR	NA	LMWH*	NR	NR	NR	NR
Clark	UFH	SC	IV/SC	NA	UFH	Full	SC	BID	No
Daskalakis	Calciparine	SC	BID	14	Nadroparin	Intermediate	SC	OD	No
Deiter	UFH	IV	QID	NR	UFH	Intermediate	IV	4 times	Yes
Deruelle	Enoxaparin, Dalteparin, Nadroparin Tinzaparin	SC	OD/BID	30	Enoxaparin/Dalteparin, / Nadroparin/Tinzaparin	Full /Intermediate	SC	OD	No
Dulitzki	Enoxaparin	SC	NR	NR	Enoxaparin	Intermediate	NR	NR	NR
Ellison	Enoxaparin	SC	BID	NA	Enoxaparin	Full	NR	NR	Yes
Fionnuala	Tinzaparin	SC	OD	NA	Tinzaparin	Full	SC	OD	Yes
Ginsberg	UFH	IV	NA	<14	UFH	Full	SC	BID	Yes
Jacobsen	Dalteparin	SC	BID	NA	Dalteparin	Full	SC	BID	Yes
Knight	Enoxaparin/Dalteparin /Tinzaparin	SC	OD /BID	NA	NR	Full	NR	NR	NR
Lepercq	Enoxaparin	SC	BID	84	Enoxaparin	Prophylactic	SC	OD	NR
Lykke	Tinzaparin	SC	OD/BID	NA	Tinzaparin	High	SC	OD /BID	Yes
Malcom	Dalteparin/UFH/ Tinzaparin	SC/IV	OD/BID/continuous	NA	Dalteparin/UFH/ Tinzaparin	Full	SC	OD/BID	Yes
Mitic	Nadroparin/UFH	SC/IV	BID/continuous	<42	Nadroparin	Intermediate	SC	BID	No
Myers	Enoxaparin/Dalteparin /Tinzaparin	SC	OD/BID	90	Enoxaparin/Dalteparin / Tinzaparin	Intermediate	SC	OD	Yes
Narin	Enoxaparin	SC	OD/BID	NA	Enoxaparin	Full	SC	OD/BID	Yes
Nelson-Piercy	Tinzaparin	SC	OD	NA	Tinzaparin	Full	SC	OD	NR
O'Connor	Enoxaparin/Dalteparin /UFH	SC	NR	NA	Enoxaparin/Dalteparin /UFH	Full	SC	NR	No
Rey	UFH	IV	Continuous	3	Dalteparin	Full	SC	BID	No
Rodie	Enoxaparin	SC	BID	NA	Enoxaparin	Full	SC	BID	Yes
Rowan	Enoxaparin	SC	BID	90	Enoxaparin	Prophylactic	SC	OD	No
Smith	Tinzaparin	SC	OD	42	Tinzaparin	Intermediate	SC	OD	Yes
Ulander	UFH/Dalteparin	IV/SC	Continuous/BID	7	Dalteparin	Intermediate	SC	OD	Yes
Voke	Enoxaparin/Dalteparin /Tinzaparin	SC	OD/BID	NA	Enoxaparin/Dalteparin / Tinzaparin	Full	SC	OD/BID	Yes

* 10% of the patients were on Warfarin; NR not reported; NA not applicable

Table 9 Outcomes of patients treated with LMWH

Author	Sample	Dose	Monitoring %	Recurrent VTE	Major bleeding	Ante-partum bleeding	Post-partum bleeding	HIT	Osteoporosis	Fetal malformation	Miscarriage/ stillbirth
Andersen	6	Full	No	0	0	0	NR	0	0	0	NR
Blanco-Molina	154	Full	NR	2	1	NR	NR	0	NR	NR	NR
Daskalakis	18	Intermediate dose	NO	0	0	0	0	0	nr	0	1
Deruelle	7	Full/Intermediate	No	0	0	0	0	0	NR	0	NR
Dulitzki	6	Intermediate dose	No	0	0	0	0	0	0	0	0
Ellison	9	Full	Yes	0	1	1	NR	0	0	0	0
Ainle	26	Full	Yes	0	3	0	3	0	0	0	0
Jacobsen	20	Full	Yes	0	0	0	0	0	0	0	1
Knight	131	Full	NR	3	0	0	0	0	0	0	1
Lepercq	49	Prophylactic	NR	4	1	1	NR	0	0	0	0
Lykke	22	Full	Yes	0	0	0	0	NR	NR	NR	NR
Malcom	11	Full	NR	1	0	0	0	0	NR	0	0
Mitic	72	Intermediate dose	No	0	0	0	0	0	NR	0	1
Myers	53	Intermediate dose	Yes	0	1	0	1	0	NR	NR	NR
Narin	35	Full	Yes	0	2	2	0	0	0	0	0
Nelson-Piercy	254	Full	NR	2	3	0	3	0	0	NR	2
O'Connor	23	Full	No	0	NR	NR	NR	NR	NR	NR	NR
Rey	5	Full	No	0	0	0	0	0	0	0	0
Rodie	29	Full	Yes	0	1	0	1	0	0	0	0
Rowan	13	Prophylactic	No	0	0	0	0	0	0	0	0
Smith	12	Intermediate dose	Yes	0	NR	NR	NR	0	NR	0	0
Ulander	35	Intermediate dose	Yes	1	3	0	3	0	0	0	1
Voke	119	Full	Yes	0	3	0	3	0	0	1	4

NR not reported; NA not applicable

Table 10 Outcomes of patients treated with UFH

Author	Sample	Dose	Monitoring %	Recurrent VTE	Major bleeding	Ante-partum bleeding	Post-partum bleeding	HIT	Osteoporosis	Fetal malformation	Miscarriage/ stillbirth
Aburahma	15	Prophylactic	No	2	1	1	NR	NR	NR	0	0
Deiter	4	Intermediate	Yes	0	0	0	0	0	NR	0	0
O'Connor	11	Full	Yes	0	NR	NR	NR	NR	NR	NR	NR
Malcom	12	Full	Yes	1	0	0	0	0	NR	0	1
Ginsberg	43	Full	Yes	0	NR	NR	NR	NR	0	0	3
Clark	14	Full	Yes	0	0	0	0	0	NR	0	0
Bergqvist	16	Full	No	0	1	1	0	NR	NR	0	1

Recurrent VTE during the acute treatment period (<30 days) with LMWH or UFH

The pooled proportion of recurrent VTE during the acute treatment period (less than 30 days after the initiation of treatment) was 0.007 (95% CI = 0.003 to 0.01; I^2 0%) for those treated with LMWH and 0.02 (95% CI = 0.004 to 0.05; I^2 0%) in those treated with UFH.

Full dose LMWH or UFH for secondary prevention

Eight hundred and forty four patients were treated with full dose LMWH(46;82;154;227;232;251;253;256;258;260;261;263;264;266;267;270) and 96 with full dose UFH (251;252;262;270;271). The pooled proportion of recurrent VTE in patients treated with full dose LMWH during secondary prevention was 0.012 (95% CI = 0.006 to 0.02; I^2 0%), as shown in Figure 3, while the pooled proportion of recurrent VTE in patients treated with full dose UFH was 0.017 (95% CI = 0.001 to 0.05; I^2 0%).

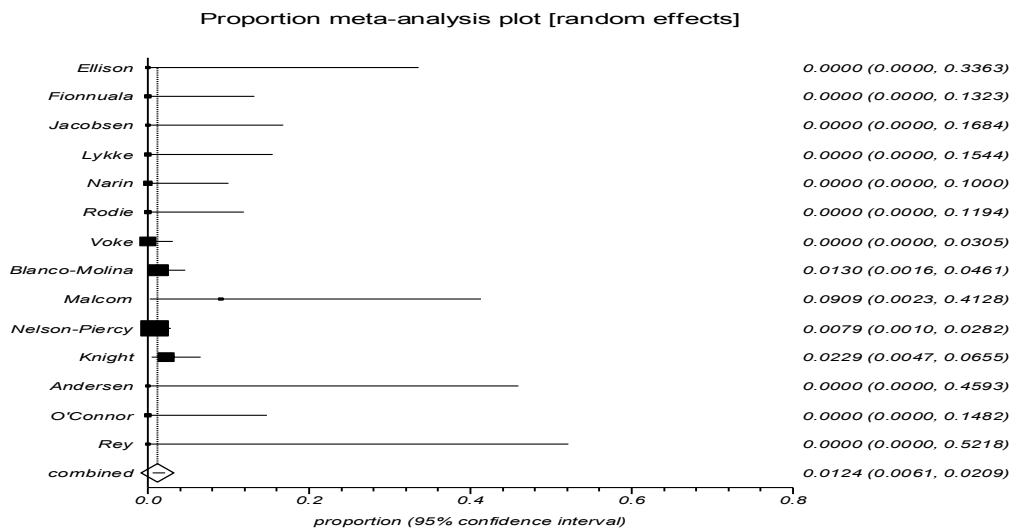


Figure 2 Recurrent VTE in patients treated with full doses of LMWH

The pooled proportion of major bleeding during the ante-partum or post-partum period was 0.026 (95% CI = 0.011 to 0.047; I^2 37%) for patients treated with full dose LMWH, as shown in Figure 4, and 0.038 (95% CI = 0.002 to 0.11; I^2 0%) for those treated with full dose UFH. Only two studies

(270;274), including 26 patients, reported the specific rate of ante or post-partum bleeding in patients treated with UFH. Neither study reported bleeding complications.

The pooled proportion of ante-partum bleeding was 0.006 (95% CI = 0.001 to 0.01; I^2 18%) for patients treated with full dose LMWH vs. 0.038 (95% CI = 0.002 to 0.11; I^2 0%) for those treated with UFH.

In studies reporting the pooled proportion of post-partum bleeding for patients treated with full dose LMWH, the pooled proportion was 0.017 (95% CI = 0.007 to 0.03; I^2 4%) vs. 0.016 (95% CI = 0.000 to 0.07; I^2 0%) for those treated with UFH.

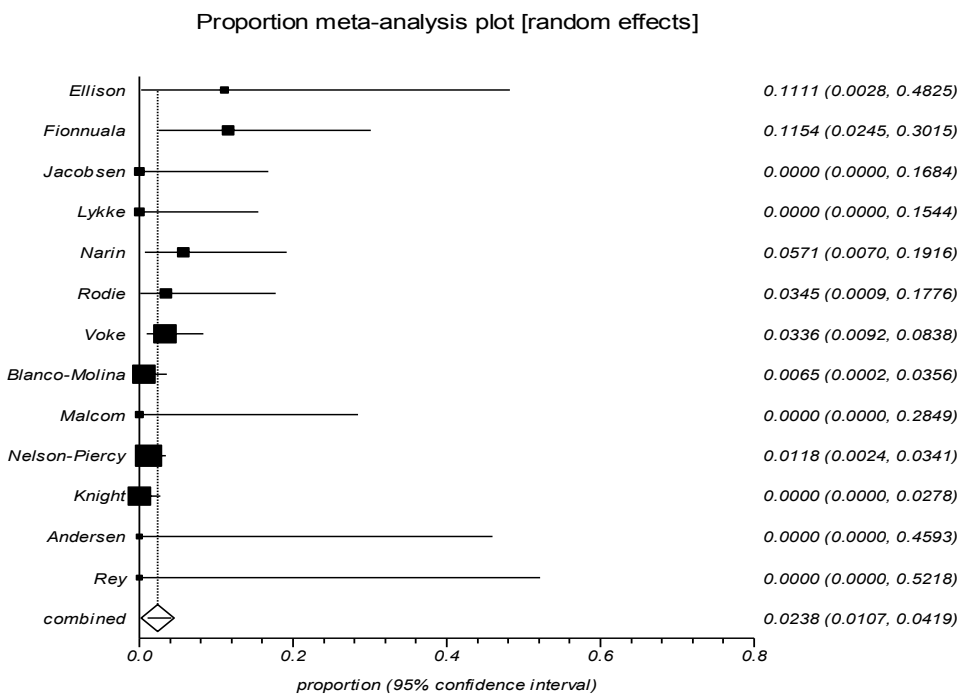


Figure 3 Major bleeding patients treated with full doses of LMWH

Seven studies reported outcomes for patients treated specifically with full dose LMWH with anti-Xa monitoring(82;154;232;260;261;263;264;267;270), and three(251;253;266) reported the outcomes of full dose treatment without monitoring. No patients experienced recurrent VTE in either group (0 out 260 and 0 out 19, respectively). The pooled proportion of recurrent VTE in those who were monitored was 0.005 (95% CI = 0.0002 to 0.02; I^2 0%).In patients treated with full dose LMWH monitored by

anti-Xa levels the pooled proportion of recurrent VTE during secondary prevention was 0.008 (95% CI = 0.0001 to 0.038; I^2 0%) in prospective studies vs. 0.005 (95% CI = 0.00003 to 0.019; I^2 0%) in retrospective studies. The pooled proportion of any major bleeding was 0.04 (95% CI = 0.01 to 0.09; I^2 0%) in prospective studies vs. 0.018 (0.006 to 0.03; I^2 29.1%) in retrospective studies.

None of the 11 unmonitored patients experienced major bleeding complications during the ante or post-partum period. Of the 260 patients who were monitored during treatment, 10 suffered a major bleeding complication. The pooled proportion of any major bleeding was 0.04 (95% CI = 0.02 to 0.07; I^2 14%) for those who were monitored during treatment. The pooled proportion of bleeding during the ante-partum period was 0.02 (95% CI = 0.002 to 0.04; I^2 14%), while the pooled proportion of post-partum bleeding was 0.03 (95% CI = 0.01 to 0.05; I^2 4%).

For our outcome of interest we calculated the pooled proportion of recurrent VTE and bleeding in prospective studies using full dose LMWH given twice a day based on anti-Xa levels, which is arguably the most conservative treatment. The analysis included three studies for a total of sixty seven patients. The pooled proportion of recurrent VTE during secondary prevention was 0.01 (95% 0.0001 to 0.048; I^2 0%), there were no events of recurrent VTE. The pooled proportion of any major bleeding was 0.051 (0.008 to 0.12; I^2 25%).

Heterogeneity was low to moderate in general and mostly occurring when retrospective studies were included.

Prophylactic doses of LMWH of UFH for secondary prevention

Three studies used fixed prophylactic doses for secondary prevention, of those two with LMWH and one with UFH. Abarahuma et al. evaluated the use UFH 5000 U BID SC for the secondary prevention of extensive pregnancy associated DVT. In their study 2 patients out of 15 experienced a recurrent event during secondary prevention; one event was a fatal PE that occurred during the acute treatment phase.

Two studies, including 62 patients, evaluated 40 mg of enoxaparin given for secondary prevention after 90 days of full dose LMWH. Four patients experienced a recurrent VTE with a pooled proportion of 0.07 (95% CI = 0.01 to 0.16), as shown in Figure 5. One out of 62 participants suffered a post-partum major bleeding event after switching to prophylactic doses.

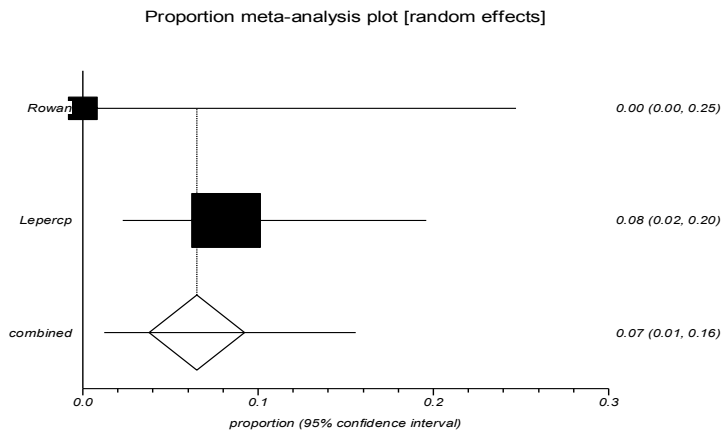


Figure 4 Recurrent VTE in patients treated with prophylactic doses of LMWH

Intermediate dose of LMWH or UFH for secondary prevention

Seven studies (100;115;228;258;259;265;269) that specifically used intermediate doses of LMWH for the secondary prevention of PAVTE were identified. One study (258) was excluded as less than five patients were treated with intermediate doses.

Four different drugs were used: enoxaparin (228;259), dalteparin (228;269), nadroparin (115;265) and Tinzaparin (100;228). Four studies were prospective (100;115;265;269) and two were retrospective (250;259). In two studies (115;269), the dose was reduced less than three weeks after starting treatment, in one study dose reduction occurred after three weeks (228) and in three studies after six weeks. Three of the studies guided therapy with Anti-Xa levels (100;228;269). In those managed with an intermediate dose only one (158) patient out of 196 experienced a recurrent event after the dose of LMWH was reduced for secondary prevention. The pooled proportion of recurrent VTE during secondary prevention was 0.01 (95% CI = 0.001 to 0.029; I^2 0%), as shown in Figure 6.

The impact of the timing for dose reduction was also analyzed, along with dosing based on anti-Xa monitoring and dosing. In two studies(115;269) that reduced the dose within 14 days of initiating therapy, the pooled proportion of recurrent VTE during secondary prevention was 0.029 (95% CI = 0.002 to 0.09). When the dose was reduced after 30 days of treatment the proportion of recurrent VTE was 0.005 (95% CI = 0.0001 to 0.023; I^2 0%). Those monitored with anti-Xa levels(100;228;269) had a pooled proportion of recurrent VTE during secondary prevention of 0.015 (95% CI = 0.001 to 0.048; I^2 0%) compared to those not managed by anti-Xa levels who had a pooled proportion of 0.006 (95% CI = 0.0003 to 0.03; I^2 0%).

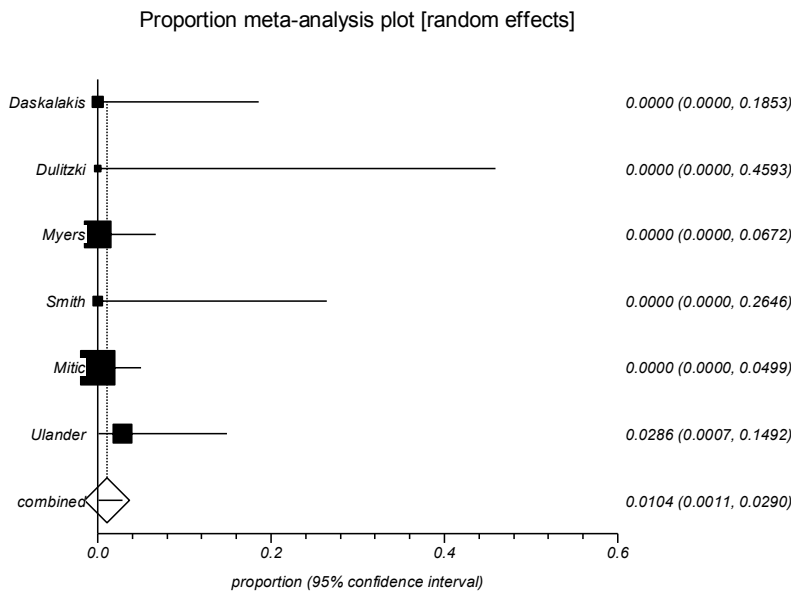


Figure 5 Recurrent VTE in patients treated with intermediate doses of LMWH

The pooled proportion for any major bleeding, for all patients treated with intermediate doses of LMWH, 0.02 (95% CI = 0.003 to 0.06; I^2 38%), as shown in Figure 7. None of the 196 patients included had a major ante-partum bleeding complication.

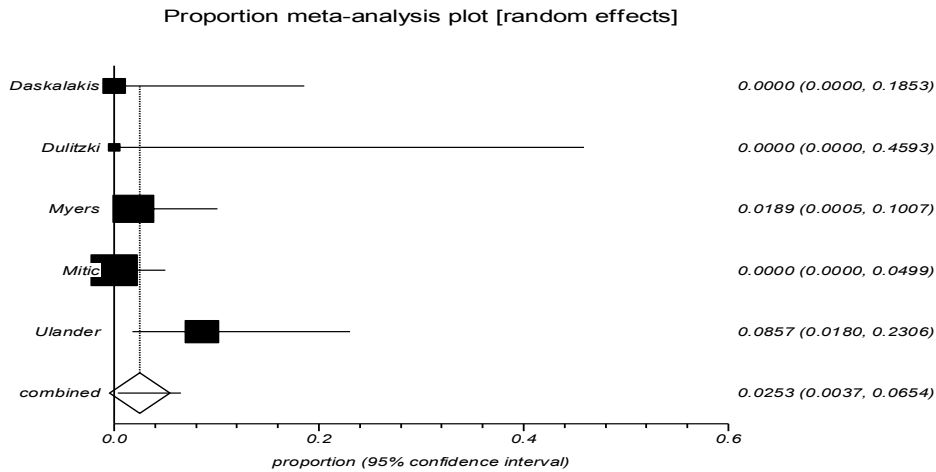


Figure 6 Major bleeding in patients treated with intermediate doses of LMWH

Heterogeneity was low to moderate for most of the analysis where it could be evaluated, except for the pooled proportion of major bleeding in prospective studies where it was high. A potential explanation could be a difference in the definition of major bleeding. Publication bias in this group of studies was not assessed as the number of studies identified was low.

4.4.3 Osteoporosis and heparin induced thrombocytopenia in patients treated with LMWH or UFH.

None of the studies including patients treated with LMWH or UFH reported any cases of heparin induced thrombocytopenia [0.003 (95% CI = 0.000931 to 0.008; I^2 0%) or heparin induced osteoporosis [pooled proportion 0.003 (95% CI = 0.000455 to 0.008; I^2 0%).

4.4.3 Fetal outcomes in patients treated with LMWH or UFH.

Sixteen studies reported on the pooled proportion of fetal outcomes in patients with LMWH and six in patients treated with UFH. The pooled proportion of miscarriage or fetal death was 0.02 (95% CI = 0.01 to 0.03; I^2 0%) in those treated with LMWH, and 0.075 (95% CI = 0.03 to 0.13) among those treated with UFH. The pooled proportion of fetal malformation was 0.009 (95% CI = 0.003 to 0.019; I^2 0%), among those treated with LMWH, and 0.012 (95% CI = 0.0003 to 0.04; I^2 0%) in those treated with UFH.

4.4.4 Publication bias

Publication bias analysis was conducted in ten of the analyses that included more than ten studies (see appendix 1). There was a trend for publication bias in studies evaluating the pooled proportion of bleeding among those treated with full dose LMWH (p- value 0.06) and for the incidence of fetal malformation among those treated with LMWH (p- value 0.056).

4.5 Analysis of the results

The systematic review included 1122 patients treated with either LMWH or UFH, but no randomized placebo or controlled studies were identified. Twelve different strategies were used for secondary prevention of PAVTE (nine for those treated with LMWH and three for those with UFH). Low molecular weight heparin and UFH seemed to have a similar efficacy and safety profile for the management of pregnancy associated VTE. The pooled proportion of recurrent VTE during secondary prevention was similar in patients treated with full doses of LMWH or UFH 0.012 (95%CI= 0.006 to 0.02) and 0.017(95%CI= 0.001 to 0.05) respectively. Both drugs shared a similar bleeding risk profile 0.023 (95% CI=0.01 to 0.041) and 0.038(95%CI= 0.002 to 0.11) respectively. The use of either drug was safe for the mother (no cases of heparin induced thrombocytopenia or osteoporosis were identified) and fetus.

When patients are treated PAVTE, clinicians appear to favour more aggressive treatment strategies for VTE (using full dose LMWH, given twice a day and targeting anti-Xa levels) during pregnancy in order to overcome physiological changes associated with pregnancy. Despite this a quarter of the patients were treated with intermediate doses or prophylactic doses of LMWH. Those treated with full doses and intermediate doses experienced similar proportions of recurrent VTE during secondary prevention 0.012 (95% CI= 0.006 to 0.02) and 0.011(95% CI= 0.0011 to 0.029)respectively, and major bleeding 0.023 (95% CI=0.01 to 0.041)and 0.025(95% CI= 0.003 to 0.065) respectively, during secondary prevention. In studies using prophylactic doses after 90 days of full dose treatment the

proportion of recurrent VTE was 0.06 (95% CI= 0.01 to 0.15), suggesting that this approach might not be safe for this population.

One interesting finding was that an early dose reduction (within three weeks of the initiation of treatment) could be associated with an increased proportion of recurrent VTE 0.029 (95% CI = 0.002 to 0.09) when using an intermediate dose but not after four weeks 0.005 (95% CI = 0.0001 to 0.023).

These findings suggest that after the initial period of 30 days reducing the dose of LMWH to an intermediate dose without monitoring and given once a day, might be a safe alternative to a more costly and cumbersome full dose regimen and is potentially associated with a lower pooled proportion of major bleeding (especially when prospective studies were evaluated).

Compared to the systematic review of Greer et al(74), our primary outcomes were evaluated for each separate treatment strategy and specifically for secondary prevention providing more meaningful estimates. Whereas Greer et al(74) et al included only 174 patients using LMWH treated with at least three different treatment strategies and provided an estimate of efficacy pooling all the strategies together, in this systematic review includes 1107 patients treated with LMWH and 115 with UFH were included, and evaluates patients according to each individual strategy for during the acute treatment period and secondary prevention.

Table 11 Summary of results

Intervention	n	Recurrent VTE Pooled proportion (95% CI; I ²)	Any major bleeding# Pooled proportion (95% CI; I ²)	Ante-partum bleeding Pooled proportion (95% CI; I ²)	Post-partum bleeding Pooled proportion (95% CI; I ²)
LMWH full dose	844	0.012 (0.006 to 0.02; 0%)	0.023 (0.01 to 0.041; 38%)	0.006 (0.001 to 0.02; 17%)	0.019 (0.008 to 0.03; 21%)
LMWH intermediate dose	196	0.011 (0.0011 to 0.029; 0%)	0.025(0.003 to 0.065; 39%)	0.005 (0.0000 to 0.021; 0%)	0.025(0.003 to 0.065; 39%)
LMWH prophylactic dose	62	0.06(0.01 to 0.15)	--	--	0.026 (95% CI = 0.001 to 0.079) ^{&}
<i>Dalteparin full dose</i>	73	0.026 (0.003 to 0.06; 0%)	0.015 (0.0001 to 0.06; 0%)	0.015 (0.00001 to 0.06; 0%)	0.015 (0.00001 to 0.06; 0%)
<i>Enoxaparin full dose</i>	215	0.02 (0.006 to 0.04; 0%)	0.041 (0.009 to 0.09; 0%)	0.022 (0.001 to 0.07; 67%)	0.017(0.003 to 0.04; 13%)
<i>Nadroparin</i>	75	0.018 (0.001 to 0.05)	0.018 (0.001 to 0.055)	0.018 (0.001 to 0.05)	0.018 (0.001 to 0.05)
<i>Tinzaparin full dose</i>	393	0.012 (0.003 to 0.03; 0%)	0.025 (0.004 to 0.06; 37%)	0.003 (0.00001 to 0.01; 0%)	0.025 (0.01 to 0.06; 37%)
UFH full dose	96	0.017(0.001 to 0.05; 0%)	0.038 (0.002 to 0.11; 0%)	0.038 (0.002 to 0.11; 0%)	0.016 (0.001 to 0.07; 0%)

*Any recurrent events that occurred during initial 30 days was considered an acute event, unless the dose was reduced within the first month
#Relevant major bleeding as considered by the study investigators
& Only during the use of prophylactic doses

In general the systematic review findings for full dose LMWH (1.4%; 95% CI 0.7-2.4%) given for the duration of pregnancy compare favourably with recurrence rates of 3%(140;142) reported in trials carried out in non-pregnant patients treated with LMWH followed by vitamin K antagonists. Potential explanations as to why the rates of recurrent VTE during treatment are lower in this population are:

1-The inclusion of non-randomized studies lead to an over-estimation of the effect of LMWH used for long term prevention of recurrent VTE(167) in pregnant patients (1.2%; 95% CI 0.7 to 2.1%) compared to non-pregnant patients completely treated with LMWH (4.5%; 95% CI 3.1to6.2). Still, estimates about the efficacy of long term LMWH in non-pregnant patients are based on seven studies, four of them using fixed prophylactic doses after full dose anticoagulation. In pregnant patients the use of fixed prophylactic doses was associated with pooled proportion of recurrent VTE of 7% (95% CI 1to16); AND-OR

2-The use of LMWH for the whole duration of treatment is more effective than vitamin K antagonists. This assumption could provide the most logical explanation for our findings as studies have shown, that in the non-pregnant and oncology populations the use of LMWH for the duration of treatment is associated with a lower rate of recurrent VTE compared to those treated with vitamin K antagonists; as shown in a recent meta-analysis of 11 randomized controlled trials including 2,907 participants(110).

4.6 Limitations

The systematic review has several limitations. The most relevant are that nonrandomised controlled trials evaluating the efficacy of different treatment strategies were identified and that the quality of the observational studies included was low. Both these limitations have important connotations for the interpretation of the results. Well-designed randomized

controlled trials are considered the highest quality of evidence(166), and should be the cornerstone of the meta-analysis to evaluate efficacy. The role of observational studies in systematic reviews remains a matter of debate. Although some experts recommend the use of observational studies to improve the accuracy of the estimates of systematic reviews where there no randomized controlled trials or the quality of the studies is low, this approach should be used cautiously given its inhered limitations. A meta-analysis of observational studies could potentially provide estimates similar to those of meta-analysis of randomized controlled trials (126;166;167), assuming that the quality of the studies is high and there is a clear understanding of the confounders that could affect the efficacy of the intervention. Meta-analysis of low quality studies could lead to discrepant results. Ioannidis, Benson and Concato found that prospective well design cohorts studies tend to produce similar estimates to randomized studies(126;166;167), whereas, retrospective or lower quality designs produced different estimates(126;166;167;208). Deeks(184) et al conducted a systematic review of the prior studies and suggested that systematic reviews of observational studies have inherited limitations, mostly driven by the limitation of methods to adjust for confounders. As shown in Table 7 only one of the studies included was compliant with all points of the Newcastle-Ottawa quality scale for observational studies. Of the studies included, seven included patients treated for multiple indications. Most of them did not use objective methods to evaluate the outcome of interests, so we cannot rule out classification bias. This fact could be reflected by the lower proportion of adjudicated recurrent VTE in retrospective studies compared to prospective studies. Given the quality of the studies and the low numbers of events included in this systematic review the results should be

interpreted carefully, and are more likely to help generate hypothesis than to guide treatment strategies in daily clinical practice.

Other relevant limitations are: First, some studies used multiple drugs and different dosing strategies within the same population. Ideally, the use of an individual patient data meta-analysis would have helped overcome this limitation, but the data could not be retrieved from all of the authors. However, data for each separate strategy was extracted whenever possible or authors were contacted to retrieve more detailed information. Strategies were analyzed as different subgroups within studies when needed.

Second, the management of zero events rates (i.e. no recurrent VTE or bleeding episodes reported in individual studies). There has been a great matter of debate on the best statistical approach for studies with zero or rare events (275). Whereas multiple methods are available for meta-analysis of randomized controlled trials or observational studies are available(276;277), the management of “zero cells” within proportions included in meta-analysis is not clearly defined in the literature(278). One proposed approach has been to add 0.5 to each “zero cells” or to not perform any analysis when more than 20% of the studies have “zero cells”(278). None of these approaches has been validated. Although the Freeman-Tukey arcine conversion can be applied to proportions of zero, this approach could produce an overestimate of the effect depending on the sample size of the study evaluated(279). In order to deal with “zero cells” a delayed continuity correction was applied using 0.001 instead of 0.5 for each cell , to reduce potential bias(280). Third, baseline characteristics of the groups could not be retrieved from the studies to allow any sensitivity analysis based on the type of index event or provoking factors associated with the index events.

Fourth, the systematic review was limited to three languages. Although not recommended, a language restriction was needed due to financial constraints. In order to overcome this limitation, authors of relevant studies in languages other than the three selected were contacted to retrieve information about the study. Fifth, it did not include a formal evaluation of the grey literature after the initial literature search(281). The inclusion of grey literature inclusion of an unbiased sample of relevant studies is central to the validity of systematic reviews and meta-analyses and to reduce publication bias. Grey literature searches aim to identify unpublished studies within the time-frame of the systematic review and negative studies(282). Still, grey literature studies tend to be of lower methodological quality than published studies potentially introducing bias into the results which could have further the validity of the results(282). In order to identify unpublished studies within the time-frame of the systematic review, a thorough review of abstracts books from relevant meetings was conducted. Sixth, did not assessed the quality of the data abstracted by the reviewers by the kappa method. Finally, the pooled proportions could not be calculated as events per patients month as most of the studies did not report the duration of treatment.

4.7 Conclusions

To date, this is the most extensive systematic review evaluating the role of different treatment strategies used for the management of pregnancy associated VTE. Multiple treatment strategies using LMWH have been evaluated for the management of PAVTE but none of them in well-designed randomized controlled trials, or even, well design observational studies.

The findings of the systematic review suggest that that the outcome of patients treated with intermediate doses or full doses for secondary prevention are similar. Given the low quality

of the studies included the results should be interpreted cautiously, and call for high quality studies evaluating the role of different treatment strategies for the secondary prevention of PAVTE.

5.0 Survey

5.1 Rationale for the survey

As discussed above, management of PAVTE is often based on small observational studies and extrapolations from studies evaluating non-pregnant patients. Evidence from the systematic review suggests that the use of an intermediate dose of LMWH for secondary prevention of PAVTE could be associated with a similar rate of recurrent VTE and potentially less bleeding when compared to full-dose LMWH (given twice a day and monitored with anti-Xa levels). Furthermore, an intermediate dose given once a day and without monitoring could possibly reduce the cost of care and improve patient comfort. Before conducting a single arm study evaluating the efficacy and safety of an intermediate dose, it was necessary to address the following questions:

What is the accepted absolute increase in the rate of recurrent VTE in the absence of randomized controlled trials to determine- Δ ? What is the most common strategy for secondary prevention (or comparator)? Is the proposed intervention used outside clinical studies and if so how often? Is the evidence needed? If a study evaluating an intermediate dose of LMWH for secondary prevention of PAVTE was conducted, will physicians participate in the study?

5.2. Aims of the Survey

The principal aim of this survey was to define- Δ for the sample size calculations needed for the future single arm study described earlier.

The secondary goals of the survey were:

- i. Gain knowledge about clinical equipoise
- ii. Assess the potential participation rate in the study
- iii. Assess current practices for secondary prevention (selection of the comparator)

5.3. Methods

5.3.1 Design

An electronic self-response survey, using Survey Monkey software (pro-edition) was conducted. The target sample was experts and clinicians with ample experience in the management of VTE associated with pregnancy. The original goal was to survey members from the International Society of Thrombosis and Hemostasis (ISTH). This society includes members from multiple countries who are interested in the management of VTE. The request for the release of member information was rejected by ISTH due to their privacy bylaws. Similar problems occurred when two other international societies of experts in thrombosis disorders were contacted (European Society of Cardiology Thrombosis Interest group and the North American Thrombosis forum). Only two groups agreed to collaborate with this project: 1-The Thrombosis Interest Group of Canada and 2-the International society of Obstetrics medicine. The final sample consisted of 300 physicians from both societies.

The protocol was approved by the Ottawa Hospital Ethics and Research board to initiating the survey. Initiation or completion of the survey constituted implied consent, as stated in

the cover sheet. The survey did not collect any personal information or linked the respondents to a database.

5.3.2 Survey Instrument

The survey instrument consisted of 20 questions using different formats and was pilot tested with physicians of the Thrombosis Unit at the Ottawa Hospital. Minor changes were made after their evaluation.

The elicitation of $-\Delta$ aimed to evaluate the largest loss in efficacy that would be acceptable when comparing the proposed strategy against the comparator in a single arm study. As previously discussed, guidelines and experts have yet to reach consensus regarding the standard of care for the secondary prevention of pregnancy associated VTE. It seems clear that most guidelines and experts favor the use of full dose LMWH given twice a day over once a day strategies. Treatment management based on anti-Xa levels has been a matter of debate, and although not widely recommended, evaluation of real life practice has shown that up to 76% of physicians used anti-Xa monitoring(82;101). For the reasons stated above, it was decided that the comparator for the elicitation of the margin would be full dose LMWH given twice a day with anti-Xa monitoring. Elicitation of the absolute accepted increase in the rate of recurrent VTE was accomplished using two types of answers options. The first was in open-ended format, and the second consisted of multiple choices with anchors. The following statement was provided to physicians regarding the efficacy of LMWH for the treatment of pregnancy associated VTE:

“The average rate of recurrent VTE in pregnant patients during pregnancy and the post-partum period treated with monitored split q12 h full dose LMWH (given twice a day and monitored with Anti-Xa levels) appears to be approximately 1.15% (Greer et al. Blood

2005). The rate of significant bleeding during the ante-partum period appears to be 0.6%, and 1.1% during the postpartum period (Greer et al. Blood 2005).

After the initial 30 days of treatment, some experts recommend reducing the dose to 75% without monitoring and administering the drug once a day. The efficacy and safety of this practice in the context of pregnancy awaits confirmation.

Assuming that a $\frac{1}{4}$ dose reduction strategy LEADS TO A POTENTIAL REDUCTION IN SIGNIFICANT BLEEDING, is given once a day and needs no monitoring, what is the maximum potential increase in the absolute rate of recurrence during pregnancy and the post-partum period that you would accept to consider the $\frac{1}{4}$ dose reduction strategy non-inferior to ongoing monitored twice daily full-dose treatment?

Multiple choice options were presented using the absolute risk (AR) and number needed to harm (NNH). This approach was used to reduce the variability of the estimation of absolute accepted increase in the rate of recurrent VTE produced by expressing effects using a single measure (i.e. RR vs. NNH) (228;283) See example below:

- 0% In other words no increase in absolute rate of recurrent VTE during pregnancy and the post-partum period is acceptable. The number needed to harm with $\frac{1}{4}$ dose reduction is infinite i.e. you would need to treat infinite patients with $\frac{1}{4}$ dose reduction to increase by one the number VTE compared to full dose treatment
- 0.05%
- 0.1%
- 0.3%
- 0.5%
- 1% In other words an increase in absolute rate of recurrent VTE during pregnancy and the post-partum period of 1% (i.e. an increase from 1.15% with full dose to 2.15% with dose reduction is acceptable). The number needed to harm with $\frac{1}{4}$ dose reduction is 100 i.e. you would need to treat 100 patients with $\frac{1}{4}$ dose reduction to increase by one the number of recurrent VTE compared to full dose treatment
- 2%
- 3%
- 4%

- 5%
- *10% in other words and increase in absolute rate of recurrent VTE during pregnancy and the post-partum period of 10% (i.e. an increase from 1.15% with full dose to 11.15% with dose reduction is acceptable). The number needed to harm with ¼ dose reduction is 10 i.e. you would need to treat 10 patients with ¼ dose reduction to increase by one the number of recurrent VTE compared to full dose treatment*

The baseline rate of recurrent VTE and bleeding was extracted from the systematic review conducted by Greer at al., as the systematic review for this thesis was started at the same of the survey. To improve the elicitation of the margin, given the uncertainties regarding the proposed strategy, physicians were presented with three extra scenarios:

- A quarter dose reduction is given once a day without monitoring but is not associated with a reduction in bleeding
- A quarter dose reduction is given once a day with monitoring and is not associated with a reduction in bleeding
- A quarter dose reduction is given twice a day with monitoring and is not associated with a reduction in bleeding

For the evaluation of clinical equipoise and future participation in the study, closed-ended yes or no questions were used.

The evaluation of practices was conducted using a multiple choice option format with the possibility of an open ended answer to increase the response rate. Information regarding the type of heparin used for initial treatment and dosing; the type of heparin used for secondary prevention and dosing; and finally the use of Anti-Xa levels to guide therapy during the acute and secondary therapy period was collected.

Information was also gathered regarding years of practice, specialty, and knowledge about research methodology.

Finally, to ensure that the survey was answered by physicians with ample experience in the management of pregnancy associated VTE, a screening question was inserted at the

beginning of the survey trying to identify physicians who have treated more than two PAVTE during the last year. This number was reached by consensus among two thrombosis experts (MR and MC).

5.3.4 Survey delivery

The target sample was contacted by electronic mail. An information sheet/electronic statement indicating that participation was voluntary and ensuring confidentiality was provided with each survey. The following were done to increase the response rate:

- 1-Two weekly electronic reminders were sent after the original survey
- 2-The survey included a cover letter explaining the goals and importance of the study
- 3-Completion of the survey required a response to each question

Since the initial response rate was low (23%) following the 2 electronic reminders, two additional measures were taken to increase the response rate:

1. The survey was endorsed by three highly respected experts in the area of PAVTE and a revised cover letter was included.
2. After receiving approval from the ethics board, compensation in the form of a voluntary raffle wherein participants could win one of four gift cards valued at fifty dollars each was offered.

5.3.5 Analysis

The absolute accepted increase in the rate of recurrent VTE was analyzed as median and SD. The rest of the survey results are reported using descriptive statistics (percentages and 95% CI). Stratified analysis was conducted by years of practice, specialty, and knowledge about research methods using the student T-test or Wilcoxon rank sum, accordingly for each question. The statistical power to detect a real difference between the accepted absolute

increases in the rate of recurrent VTE in different scenarios was calculated by the normal approximation methods with a 95% CI. Data was collected using Microsoft excel, and the analysis was conducted using SAS.

5.4 Results

The survey was electronically mailed to 300 participants; 246 from the ISOM and 54 from TIGC.

At the end of the survey 69/300 (23 %) had completed the entire survey. Five out 300 (1.6 %) were disqualified after the initial screening question. Sixty five percent of the responses were obtained during the first week.

The final sample consisted of 27/69 hematologists (39.1 %), 30/69 internists (43.5%), 8/69 obstetricians (11.6 %), and 4/69 from other specialties (4.5%). Fifty out 69 (72.5 %), reported at least 10 years of clinical practice and 41/69 (59.5) % reported some formal training in research methodology.

5.4.1 Elicitation of Δ

When asked “*After the initial 30 days of treatment, some experts recommend reducing the dose to 75% without monitoring and administering the drug once a day. The efficacy and safety of this practice in the context of pregnancy awaits confirmation. In the box below please provide the increase in absolute rate of recurrent VTE that is acceptable (suggested range 0 to 10%)*” using an open ended question the absolute accepted increase in the rate of recurrent VTE was 1.3% (SD 1.45) corresponding to a- Δ of 2.45%. When the same question was posed as multiple options with anchors, see Figure 8, the absolute accepted increase in the rate of recurrent VTE was 1.2% (SD1.16) corresponding to a- Δ of 2.35%, with no statistical difference between the two formats (p-value 0.2). The absolute accepted increases

in the rate of recurrent VTE when the intervention had no association with a reduction in bleeding was 0.92% (SD 1.72), see Figure 9, corresponding to a- Δ of 2.05%, and was not significant (p-value 0.3). When it was suggested that the intervention had no benefit at all (no reduction in major bleeding, need for monitoring and was given twice a day) the absolute accepted increase in the rate of recurrent VTE was 0.3%(SD 0.30; p-value 0.0001 for the comparison to a reduction in major bleeding, no need for monitoring and was given once a day) corresponding to a- Δ of 1.45%. In table 12, the absolute accepted increase in the rate of recurrent VTE is shown for each answer (different benefits) along with the statistical power to detect a real difference between the accepted rates by scenarios and type of question.

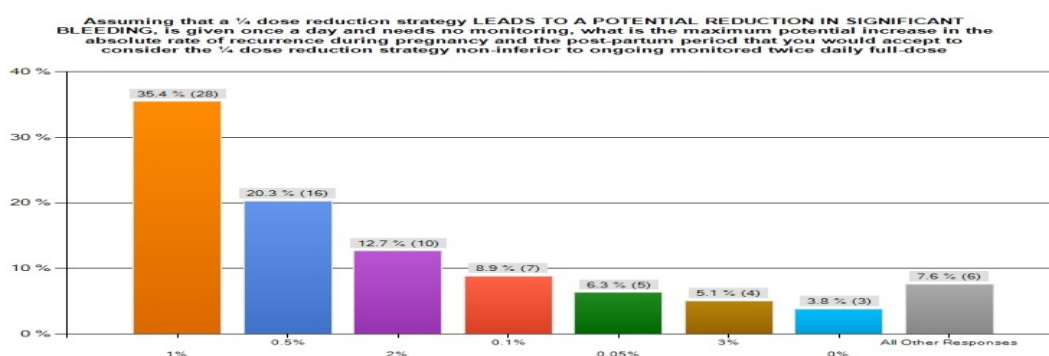


Figure 7 Absolute accepted increase in the rate of recurrent VTE if an intermediate dose of LMWH was associated with multiple dosing benefits and a clinically relevant reduction in bleeding

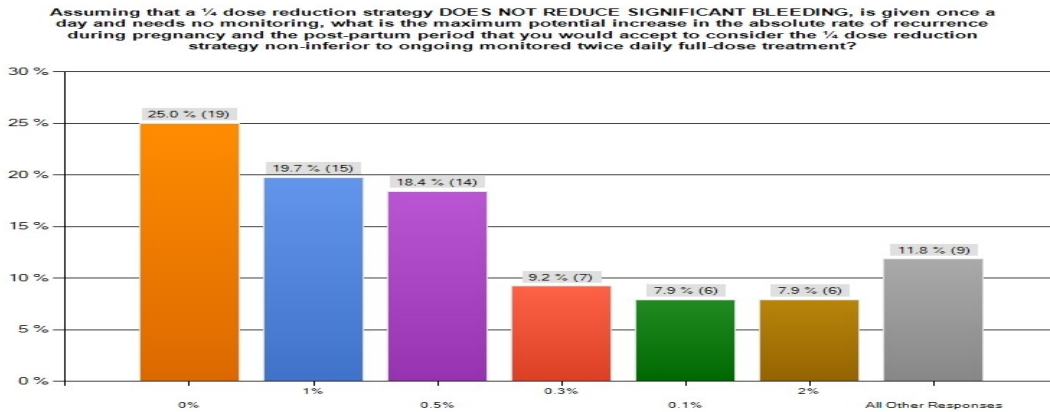


Figure 8 Absolute accepted increase in the rate of recurrent VTE if an intermediate dose of LMWH was associated with multiple dosing benefits and but does not reduce bleeding

Training in research methodology had no impact on the accepted rate of recurrent VTE for the main question using an open ended format [1.21 (SD 1.01) vs. 1.69 (SD 2.05); p-value 0.3]. Under the assumption that a quarter dose reduction did not reduce the incidence of bleeding the difference in rate was higher but not significantly different (0.5 vs. 1.5; p-value 0.2). No significant variability according to physician specialty or years of practice was found. Table 13, presents the analysis based on specialty, training in research methodology, and years of practice.

Table 12 Elicitation of $-\Delta$ by type of answer and scenario

Open ended	N	Absolute rate	SD	$-\Delta$	P-value	Statistical power
Reduction in bleeding, no monitoring and given OD	79	1.3	1.45	2.45	0.36	8.76
Multiple option	N	Absolute rate	SD	Non-inferiority margin	P-value	Statistical power
Reduction in bleeding, no monitoring and given OD	79	1.2	1.56	2.35	Ref	Ref
No reduction in bleeding, no monitoring and given OD	75	0.9	1.72	2.05	0.2	18.9
No reduction in bleeding, needs monitoring and given OD	70	0.7	1.51	1.85	0.04	54
No benefit	69	0.3	1.28	1.45	0.001	98.9

Table 13. Estimation of the margin analyzed by respondent characteristics

	Trained in research methods	No training	p-value*
	Absolute rate (SD)	Absolute rate (SD)	
Reduction in bleeding, no monitoring and given OD	0.94 (0.76)	1.79 (2.05)	NS
No reduction in bleeding, no monitoring and given OD	0.57 (0.74)	1.5 (2.59)	NS
No reduction in bleeding, needs monitoring and given OD	0.41 (0.72)	1.13 (2.16)	NS
No benefit	0.28 (0.71)	0.38 (0.72)	NS
	Less than 10 years of experience	More than 10 years of experience	p-value
Reduction in bleeding, no monitoring and given OD	0.87 (0.75)	1.44 (1.97)	NS
No reduction in bleeding, no monitoring and given OD	0.6 (0.96)	1.08 (2.01)	NS
No reduction in bleeding, needs monitoring and given OD	0.48 (0.98)	0.79 (1.68)	NS
No benefit	0.08 (0.24)	0.39 (0.81)	NS
	Hematologist	Internist	p-value*
Reduction in bleeding, no monitoring and given OD	0.94 (0.8)	1.47 (1.83)	NS
No reduction in bleeding, no monitoring and given OD	0.74 (0.88)	0.94 (1.94)	NS
No reduction in bleeding, needs monitoring and given OD	0.56 (0.88)	0.70 (1.93)	NS
No benefit	0.18 (0.45)	0.30 (0.78)	

*p-values >0.05 are reported as non-significant

5.4.2 Current clinical practices

In patients with pregnancy associated DVT, the most common strategy during the acute treatment period was LMWH given twice a day 42/69 (62%), followed by LMWH given once a day 25/69 (36%). These results were similar for patients with PE, although 6% of the respondents favored UFH for the initial treatment period.

For secondary prevention more than 70% of the respondents favored treatment with full doses of LMWH given once a day or twice a day. An intermediate dose (once a day) for secondary prevention was used by minority physicians 16/69 (23.2 %) for patients diagnosed with DVT and 15/69 (21.7%) for patients diagnosed with PE.

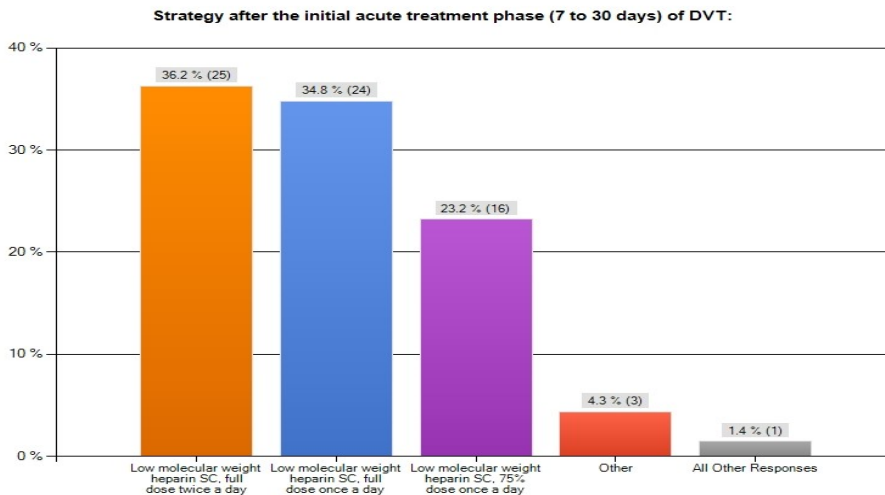


Figure 9 Strategies used for secondary prevention in patients treated for DVT

A wide variation in practice was identified when the use of Anti-Xa levels was evaluated. Forty eight physicians out of 69 (69.2%) used monitoring during the first 30 days (20.3% weekly and 26.1% monthly in the absence of special indications such as extreme body weight or kidney disease). Only 14/69 (20.3%) did not monitor Anti-Xa levels during the first month.

For secondary prevention, 24/69 (34.8 %) physicians never used Anti-Xa levels, while 21/69 (30 %) only did so on a weekly or monthly basis. The use of anti-Xa monitoring varied according to the strategy used for secondary prevention. Among those using intermediate doses, 18% (95% CI 5to43) used some form of anti-Xa monitoring for all patients. Among those using full doses once a day 21% (95% CI 8to41) used some form of anti-Xa monitoring for all patients; whereas 45% (95% CI 27to65) of those using twice a day full doses used monitoring used some form of anti-Xa monitoring for all patients.

No association was identified between physician specialty, research training, and years of practice with respect to dosing and the use of anti-Xa monitoring.

5.4.3 Clinical equipoise and potential participation in a future study

When physicians were asked if they thought a study evaluating the efficacy of a quarter dose reduction strategy for secondary prevention of PAVTE was needed, 68/69 (98.4 %) of them answered yes , and 66/69 (95.7%) said they would be willing to participate in such a study.

5.5 Analysis of the results

A clinically accepted norm for $-\Delta$ is a proportional difference of 15% to 20% or less, smaller than the typical 20% to 25% “minimally clinically important difference” criterion employed in superiority trials(136). However, what constitutes a clinically acceptable difference is ultimately a matter of judgment and might vary widely for each patient, physician, investigator, regulator or payer, and the clinical circumstance(137). For example, any difference in hard outcomes such as mortality or irreversible morbidity might have a greater clinical meaning, thereby warranting a more narrow and conservative $-\Delta$ (284).

Although recommended by funding agencies(131), surveys have not been widely used for the elicitation of $-\Delta$ or even the minimally important difference. The main advantage of surveys is that they provide researchers with perspective on the group that would potentially use the intervention(283;285). On the other hand, the main limitation is the variation of the estimates based on the way the effect is presented (relative risk, number needed to treat or absolute risk) or the sample that was targeted (specialists against non-specialists) (283) that can provide different estimates.

In this study we were able to elicit $-\Delta$ for single arm study using a survey, and to our knowledge it is the first one to use this technique for the design of studies evaluating the safety and efficacy of anticoagulation in pregnant patients.

Surveys have been used for the elicitation of the minimally important clinical difference, but this method is not widely used because 1- it is labor intensive and 2- the results vary according to the target population and the method used for the elicitation of the margin.

In order to allow for better discussion of the results, $-\Delta$ s were transformed to odds ratio OR, and will be referred as such for the remainder of the thesis. Relative scales, such as the odds ratio (OR), are usually preferred over absolute scales (risk difference), to allow $-\Delta$ to adapt in case of unanticipated differences in the observed and expected event rates(286).

Under the assumption that the proposed strategy was more comfortable for the patient (given once a day and without anti-Xa monitoring) and had a reduction in bleeding, respondents were willing to accept an absolute 1.1% loss in efficacy (corresponding to an OR of 2.1).

The $-\Delta$ corresponding to an OR of 2.1 was similar to the $-\Delta$ used in recent randomized controlled trials evaluating a new oral anticoagulant agent rivaroxaban (RR 1.7), where they used statistical reasoning; or comparing LMWH against UFH(287) (RR 2) where it was

elicited from historical observational studies of UFH against placebo. The- Δ was more conservative than the one used in a recent study evaluating dabigatran (RR 2.75), where the margin was elicited using historical studies comparing warfarin against placebo after 6 weeks of treatment(142). Compared to prior studies conducted in the non-pregnant population, the assumption of the- Δ included a reduction in a hard endpoint, which was not explicitly assumed in studies conducted in non-pregnant patients.

The results could be explained by the number of physicians trained in research methodology who participated in the study, but these groups provide us with a non-significant more conservative margin than those not trained in research methodology (OR 1.7 vs. 2.3).

Another relevant finding was that the selection of the- Δ varied only if the intervention had no benefits. Reductions of a hard endpoint such a bleeding led to an increase in the upper margin when compared to no benefits at all (OR 2.1 vs. 1.2: p-value <0.001), but not when the strategy was more comfortable for the patient (given once a day and with no monitoring; OR 1.9 vs.1.2; p-value NS). However, the survey was underpowered to show a statistically significant decrease in the- Δ when benefits of the proposed intervention did not translate into increased safety or a hard endpoint.

Compared to other authors(283), the presentation of information for the elicitation of the margin (using multiple choices with anchors vs. open ended questions) did not vary the margin selected, although it was underpowered to detect a real difference. Our results could have been different if a larger sample was used, and if the we have used different approaches to elicit the margin, although the best approach remains to be proven (288).The survey showed that the use of full dose of LMWH is the standard of care for secondary prevention of pregnancy associated VTE. A wide variation in strategies used for the initial acute

treatment period and for secondary prevention was found for dosing (once a day vs. twice a day) and for the use of Anti-Xa monitoring corresponding to the uncertainty reported by recent guidelines, expert reviews, and observational studies. Less than a quarter of the respondents favored the use of an intermediate dose of LMWH given once a day for secondary prevention for both DVT and PE, while 71% preferred the use of full doses (50% once a day and 50% twice a day). Monitoring with anti-Xa levels was widely used during the acute treatment period (45% monitored all patients at least once), while 34% monitored all patients after the acute treatment period. Although our findings regarding dosing strategies are similar to a prior study conducted by Voke et al(82), a significant variation in the use of anti-Xa level monitoring, especially for secondary prevention, was found. The study by Voke et al(82)reported that 76% of physicians used anti-Xa level during treatment, but did not specifically report the responses for secondary prevention.

Most of the physicians answering the survey were not obstetricians, a phenomenon also observed in a study by Coppelton et al(101). This finding may represent the current trend wherein the care of patients who develop conditions during pregnancy is transferred to internal medicine specialists.

Finally, equipoise for conducting the study was identified as more than 90% of the respondents agreed that a study evaluating an intermediate dose of LMWH strategy for the secondary prevention of PAVTE was needed and if such a study were to be conducted, they would participate.

5.6 Limitations

The survey has limitations. First, the original target sample was not achieved as the ISTH and the European society of Cardiology were unable to participate in the survey due to their

privacy bylaws. Only the TIGC and ISOM collaborated with the survey (all emails to TIGC members were sent by their own administrative staff). Still, these two societies represent a group of selected experts in the field of thrombosis, or physicians with expertise and interest in obstetric medicine, providing us with a small but representative sample of physicians involved in the care of pregnant patients treated for VTE. One relevant finding is that the rate of obstetricians answering our survey was small (11.8%). This finding may represent the current trend, where conditions that develop during pregnancy are managed by internal medicine specialists.

Second, the response rate was low (35%) and consequently the sample size was 60% smaller than expected. Although the utilization of incentives and endorsement from recognized experts had an impact on the final response rate (increasing it by 23%), a mixed model (using multiple response options) approach could not be used as originally planned. Mixed models of response are associated with higher responses rates than surveys conducted using a single method, although for this survey recommended measures to increase response rates were taken(289;290). Two other factors can explain our rates: 1- the number of studies that use e-mail to collect data has been increasing over the last years while the average response rate to the surveys appears to be decreasing(289). Although, there widespread use of internet surveys could be associated to a lower response rate, in recent comparisons of web-based surveys to traditional methods it was concluded that both methods achieved a similar response rate(289;291)

These two facts suggest that the results could potentially be biased by a positive selection of respondents. Nevertheless, it has been recognized that sample size and response rate do not change the accuracy of the predictions achieved by surveys. Low response rates achieved by

mail have shown to be more accurate in their predictions than higher response rates using the telephone(292;293). The explanations to these findings are(292): 1- that respondents are more likely to get involved in the topic of the survey when using as delivery method; 2- mailed surveys provide respondents with the opportunity to analyze their own answers by allowing to review the answers increasing the chances of participation; and 3-the group of respondents might be involved in the topic of interest. Finally respondents of mail surveys are more likely to have future involvement in the activity or issue surrounding the topic of the survey.

Third, the- Δ was elicited using only one comparator (full doses LMWH twice a day monitored with anti-Xa), a fixed rate of recurrent VTE and without an upper bound of the 95% CI. It is unknown if the margin would have been similar to the one elicited if other strategies were used as the comparator or if the rate of recurrent VTE was lower. For example, if an intermediate dose of LMWH was compared against full doses of LMWH (given once a day and without monitoring); the margin could have been smaller as the reduced dose strategy would have only reduced bleeding. Still, the most relevant limitation for the interpretation of the margin is not presenting the complete efficacy of the treatment by a 95% CI. In the systematic review conducted by Greer et al(74) the upper bound was 4.1%, which was not provided in the statement used for the elicitation of the- Δ . Using Greer's upper 95% CI of 4.1% would have misguided respondents to accept an estimation of efficacy based on 174 patients from observational studies. When the total of treatment cannot be calculated, one solution is to simply use what is believed to be a conservative estimate of the effect of the active control over placebo(133). The use of surveys or Delphi groups to define the margin is accepted by the EMA, even in the absence of prior placebo

controlled studies, provided that it would lead to a confident assumption that the product would have been shown to be efficacious if a placebo-controlled trial had been performed(131;186)

5.7 Conclusions

The results of the survey have multiple implications for the design of the future study. The Δ could be elicited using this technique and did not show variations in comparison to commonly used methods for the elicitation of the $-\Delta$ used in randomized studies conducted in the non-pregnant population. Assuming that an intermediate dose of LMWH (given once a day without anti-Xa monitoring) for secondary prevention of PAVTE leads to a significant reduction in bleeding, respondents would accept an absolute increase of 1.2%, corresponding to an OR of 2.1, in the rate of recurrent VTE to claim non-inferiority. A relevant finding was that the proposed strategy was already in use in clinical practice. The main limitation of the survey was that although the use of full dose LMWH for secondary prevention is the standard of care, it could not identify any specific strategy (defined by dosing or anti-Xa monitoring) as comparator. Still, more than 90% of the respondents agreed that a study evaluating a quarter dose reduction strategies after the acute initial treatment period is needed and would participate if the study was conducted.

6.0 Should a single arm study evaluating an intermediate dose of LMWH (given once a day without monitoring) for the secondary prevention of PAVTE be conducted?

As discussed, the evidence guiding management of PAVTE is based on low quality studies and the extrapolation of data from non-pregnant populations. Nonetheless, the results of the systematic review and survey clearly show that:

1- Low molecular weight heparin is the drug of choice for most physicians who answered the survey. Results from the systematic review showed that compared to UFH, LMWH is possibly associated with a reduction in major bleeding, lower rates of recurrent VTE, and fewer incidents of fetal miscarriage or stillbirth.

2- There is a wide variation in practice regarding dosing, dose reduction, and anti-Xa level monitoring. A quarter of the physicians favored a dose reduction after a month of treatment, two thirds did not guide therapy based on anti-Xa levels after the first thirty days of treatment, and more than fifty percent of the respondents favor the use of dosing once a day for patients treated with full doses during secondary prevention. In the systematic review, anti-Xa level monitoring or dosing once a day vs. twice a day did not appear to influence the rate of recurrent VTE. However, those managed according to anti-Xa levels seemed to have a higher incidence of major bleeding regardless of the dose used. The use of once a day dosing did not appear to increase the proportion of recurrent VTE or the proportion of major bleeding.

3- Compared to full dose treatment an intermediate dose used for secondary prevention did not seem to be associated with a reduction in efficacy for secondary prevention. Moreover the use of intermediate dosing without anti-Xa monitoring appears to be associated with less major bleeding compared to the use of full doses of LMWH with anti-Xa monitoring.

4-Most of the survey respondents believe that a study evaluating dose reduction is needed and 95.7% would be willing to participate should the study be conducted.

5- The $-\Delta$ for a non-inferiority study was elicited and appears to be an absolute increase of 1.2%, corresponding to an OR of 2.1.

In conclusion, evidence suggests that using an intermediate dose of LMWH(given once a day without monitoring) for secondary prevention of PAVTE is beneficial; that high quality evidence is needed to support the management of PAVTE; that physicians need this information; and finally, physicians would participate in the study if conducted.

7.0 Design of an single arm study for the evaluation of an intermediate dose of LMWH for secondary prevention of pregnancy associated VTE

Single arm studies are recommended in situations where(196):1- historical data is available; 2- the margin is an acceptable value that is clinically relevant; 3- there is an accepted standard; and 4- there are no concerns over the safety of the accepted standard.

For the evaluation of the use of intermediate dose of LMWH for secondary prevention of PAVTE, all the criteria for conducting a single arm study are met: 1-it is clear from the survey and systematic review that the standard of care for secondary prevention of PAVTE is the use of full dose LMWH and historical data from observational studies was found to produce an estimate of efficacy. One could argue that the quality of the component studies of my systematic review is too poor to provide a historical control estimate, however, even if we assume full dose treatment is perfect (i.e. 100% effective) we could design a single arm study that shows that a new intervention is or is not close enough to perfect to be adopted; 2- the margin was elicited by surveying physicians with interest in the management of PAVTE; and 3- It was strongly suggested in the systematic review that safety outcomes such as

heparin induced thrombocytopenia; maternal death, fetal death/malformation and osteoporosis are rare during treatment with LMWH.

For a single arm study to be relevant for practicing physicians treating PAVTE, it should be based on a summary of the efficacy of multiple strategies, a principle similar to the one used for the approval of mechanical valves, where the OPC/G is defined by the pooled rate of thrombotic events for all of the devices previously approved. Similar designs have been used in prior studies to assess efficacy of anticoagulation strategies in special populations or diagnostic strategies as shown in Table 5, and some of them have even led to a change in medical practice.

Under that assumption that all full dose strategies are similar in efficacy, and that a strategy based on intermediate doses does not seem to be associated with a loss in efficacy for the prevention of recurrent VTE, pooled proportion of 0.011(95% CI= 0.0011 to 0.029), and that the use of intermediate doses without anti-XA monitoring could be associated with a reduction in major bleeding (0.006 vs. 0.025 in patients treated with full dose), it seems reasonable to use the pooled proportion of recurrent VTE for all patients treated with full doses of LMWH as the baseline value for efficacy to prevent recurrent VTE (0.012). The selection of the $-\Delta$ for efficacy should be based on the results of the survey. The elicited $-\Delta$ was 2.35% (corresponding to an absolute increase in the rate of recurrent VTE of 1.2%) with multiple options questions and 2.45% (corresponding to an absolute increase in the rate of recurrent VTE of 1.3%) using an open ended question, assuming that the rate of recurrent VTE with full doses of LMWH was 1.15% and that an intermediate dose of LMWH leads to a reduction in bleeding. To be conservative, the margin elicited with multiple options will be used. To adjust for differences rate of recurrent VTE used for the elicitation of the margin

(1.15%) and the pooled proportion estimated in the systematic review (0.012 corresponding to 1.2%), the margin was transformed to an OR of 2.1, leading to a $-\Delta$ of 2.5% (or an absolute loss in efficacy of 1.3%). The statistical hypothesis of efficacy for the study is:

- H0: The rate of recurrent VTE in patients treated with an intermediate dose of LMWH given once a day and without anti-Xa monitoring is $>2.5\%$
- H1: The rate of recurrent VTE is in patients treated with an intermediate dose of LMWH given once a day and without anti-Xa monitoring is $<2.5\%$

Alternatively, the study could be designed whereby the comparison is to “perfect” effectiveness of full dose LMWH. This study design would have the following statistical hypothesis:

- H0: The rate of recurrent VTE in patients treated with an intermediate dose of LMWH given once a day and without anti-Xa monitoring is $>1.2\%$
- H1: The rate of recurrent VTE is in patients treated with an intermediate dose of LMWH given once a day and without anti-Xa monitoring is $<1.2\%$

However, most clinicians accept that no therapy is perfect and would accept that 1.2% determined in the systematic review is a more estimate of full dose LMWH’s efficacy.

The rationale for using an intermediate dose is that it may potentially reduce the incidence of major bleeding. For the evaluation of safety it was assumed that an intermediate dose of LMWH used for secondary prevention would lead to a 60% reduction in major bleeding. Assuming that the pooled proportion of major bleeding in patients treated with full doses of LMWH is 0.025 (corresponding to 2.5%), and that the pooled proportion of major bleeding

in patients treated with intermediate doses given once a day and without monitoring is 0.006 (corresponding to 0.6%), the statistical hypothesis for safety is:

- H0: The rate of major bleeding in patients treated with an intermediate dose of LMWH given once a day and without anti-Xa monitoring is $>1\%$
- H1: The rate of major bleeding is in patients treated with an intermediate dose of LMWH given once a day and without anti-Xa monitoring is $<1\%$

Sample size calculations were based on the normal approximation to the binomial distribution using the following formula(188):

$$N = \frac{\{Z_{\alpha} \sqrt{[\pi_0 * (1 - \pi_0)]} - Z_{\beta} \sqrt{[\pi_1 * (1 - \pi_1)]}\}^2}{\pi_0 - \pi_1} = X^2$$

In this formula π_0 represents the null hypothesis, π_1 represents the alternative hypothesis, $\pi(1 - \pi)$ is the standard deviation, Z_{α} is the Z value for an alpha = 0.05 (1.645 for a single sided test and 1.84 for a two-sided test) and Z_{β} the lower one-sided Z value for beta = 0.84.

As such, we would accept a 5% chance of falsely rejecting the null hypothesis: one-sided alpha = 0.05 for efficacy and two-sided alpha = 0.05 for safety. The one sided test for efficacy is based on the assumption that the use of an intermediate dose would not be more effective than full doses of LMWH, and that by reducing the sample size fewer patients would be exposed to the intervention if it was less effective. We would accept a 20% chance of falsely not rejecting the hypothesis (power = 80%).

To achieve these standards a study sample size of 716 participants is needed to assess efficacy and 676 to assess a statistically significant reduction in bleeding. Assuming a conservative 5% of participants lost to follow up the sample size needed was calculated at 754. Given the expected limitations for enrolment discussed previously in section 2.3, the design of pilot study aiming to evaluate the feasibility of enrolment rate is presented.

8.0 Pilot study

Hypothesis

The principal hypothesis of the current proposal is that an intermediate dose of LMWH (given once a day and without anti-Xa monitoring) for secondary prevention of PAVTE does not lead to an increase in rate of recurrent VTE and is associated with a reduction in major bleeding compared to commonly used strategies.

Study Objective

Evaluate the feasibility for conducting a multicenter single arm trial aiming to evaluate the safety and efficacy of an intermediate dose of LMWH (given once a day and without anti-Xa monitoring) for the secondary prevention of pregnancy associated VTE.

8.1 Study design

The pilot study will evaluate the enrollment feasibility of a single arm study. A randomized controlled trial, which would provide Level 1A evidence to guide practice, would be the ideal study design. However, due to the expected low recurrent VTE and low prevalence of the disease, large unachievable sample sizes would be required to test our principal hypothesis. A non-inferiority randomized controlled trial design comparing our proposed strategy to standard of care would require a total of 4400 patients (power 90%, alpha 0.025), making the study unfeasible.

In order to reduce the sample size, the use of a single arm study is proposed. In single arm studies a set of values are established, based on prior data and suggestions of those more likely to use the new intervention, against which a new intervention might be compared for efficacy and safety.

The efficacy hypothesis of the study is that the rate of recurrent VTE in patients treated with intermediate doses of LMWH would not exceed 2.5%. If the hypothesis is met, then it could

be assumed that an intermediate dose of LMWH for the secondary prevention of PAVTE (given once a day and without monitoring) is non-inferior to full dose strategies, leads to a reduction in major bleeding, could reduce cost of care, and be more comfortable for the patient. The sample size needed for the study was set at 756.

Given the low prevalence of the disease (1-2 events per 1000 pregnancies) and high number of participants required to conduct the study, along with the expected difficulties to enroll pregnant participants in the study, the use of a pilot study to evaluate feasibility is indispensable.

The pilot study will be conducted at five Canadian sites. In addition to feasibility data, we will carefully collect clinical data in the pilot study and strive to conduct the pilot in the same manner as the eventual full trial(294;295). All patients will be enrolled in the pilot study using the same inclusion and exclusion criteria that we have defined for the main study(295), and will receive the same intervention (an intermediate dose of LMWH after the acute treatment period). This approach will allow us to include patients from the pilot study into the main study sample by using an adaptive study approach, further reducing the number of patients needed to enroll for the main study(294).

8.3 Study population

We will strictly adhere to the criteria listed below to recruit eligible women to the trial. All patients will be enrolled within 30 days of the objective diagnosis of pregnancy associated DVT and/or PE. A research nurse, in conjunction with a study investigator, will be responsible for screening patients and assessing their eligibility so that all potentially eligible women are given the opportunity to participate.

8.3.1 Inclusion Criteria

1) All pregnant patients (pregnancy is defined as a positive serum or urine β HcG and /or a viable fetus shown in ultrasonography) with a confirmed diagnosis of DVT, PE or both and more than 4 weeks before the expected due date. The diagnosis of PE and DVT are defined as:

- i) High probability V/Q scan or a CTPA showing a filling defect in a segmental or larger vessel (single sub-segmental embolus will be considered as PE if ultrasonography is positive for DVT);
- ii) Non-high-probability V/Q scans with an ultrasound positive for DVT
- iii) A non-compressible segment of the lower extremity proximal venous system (over the trifurcation of the popliteal vein and up to the iliac vein) confirming the diagnosis of DVT on ultrasonography; or venography demonstrating a constant intraluminal filling defect of the lower extremity proximal venous system (over the trifurcation of the popliteal vein and up to the iliac vein). A DVT that does not fit the above criteria will be excluded from the study; AND

2) The event was diagnosed within 30 days of the day of enrollment; AND

3) Received an acceptable treatment strategy as defined by the study protocol during the first 30 days after the diagnosis of a pregnancy associated venous thromboembolism: dalteparin (200 u/kg OD or 100 u/kg BID), enoxaparin (1 mg/Kg bid or 2mg/Kg OD), nadroparin (171 U/Kg OD or 78 U/Kg BID) tinzaparin (175 u/kg od); or IV/SC UFH (using a full dose protocol) after the diagnosis of pregnancy associated venous thromboembolism. The initial drug and dosing strategy will be left to the treating physician discretion. During the acute treatment period physicians will be allowed to manage patients according to Anti-

Xa levels. After the initial 30 days of treatment changes in dose based on Anti-Xa levels or dosing changes from once a day to twice a day will be considered protocol violations.

8.3.2 Exclusion criteria

- i. Objectively diagnosed recurrent VTE during the first 30 days of treatment
- ii. Patients initially treated for venous thromboembolism with surgery; an endovascular procedure with or without stent; or had an inferior vena cava filter not removed within thirty days of the initiation of treatment
- iii. Patient age is less than 18 and legal guardians do not provide informed consent
- iv. Patient has a major contraindication to anticoagulation defined as: severe bleeding diathesis, < 50000 platelets; neurosurgery, intra-ocular surgery or intracranial bleeding during the last ten days; major head trauma; brain metastases; gastrointestinal or urinary bleeding in the last 14 days
- v. Extreme weight of greater than 150 KG or less than 40 kg at the time of enrollment
- vi. Patient needs lifelong anticoagulation for other indications (mechanical valves, Stroke, atrial fibrillation or APL syndrome)
- vii. A serum creatinine is greater than 80 mmol/L or the 24hs calculated clearance is <30 ml/min
- viii. Have a known allergy to LMWH or any of the components in the solution used as vehicle. Patients with confirmed heparin induced thrombocytopenia during the first 30 days of treatment
- ix. Have cancer (under treatment or less than 6 months free from disease)

- x. Have co-morbid condition (such as heart failure, COPD or dementia) with a life expectancy less than 3 months.
- xi. Refuse or are unable to provide informed consent
- xii. Geographic inaccessibility to follow-up

The ideal study design would involve enrolling all women diagnosed with pregnancy associated VTE. Enrolling participants who are diagnosed with VTE within less than 4 weeks of the expected due date, would reduce the exposure time to the intervention.

Furthermore, as shown in our survey, there is a wide variation of practices for the management of venous thromboembolism close to the peri-partum period, thereby making it difficult to create a uniform study protocol. The exclusion of patients with extreme body weight is justified as these patients require a more tailored approach based on Anti-Xa monitoring and more frequent dose adjustments.

The exclusion of patients managed with an interventional approach is justified given the uncertainty regarding the rate of recurrent VTE, especially in those who are treated with stent insertion.

Finally, patients with a creatinine clearance of less than 30 ml/min have a contraindication for the use of LMWH due to accumulation of the drug and potentially increased risk of bleeding

8.4 Study Intervention

Women with an objective diagnosis of PAVTE will be recruited during the first 30 days of treatment provided they are receiving one of the following strategies: dalteparin (200 u/Kg

OD or 100 u/Kg BID), enoxaparin (1 mg/Kg BID or 2 mg/Kg OD)¹, nadroparin (171 U/Kg OD or 78 U/Kg BID) tinzaparin (175 U/Kg OD); or IV/SC UFH (using a full dose protocol). Women who meet the inclusion criteria for the study and provide written, informed consent, will have blood drawn (creatinine, PTT, INR and CBC) to ensure there is no contraindication to LMWH therapy.

Following the initial 30 days of initial treatment, patients will start the study intervention period. All patients will be treated with 75% of the original dose without monitoring, administered subcutaneously once a day, and adjusted to extreme body weight changes defined as changes of more than 10% of the initial enrollment body weight.

This dose will be maintained throughout the duration of pregnancy and for at least six weeks after delivery to complete a minimum duration of treatment of 90 days. Dose adjustments based on anti-Xa levels during this study period will be considered a protocol violation, along with changes to twice a day dosing.

The recommended intermediate doses of LMWH are:

- i. Tinzaparin 131 U/Kg OD
- ii. Nadroparin 128 U/Kg OD
- iii. Dalteparin 150 U/Kg OD
- iv. Enoxaparin 1.5 MG/Kg OD²

To avoid variations in practice, a detailed management strategy for managing the peri-partum period is described below:

- i. Induced labor or c-section before expected due date

¹ As per the recommendations of the 2012 ACCP guidelines, the use of 1.5 mg/Kg of enoxaparin once daily is not advised(3)

² As per the recommendations of the 2012 ACCP guidelines 1.5 mg/Kg of enoxaparin would correspond to the 75% dose(3)

- ii. One day before the planned delivery date, switch once a day dosing of LMWH to twice a day, to be stopped 12 hours before delivery. The rationale for splitting the dose is to minimize the risk of full anticoagulant effect and “time in the therapeutic range” during labor.
- iii. Start prophylactic dose of LMWH (enoxaparin 40 mg, dalteparin 5000 U or tinzaparin 4500 U once a day) restarted 6 hours post vaginal delivery or 12 hours post C-section if no major bleeding occurred; and/or once epidural catheter is removed.
- iv. Forty eight hours after delivery restart once a day ante-partum dose for a minimum of 6 weeks, and ideally to complete for at least 3 months of treatment for those with a clear provoking factor (immobilization or surgery) and 6 months for those with unprovoked events .

The 75% dose will be given for the duration of pregnancy and at least 6 weeks after delivery (to complete at least 90 days of treatment including the acute treatment period) in accordance with the ACCP guidelines of 2012. The total duration of treatment beyond 90 days will be left to the discretion of the treating physician. The intervention will be discontinued early and appropriate clinical management will be initiated in the case of the following outcome events: A patient should be withdrawn from study if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient. Termination of study drug prior to completion of treatment may be considered in the case of adverse events such as: 1) Recurrent VTE (objectively documented proximal recurrent DVT or PE 2) Stillbirth (fetal death > 20 weeks gestation) considered to be associated with LMWH, 3) Miscarriage (fetal death < 20 weeks) considered to be associated with LMWH, 4) Major

hemorrhage, 5) Thrombocytopenia defined as a platelet count of less than 50.000, or confirmed heparin induced thrombocytopenia, and 6) Unprovoked bone fractures.

All patients who develop thrombocytopenia will have PF4 heparin induced thrombocytopenia ELISA and serotonin release assays to confirm or refute a diagnosis of heparin induced thrombocytopenia, before considering the termination of their treatment. Reasons for withdrawal will be clearly recorded and source documentation should be obtained for all relevant test results leading to the withdrawal (e.g. CT scan showing major bleeding or recurrent venous thromboembolism).

8.5 Primary and secondary outcome measures

1. Main outcome:
 - i. Obtain a precise estimate of the potential recruitment rate per center for the future single arm study (study feasibility)
2. Secondary outcomes:
 - i. Obtain a precise estimate of the primary efficacy outcome event rate for the main study (recurrent VTE)
 - ii. Obtain a precise estimate of the primary safety outcome event rate for the main study (major bleeding)
 - iii. Estimate the percentage of eligible candidates to enroll
 - iv. Estimate the percentage of patients who will complete follow-up compliant with an intermediate dose
 - v. Obtain a precise estimate of other relevant outcomes

8.5.1 Recruitment rate and study feasibility

The following criteria were set to claim feasibility of study

- 1- Yearly recruitment rate per center was defined as a minimum of three patients per center or at least 15 patients across all the five centers. The rationale is that 67 centers would potentially collaborate with the study and it will require less than 5 years completing the study if each center enrolls three patients per year.
- 2- Percentage of eligible candidates enrolled. The criterion for success was defined as more than 70%. The rationale for the criterion was to avoid selection bias that would eventually reduce the external validity of the results.
- 3- Percentage of patients who will complete follow-up compliant with an intermediate dose. The criterion for success was defined as more than 90% of participants completing follow up. If more than 10% of the patients cross-over to different strategies the interpretation of the results would be jeopardized.

8.5.2 Efficacy and safety outcomes

Rate of objectively adjudicated recurrent VTE (fatal or non-fatal) will be the main secondary outcome measures for this study and the primary efficacy outcome if a single arm study was feasible. The main safety outcome for the single arm study is major bleeding as defined by the ISTH. Secondary outcomes will also be assessed: PE related mortality, all-cause mortality, fatal recurrent VTE, ante-partum bleeding, post-partum bleeding, minor bleeding, heparin induced thrombocytopenia, fetal malformation and osteoporotic fractures. All clinically relevant secondary outcomes will be reviewed and adjudicated by an independent committee of experts.

1-Recurrent DVT

- i. Compression ultrasound revealing a new (compared to baseline ultrasound) area of non-compressibility of a venous segment above the trifurcation of the popliteal vein will be considered diagnostic of a DVT;
OR
- ii. Magnetic resonance showing a constant intraluminal filling defects above the trifurcation of the popliteal vein; OR
- iii. Venography demonstrating a constant intraluminal filling defects above the trifurcation of the popliteal vein

2-Recurrent PE

All patients with suspected recurrent PE will have a bilateral leg ultrasound before performing a V/Q scan. If a new DVT or a recurrent DVT is diagnosed following the previous criteria, recurrent PE will be diagnosed. If the ultrasound shows no evidence of DVT a V/Q scan will be performed. If the V/Q scan perfusion study shows no evidence of defects or reported as normal when compared to their baseline study, PE will be considered excluded. Recurrent PE will be confirmed if:

- i. If the V/Q scan is not-normal and presents a new unmatched segmental or greater perfusion defect is documented then PE will be diagnosed; OR
- ii. If a new matched or sub-segmental perfusion defect is documented in the V/Q scan a spiral CT scan will performed. If the spiral CT demonstrates an intraluminal-filling defect in a segmental or greater vessel in an area of normal perfusion on the baseline V/Q scan then PE will be diagnosed;
OR

- iii. All other patients will require pulmonary angiography to diagnose or exclude suspected recurrent or new PE. Pulmonary angiography demonstrating a constant intraluminal filling defect or a cutoff of a vessel > 2.5 mm in diameter is considered diagnostic for PE. PE found at autopsy will be also considered diagnostic of recurrent VTE; OR
- iv. The patient died from an autopsy proven PE or the cause of death was classified as secondary to PE. All cases where the cause of death could not be determined will be classified as secondary to PE

3-PE related mortality and all-cause mortality

An autopsy will be conducted whenever possible. Causes of death will be classified as being due to PE, being due to an alternative disorder, or as sudden death or unexplained sudden cardio-respiratory deterioration (both therefore potentially due to PE) according to the expert adjudication committee. Any death associated with PE occurring after the dose is reduced will be considered a recurrent VTE.

4-Major bleeding

Will be defined as per the ISTH recommendations(57;58):

- i. Fatal bleeding, and/or
- ii. Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intra-spinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon, and/or
- iii. Extra-surgical site bleeding causing a fall in hemoglobin level of 20 g L⁻¹ (1.24 mmol L⁻¹) or more, or leading to transfusion of two or more units of whole

blood or red cells, with temporal association within 24–48 h to the bleeding, and/or

- iv. Surgical site bleeding that requires a second intervention— open, arthroscopic, endovascular – or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection, and/or
- v. Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associated fall in hemoglobin level of at least 20 g L⁻¹ (1.24 mmol L⁻¹), or transfusion of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding.
- vi. The population is those who were treated for at least one day with the study intervention.

5-Obstetrical ante-partum Bleeding

Ante-partum hemorrhage (APH) is defined as bleeding from the birth canal after the 20th week of pregnancy requiring admission to hospital for assessment and management.

6-Severe Post-partum Bleeding

Severe post-partum bleeding will be defined as the amount of blood loss estimated by the attending obstetrician or midwife of more than 500 ml for vaginal delivery and more than 1000 ml for c-section, respectively, within 24 h of delivery; or a drop in the hematocrit greater than 10%.

7-Minor bleeding

All bleeding events not included in the previous groups will be qualified as minor bleeding.

8-Heparin Induced Thrombocytopenia

All patients who develop non-mild thrombocytopenia (platelets less than 115 or 50% decrease from baseline) will have a PF4 heparin induced thrombocytopenia ELISA and serotonin release assays to confirm or refute a diagnosis of heparin induced thrombocytopenia. Heparin induced thrombocytopenia will be diagnosed with a positive PF4 heparin induced thrombocytopenia ELISA assay and positive serotonin release assay. Patients will have their study drug discontinued and an alternative anticoagulant will be commenced as per standard of care (e.g. danaparoid, fondaparinux or lepirudin) in consultation with a hematologist, until the assays results are back. If the functional test is positive the patients will be considered to have HIT.

9-Osteoporotic Fractures

Patients presenting with unexplained bone pain will have plain film imaging of the affected area. If a cortical disruption is noted, a fracture will be diagnosed. Bone mineral densitometry will be conducted to determine if the fracture is secondary to osteoporosis. Before adjudicating the event to LMWH, other conditions associated with osteoporosis should be ruled out.

10-Miscarriage or stillbirth

Miscarriage will be defined as the loss of an embryo or fetus before the 20th week of pregnancy. Stillbirth will be defined as the delivery of a fetus that has died before birth after 20 weeks of pregnancy. Information about these outcomes will be evaluated by data safety monitoring board to evaluate if the event was associated with the use of LMWH.

11-Fetal malformation

Fetal malformation is defined as a physical defect present in a baby at birth that is permanent. Information about these outcomes will be evaluated by the data safety monitoring board to evaluate if the event was associated with the use of LMWH.

8.6 Data collection and outcome surveillance

Feasibility: We will determine the average per center recruitment rate. Detailed screening and enrolment logs will be completed at each participating center and sent to the Multi-Center Trial office monthly

Baseline Clinical Data: At the time of enrolment, demographic data, data regarding the pregnancy, potential risk factors, type of index event (DVT or PE), body mass index, baseline blood work (to exclude renal dysfunction or platelet abnormalities), history of recent major bleeding and initial treatment will be collected by the research nurse from the clinical record and interview with the patient. The research nurse will then review the signs and symptoms of VTE and bleeding and identify the date in which the dose of LMWH should be reduced by a quarter. The patient will be given instruction about the expected date to reduce her dose and will be given a prescription for pre-filled syringes of LMWH corresponding to 75% of her enrollment body weight. Patients will be advised to contact the nurse or investigator or go directly to the emergency department in the event of these or other suspected adverse events. Each participant and a dedicated second person (partner/friend/relative), if available, will be instructed to record the dates and times of subcutaneous study drug injection in a diary.

Monthly visit: The participants will be seen monthly until delivery and at twelve weeks post-delivery. At each visit patients will be asked about symptoms of DVT or PE, minor or major bleeding, tolerability of the study drug injections and the compliance diary will be

reviewed. A physical examination including weight, blood pressure, oxygen saturation, will be performed.

All participants will have monthly CBC and liver function tests. Anti-Xa levels will be drawn 4 hours post-injection of initial treatment and will be done at baseline, days 5 or 7, week 4 prior to dose decrease, monthly after the dose was decreased, at presentation to labor and delivery (if possible) and 12 weeks post-partum. All anti-Xa monitoring results will be blinded to the participating physicians and the adjudication committee, and will be used for eventual stratification of outcomes.

Additional treatments started will be recorded to document potential co-intervention or contamination. All patients and providers will be instructed to contact the study investigator if symptoms of recurrent VTE, major bleeding or other relevant outcomes occur.

To assess fetal wellbeing all patients will undergo obstetrical ultrasound within first two months of starting the intervention.

The following data will be collected after delivery:

- i. Labor and delivery data: Date and time of delivery, spontaneous onset or induced, reason for induction, vaginal delivery or caesarean section, reason for caesarean and mode of labor analgesia.
- ii. Fetal outcome data: Birth weight, APGAR scores, special care admissions, stillbirth and neonatal deaths (less than one month after birth).
- iii. Maternal outcome data: placental abruption and ante-partum and post-partum blood loss are categorized as major or minor as defined by standardized criteria (206).
- iv. Reasons for withdrawal from the study will be explored and recorded.

- v. **Unscheduled Assessments:** Subjects who contact the study coordinator or investigator between study assessments to report symptoms of VTE will be booked into a clinic for assessment and diagnostic tests as required. Subsequent treatment will be at the discretion of the subject's treating physician. All suspected events will be recorded and adjudicated.

8.7 Management of Bias

A single arm study might be susceptible to selection bias if investigators select the patients whom they will approach for the study. To protect against this, we will:

- i. Keep detailed screening logs and review which potential participants have not been enrolled.
- ii. Educate physicians at the participating centers about the evidence supporting the intervention and the need for clinical evidence.
- iii. Used clearly defined inclusion and exclusion criteria similar to the ones used in a randomized controlled study.

Open-label studies are prone to ascertainment bias. In this study all the relevant clinical outcomes endpoints (recurrent venous thromboembolism, major bleeding and stillbirth) are 'hard' outcomes, making ascertainment bias less likely. Ascertainment bias will also be minimized using the following strategies:

- i. Instructing all trial participants on the signs and symptoms of secondary outcomes and safety events with explicit instruction to contact study staff should these arise.
- ii. An independent Central Adjudication Committee will be assembled and will blindly adjudicate all study outcomes according to pre-specified criteria.

- iii. We will ensure that the committee membership includes experts in thrombosis and obstetrical medicine.

Other expected sources of bias are:

- A. Type of intervention or drug used during the first 30 days: The analysis of recurrent VTE or bleeding will be conducted stratified by type of dosing (once a day vs. twice a day), the type of LMWH used and by the use of anti-Xa monitoring.
- B. Time of exposure to the intervention: In our study it is expected that patients could be exposed from 2 months up to 7 months; those patients who are treated for a longer period of time are at a higher risk of adverse events. We will analyze the results stratified by time of exposure
- C. Withdrawal from the study remains a possibility that we cannot control in this type of study.

Another limitation in our study is the potential for changes to full dose or management based on Anti-Xa levels. Although we cannot address these issues in advance, we hope that if participating physician are motivated by the study question, then this limitation will be minimal.

8.8 Data analysis

The primary outcome for the pilot study will be reported as an absolute number and stratified by center. Proportions along with their associated 95% confidence intervals will be reported for the following variables:

- i. Number of eligible candidates enrolled
- ii. Number of patients lost to follow up

iii. Number of patients compliant with the intervention

The efficacy measures defined as the incidence of objectively confirmed new objectively proven recurrent VTE (non-inferiority) and major bleeding (superiority) in the study population will be reported along with the associated 95% confidence interval and analyzed using an intention to treat approach. These two outcomes will also be analyzed using a stratified approach, if possible, and according to the number of subjects enrolled by: initial index event (DVT vs. PE); duration of treatment, initial treatment strategy and drug for treatment. All other outcomes will also be reported as proportions with the associated 95% confidence interval. All the statistical analysis will be conducted using SAS 9.2 for Windows (Cary, NC).

8.9 Feasibility

The VECTOR group (Venous Thrombosis Clinical Trials Organization) is a large multicenter (Ottawa, London, Montreal, Halifax) collaborative research group in venous thrombosis. This group has an excellent track record for completing VTE-related clinical trials.

8.9.1 Recruitment rate

The pilot study to assess feasibility would be conducted in five Canadian centers for the duration of one year (The Ottawa Hospital, Montreal Jewish General Hospital, the London Health Sciences Center, the Queen Elizabeth II Centre in Halifax and Hamilton Health Sciences).

The number of potential participants is expected to be 1- Ottawa: Based on an estimated population of 880.000=15 cases; London and Halifax based on an estimated population of 366.000=6; Hamilton based on a population of 519.000=9 cases; and Montreal based on a population on 3.316.000=55 cases.

8.9.2 Recruitment strategies

Enrollment of all the potential participants is the main objective of the pilot study. Due to the low potential rate of eligible patients, special efforts will be made to increase the screening of potential candidates.

Recruitment of patients will be performed through the Thrombosis and Obstetrics units at the participating centers. All the referred pregnant patients to the participating thrombosis centers during the pilot study will be assessed for eligibility by one of the study nurse coordinators.

Patients will be approached and assessed by the principal investigator after being screened and invited to participate in the study by one of the RN study coordinators. The study coordinator will provide the patient with the information about the study aims, strategies, and risks in order to obtain informed consent. Study coordinators will act as the primary source of patient contact.

To increase our screening for eligible patients, all radiology requests for suspected DVT or PE will include a questionnaire to be completed by the referring physician (including age, gender, pregnancy status, Wells criteria and exclusion criteria). All positive studies will be further assessed for eligibility and a log of all positive studies will be kept, and patients will be contacted by the study research nurse via telephone to explain the study.

We will also conduct a campaign in maternal health units, family practices, general wards and emergency departments of the participating centers to increase awareness of the study. As discussed in the study intervention, no specific LMWH will be used during the dose reduction phase and there will be no specific treatment strategy suggested for the initial 30 days of treatment. This approach will increase the participation rate by allowing physicians to continue with their current practices. Finally, by not suggesting any specific drug,

regulatory approval of drugs not used in the country of participation before the initiation of the study is avoided.

8.11 Safety

The key goal of all VTE treatments is to reduce the risk of recurrent VTE, while reducing the risk of side effects from anticoagulant therapy, particularly major bleeding.

A data safety monitoring board consisting of three physicians (to be named) will review the proportion of patients with recurrent thrombosis, bleeding and other events every 6 months or consecutively every time recruitment reaches a pre specified sample size. Criteria for stopping the trial will be determined by members of the data safety monitoring board working in collaboration with the principal investigator.

Given our sample size calculations and that Δ was set at 2.5%; more than 15 events must occur to exceed the margin at the end of study. Given the small number of patients to be recruited in the pilot study we have decided to stop the pilot study if at any point of the study duration four or more patients experienced a confirmed recurrent VTE. The lower bound of the 95% confidence interval would be higher than 5% which is considered the maximum accepted rate of recurrent VTE in the non-pregnant population during the treatment for DVT or PE.

Study participants will be followed for recurrent VTE until the completion of their treatment; they will be carefully instructed on the signs and symptoms of VTE and instructed to contact study personnel should these arise. They will be provided with a reminder card outlining the signs and symptoms of DVT and PE, along with contact numbers for research staff and the participating Thrombosis Clinics. With the participant's permission we will also teach at least one close friend or family member about these signs or

symptoms and instruct them to contact us should they arise. The expected risk of other major complications such as osteoporosis or heparin induced thrombocytopenia is low. LMWHs do not cross the placental barrier, thereby making them safe for the fetus when administered during pregnancy. A small study that specifically examined the teratogenicity potential of LMWHs found no difference in the incidence of congenital malformations between women receiving LMWH and those receiving low-dose aspirin (207) In our systematic review the rate of miscarriage or stillbirth was 2% and the rate of fetal malformation was <0.1% in those treated with LMWH vs. 5-7 and 2%, respectively, in the general population.

8.11 Anticipated results and conclusions

The results of our pilot trial will be used by the investigators to inform decisions about the conduction of the full/definitive trial. Pilot data demonstrating feasibility will also be reassuring to funding agencies before a commitment is made to fund an international multicenter trial that will likely require up to 67 sites and over 760 participants. Several factors dictate that a pilot is essential prior to initiating this trial: 1) the expense of the single arm study dictate that an accurate estimate of recruitment rates and compliance rates is essential prior to embarking on the main study. 1) Based on the findings of our systematic review, more accurate estimates of event rates in patients receiving the intervention are required to calculate a more precise estimate of sample size; 2) data concerning recruitment for this study population are limited. Regardless of the results of the pilot trial, we will make every effort to publish and present our data and conclusions about feasibility such that future researchers might benefit from this work

The results of the full trial have the potential to change the management of PAVTE, the most common cause of maternal death.

8.12 Study management

The trial will be coordinated from the Ottawa Hospital Research Institute's (OHRI) Clinical Epidemiology Unit, where the principal investigator is based. A Multicenter Trial Coordinator will be recruited and trained. The Multicenter Trial Coordinator, supervised by the principal investigator, will be responsible for overseeing the day to day conduct of the study in the different centers.

Study nurses at each site will carry out patient screening, recruitment, case report form completion, patient education, and initiation of study interventions (arranging lower extremity ultrasonography or V/Q scan in case of suspected recurrent cases).

Data management will be overseen by the OHRI CEP-data management services and a study statistician. The data management services group is responsible for database administration, data entry, and data management, including quality assurance activities. The cleaned database will be provided to the biostatistician for analysis, conducted under the supervision of Dr. Gándara and the study statistician.

Our research team will be composed of experienced researchers and clinicians with expertise in thrombosis and clinical research. Dr. Gándara is a clinical and research fellow at the University of Ottawa and the Ottawa Hospital Research Institute and is an MSc in Epidemiology candidate. Dr. Gándara will review the study progress regularly and, after consultation with co-investigators, give final approval to any changes to study procedures. Each co-investigator is responsible for conduct of the study at their respective sites.

A Steering Committee comprising all of the study's co-investigators will manage the overall conduct of the study and meet twice a year via teleconference. If funded, the steering committee will meet by teleconference in the spring of 2012 and 2013 to ensure ongoing enthusiasm for the study, review the conduct of the study, and analyze if the study is feasible.

A Data Safety and Monitoring Board will be created. The Data Safety and Monitoring Board will be independent and composed of 3 members: an expert in thrombosis medicine and single arm studies (Chair), and two experts in thromboembolic diseases or pregnancy and training in research methods. All members of the Data Safety and Monitoring Board will remain at arms-length from the study. All recurrent objectively recurrent VTE or deaths will be reported to and reviewed by the Data Safety and Monitoring Board. The Data Safety and Monitoring Board will meet after every 50th participant is enrolled (or every six months; twice during the pilot study) and will report to the principal investigator. Should safety issues arise that the Data Safety and Monitoring Board feel compromise participant safety; an extraordinary meeting will be conducted, and then of all the co-investigators will convene to decide if the trial should be amended or terminated.

9.0 Conclusions

Pregnancy associated venous thromboembolism is the most frequent cause of maternal death in developed countries. The use of anticoagulant drugs is a highly effective way to prevent recurrent VTE. Low molecular weight heparin has become the preferred agent for the management of PAVTE given its better efficacy, safety and comfort for use in comparison to other strategies. However, most of the evidence for supporting the use of LMWH during pregnancy is based on observational trials and extrapolations from other populations. Compared to the non-pregnant population where the use of an intermediate dose given once a day without anti-Xa monitoring during secondary prevention is favored as it has been found to reduce the incidence of major bleeding and facilitate patient management, the physiologic changes occurring during pregnancy have lead experts to suggest the use of more aggressive strategies for secondary prevention without supporting evidence.

Well-designed randomized controlled trials conducted in the non-pregnant population suggest that the use of intermediate doses of LMWH for secondary prevention is as effective as more aggressive strategies and evidence from observational trials in pregnant patients supports this hypothesis.

In the hierarchy of study designs, randomized controlled trials provide the best quality of information and are needed to evaluate the efficacy of interventions. Still, this approach cannot be applied in all populations. Although, a randomized controlled trial evaluating different treatment strategies for the secondary prevention of PAVTE is highly needed, it would require large multicenter collaboration over many years and at very high costs. Barriers to conducting a randomized controlled trial include: the low prevalence of the disease (1 to 2 cases per 1000 pregnancies), the proportion of outcomes during treatment (1.12%), the large sample size needed to claim non-inferiority, the absence of previous placebo controlled trials to estimate the

efficacy of full dose monitored LMWH twice a day, and difficulty in enrolling patients in experimental studies, due to fear of harm to the mother or fetus. A hypothetical randomized controlled trial would require a sample size of at least 4000 patients, and most of the assumptions about the efficacy and safety of treatment would be based on low quality studies. For these reasons there is a need to apply different study designs to provide guidance for clinical management with the best possible quality of evidence. Given the small amount of relevant clinical evidence and the need for preliminary evidence, a single arm non-randomized trial was determined to be the most reasonable approach.

Non-controlled studies require a smaller sample size but their estimates are highly dependent on the presence of confounders, bias and prior information. Any study aiming to enroll pregnant patients would face similar limitations regarding sample size needed to accurately estimate efficacy. The use of a single arm study to assess the safety and effectiveness of an intermediate dose of LMWH for secondary prevention of PAVTE was deemed an appropriate strategy to reduce sample size, while providing clinically relevant results and the foundations for future studies given the quality of the available evidence..

The thesis aimed to evaluate the feasibility for conducting a single arm study using intermediate doses of LMWH for secondary prevention of pregnancy associated VTE. From a methodological perspective there was no prior randomized placebo or active controlled study from which the Δ or the baseline rate of recurrent VTE during secondary prevention with full doses of LMWH could be calculated. To improve the assumptions required for formulating the hypothesis for the study a systematic review aiming to calculate the baseline rate of recurrent VTE in patients treated with full doses of LMWH for secondary prevention was conducted alongside a survey to elicit the Δ , evaluate current clinical practices and determine clinical equipoise.

Twenty eight relevant studies (including 1122 patients) using at least nine different strategies for secondary prevention of PAVTE were included in the systematic review, none of which was a randomized controlled study. Full doses of LMWH or UFH for the secondary prevention share a similar efficacy profile for the reduction of recurrent VTE pooled proportion 0.012 (95% CI=0.006 to 0.02) and 0.017 (95%CI= 0.001 to 0.05) respectively, and a similar bleeding risk profile pooled proportion 0.023 (95% CI=0.01 to 0.041) and 0.038(95%CI= 0.002 to 0.11) respectively. The use of intermediate doses for secondary prevention was associated with a pooled proportion of 0.011 (95% CI= 0.0011 to 0.029), not different to the pooled proportion of patients treated with full doses.

The use of a survey to elicit the $-\Delta$ has not been reported in the literature. The main advantage of this approach is that it provides the researcher with the perspective of the future users of the intervention. Under the assumption that an intermediate dose of LMWH would lead to a reduction in bleeding and would be more comfortable for the patient, physicians accepted an absolute increase in the rate of recurrent VTE to claim non-inferiority of 1.2% over a baseline absolute risk identified in the systematic review of 1.15%, corresponding to an OR of 2.1. Interestingly, with this approach physicians accepted a similar loss in efficacy to the one calculated by statistical methods in non-inferiority randomized trials conducted in the non-pregnant population.

The survey revealed that there was clinical equipoise among physicians to conduct a study evaluating the safety and efficacy of an intermediate dose of LMWH for secondary prevention pregnancy associated VTE. Although the standard of care for secondary prevention of PAVTE in the survey was the use of full dose LMWH, an intermediate dose was used by almost a quarter of the physicians. The survey also showed how a paucity of good clinical evidence translates into a wide variation in practice regarding dosing and anti-Xa monitoring.

With the results of the systematic review and the survey, a single arm study evaluating the safety and efficacy of an intermediate dose of LMWH for the secondary prevention of PAVTE is proposed. The efficacy hypothesis of the study is that the rate of recurrent VTE in patients treated with intermediate doses of LMWH would not exceed 2.5%. The safety hypothesis is that an intermediate dose would lead to 60% relative reduction in major bleeding, or the absolute rate of major bleeding would be lower than 1%. If both hypotheses are met, then it could be assumed that an intermediate of LMWH for the secondary prevention of PAVTE (given once a day and without monitoring) is non-inferior to full dose strategies, leads to a reduction in major bleeding, would reduce cost of care, and be more comfortable for the patient. The sample size needed for the study was set at 756 with a power of 80 and one sided test with an alpha of 0.05 for the efficacy hypothesis.

To avoid wasting highly needed resources and expected enrollment limitations, a pilot study aiming to assess the feasibility of enrollment, defined as 15 participants during a 12 month period across five Canadian centers, is proposed prior to embarking on a large single arm study. In conclusion, in light of the small amount of relevant clinical data to guide the management of PAVTE, there is a need for supporting evidence and a single arm study may be reasonable to provide practicing physicians that necessary information.

10.0 References

Reference List

- (1) Spencer FA, Emery C, Lessard D, Anderson F, Emani S, Aragam J, et al. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. *J Gen Intern Med* 2006 Jul;21(7):722-7.
- (2) Heit JA, Cohen AT, Anderson FA, on Behalf of the VTE Impact Assessment Group. Estimated Annual Number of Incident and Recurrent, Non-Fatal and Fatal Venous Thromboembolism (VTE) Events in the US. *ASH Annual Meeting Abstracts* 2005 Dec 14;106(11):910.
- (3) Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schunemann HJ, for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive Summary. *Chest* 2012 Feb 1;141(2 suppl):7S-47S.
- (4) Tapson VF. Acute pulmonary embolism: comment on "time trends in pulmonary embolism in the United States". *Arch Intern Med* 2011 May 9;171(9):837-9.
- (5) Rodger M, Carrier M, Gandara E, Le Gal G. Unprovoked Venous Thromboembolism: Short term or Indefinite Anticoagulation? Balancing Long-Term Risk and Benefit. *Blood Reviews* 2010 Jul;24(4):171-8.
- (6) Kline JA, Hernandez-Nino J, Jones AE, Rose GA, Norton HJ, Camargo CA, Jr. Prospective study of the clinical features and outcomes of emergency department patients with delayed diagnosis of pulmonary embolism. *Acad Emerg Med* 2007 Jul;14(7):592-8.
- (7) Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ, III. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med* 2005 Nov 15;143:697-706.
- (8) Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. *J Thromb Haemost* 2008 Apr;6:632-7.
- (9) Sultan AA, West J, Tata LJ, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study. *Br J Haematol* 2012 Feb;156(3):366-73.
- (10) Liu S, Rouleau J, Joseph KS, Sauve R, Liston RM, Young D, et al. Epidemiology of pregnancy-associated venous thromboembolism: a population-based study in Canada. *J Obstet Gynaecol Can* 2009 Jul;31(7):611-20.
- (11) Bourjeily G, Paidas M, Khalil H, Rosene-Montella K, Rodger M. Pulmonary embolism in pregnancy. *Lancet* 2009 Nov 2;375(9713):500-12.

- (12) Ray JG, Chan WS. Deep vein thrombosis during pregnancy and the puerperium: a meta-analysis of the period of risk and the leg of presentation. *Obstet Gynecol Surv* 1999 Apr;54(4):265-71.
- (13) Virkus RA, Lokkegaard EC, Bergholt T, Mogensen U, Langhoff-Roos J, Lidegaard O. Venous thromboembolism in pregnant and puerperal women in Denmark 1995-2005. A national cohort study. *Thromb Haemost* 2011 Aug;106(2):304-9.
- (14) Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006 Apr 1;367(9516):1066-74.
- (15) Berg CJ, Atrash HK, Koonin LM, Tucker M. Pregnancy-related mortality in the United States, 1987-1990. *Obstet Gynecol* 1996 Aug;88(2):161-7.
- (16) Simpson EL, Lawrenson RA, Nightingale AL, Farmer RD. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. *BJOG* 2001 Jan;108:56-60.
- (17) Andersen BS, Steffensen FH, Sorensen HT, Nielsen GL, Olsen J. The cumulative incidence of venous thromboembolism during pregnancy and puerperium. An 11 year Danish population - based study of 63,300 pregnancies. *Acta Obstet Gynecol Scand* 1998;77:170-3.
- (18) Samuelsson E, Hellgren M, Hogberg U. Pregnancy-related deaths due to pulmonary embolism in Sweden. *Acta Obstet Gynecol Scand* 2007;86(4):435-43.
- (19) Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med* 2011 May 9;171(9):831-7.
- (20) Voke J, Keidan J, Pavord S, Spencer NH, Hunt BJ. The management of antenatal venous thromboembolism in the UK and Ireland: a prospective multicentre observational survey. *Br J Haematol* 2007 Nov;139(4):545-58.
- (21) Segal JB, Streiff MB, Hoffman LV, Thornton K, Bass EB. Management of venous thromboembolism: a systematic review for a practice guideline. *Ann Intern Med* 2007 Feb 6;146:211-22.
- (22) Strijkers HW, ten Cate-Hoek AJ, Bukkems SFFW, Wittens HA. Management of deep vein thrombosis and prevention of post-thrombotic syndrome. *BMJ* 2011 Oct 31;343.
- (23) Rosendaal FR. Venous thrombosis: a multicausal disease. *The Lancet* 1999 Apr 3;353(9159):1167-73.
- (24) Bagot CN, Arya R. Virchow and his triad: a question of attribution. *Br J Haematol* 2008 Oct;143(2):180-90.
- (25) Bulger CM, Jacobs C, Patel NH. Epidemiology of acute deep vein thrombosis. *Techniques in Vascular and Interventional Radiology* 2004 Jun;7(2):50-4.

- (26) Rodger MA, Walker MC, Wells PS. Diagnosis and treatment of venous thromboembolism in pregnancy. *Best Pract Res Clin Haematol* 2003;16:279-96.
- (27) Eichinger S, Weltermann A, Phillipp K, Hafner E, Kaider A, Kittl E-M, et al. Prospective evaluation of hemostatic system activation and thrombin potential in healthy pregnant women with and without factor V leiden. *Thromb Haemost* 1999;82(4):1232-6.
- (28) Clark P, Brennan J, Conkie JA, McCall F, Greer IA, Walker ID. Activated protein C sensitivity, protein C, protein S and coagulation in normal pregnancy. *Thromb Haemost* 1998 Jun;79(6):1166-70.
- (29) bou-Nassar K, Kovacs MJ, Kahn SR, Wells P, Doucette S, Ramsay T, et al. The effect of dalteparin on coagulation activation during pregnancy in women with thrombophilia. A randomized trial. *Thrombosis & Haemostasis* 2007 Jul;98(1):163-71.
- (30) Comeglio P, Fedi S, Liotta AA, Cellai AP, Chiarantini E, Prisco D, et al. BLOOD CLOTTING ACTIVATION DURING NORMAL PREGNANCY. *Thrombosis Research* 1996 Nov 1;84(3):199-202.
- (31) Hellgren M. Hemostasis during Normal Pregnancy and Puerperium. *Semin Thromb Hemost* 2003;29(02):125,130.
- (32) Macklon NS, Greer IA, Bowman AW. An ultrasound study of gestational and postural changes in the deep venous system of the leg in pregnancy. *Br J Obstet Gynaecol* 1997 Feb;104(2):191-7.
- (33) Rodger M. Evidence base for the management of venous thromboembolism in pregnancy. *Hematology Am Soc Hematol Educ Program* 2010;2010:173-80.
- (34) Middeldorp S. How I treat pregnancy-related venous thromboembolism. *Blood* 2011 Nov 17;118(20):5394-400.
- (35) Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood* 2005 Apr 5;106:401-7.
- (36) Gates S, Brocklehurst P, Davis LJ. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period (Cochrane Review). *The Cochrane Library*. Oxford: Update Software; 2002.
- (37) Jacobsen AF, Dahm A, Bergrem A, Jacobsen EM, Sandset PM. Risk of venous thrombosis in pregnancy among carriers of the factor V Leiden and the prothrombin gene G20210A polymorphisms. *J Thromb Haemost* 2010 Nov;8(11):2443-9.
- (38) Pabinger I, Grafenhofer H, Kyrle PA, Quehenberger P, Mannhalter C, Lechner K, et al. Temporary increase in the risk for recurrence during pregnancy in women with a history of venous thromboembolism. *Blood* 2002 Aug 1;100:1060-2.
- (39) Concise Medical Dictionary. Oxford University Press; 2010.

- (40) James AH, Tapson VF, Goldhaber SZ. Thrombosis during pregnancy and the postpartum period. *Am J Obstet Gynecol* 2005 Jul;193(1):216-9.
- (41) James AH, Brancazio LR, Ortel TL. Thrombosis, thrombophilia, and thromboprophylaxis in pregnancy. [Review] [150 refs]. *Clinical Advances in Hematology & Oncology* 2005 Mar;3(3):187-97.
- (42) Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows RF, Kearon C, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot in This Pregnancy Study Group. *N Engl J Med* 2000 Nov 16;343(20):1439-44.
- (43) Jacobsen AF, Skjeldestad FE, Sandset PM. Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium--a register-based case-control study. *Am J Obstet Gynecol* 2008 Feb;198(2):233-7.
- (44) Kakkar VV, Howe CT, Flanc C, Clarke MB. Natural history of postoperative deep-vein thrombosis. *Lancet* 1969 Aug 2;2(7614):230-2.
- (45) Ray JG, Chan WS. Deep vein thrombosis during pregnancy and the puerperium: a meta-analysis of the period of risk and the leg of presentation. *Obstet Gynecol Surv* 1999 Apr;54:265-71.
- (46) Knight M. Antenatal pulmonary embolism: risk factors, management and outcomes. *BJOG* 2008 Mar;115(4):453-61.
- (47) Moser KM, Fedullo PF, Litlejohn JK, Crawford R. Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. *JAMA* 1994 Jan 19;271(3):223-5.
- (48) Gandara E, Wells PS. Diagnosis: use of clinical probability algorithms. *Clin Chest Med* 2010 Dec;31(4):629-39.
- (49) Bates SM. Optimal management of pregnant women with acute venous thromboembolism. *Haemostasis* 29(SUPPL 1)(pp 107-111), 1999 Date of Publication: Dec 1999 1999;(SUPPL. 1):107-11.
- (50) Chan W-S, Lee A, Spencer FA, Crowther M, Rodger M, Ramsay T, et al. Predicting deep venous thrombosis in pregnancy: Out in "LEFT" field? *Annals of Internal Medicine* 151(2)(pp 85-92), 2009 Date of Publication: 21 Jul 2009 2009;(2):85-92.
- (51) Roy PM, Meyer G, Vielle B, Le GC, Verschuren F, Carpentier F, et al. Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism. *Ann Intern Med* 2006 Feb 7;144(3):157-64.
- (52) Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, Hirsch A, et al. Computed Tomographic Pulmonary Angiography vs Ventilation-Perfusion Lung Scanning in Patients With Suspected Pulmonary Embolism. *JAMA: The Journal of the American Medical Association* 2007 Dec 19;298(23):2743-53.

(53) Wood KE. A History of Pulmonary Embolism and Deep Venous Thrombosis. *Critical care clinics* 25[1], 115-131. 1-1-2009.

Ref Type: Abstract

(54) Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet* 1960 Jun 18;1(7138):1309-12.

(55) Carrier M, Le Gal Gg, Wells PS, Rodger MA. Systematic Review: Case-Fatality Rates of Recurrent Venous Thromboembolism and Major Bleeding Events Among Patients Treated for Venous Thromboembolism. *Annals of Internal Medicine* 2010 May 4;152(9):578-89.

(56) Laporte S, Mismetti P, D+rcousus H, Uresandi F, Otero R, Lobo JL, et al. Clinical Predictors for Fatal Pulmonary Embolism in 15 520 Patients With Venous Thromboembolism. *Circulation* 2008 Apr 1;117(13):1711-6.

(57) Schulman S, ANGER+às U, Bergqvist D, ERIKSSON B, Lassen MR, FISHER W, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *Journal of Thrombosis and Haemostasis* 2010;8(1):202-4.

(58) Schulman S, Kearon C, the SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION OF THE SCIENTIFIC AND STANDARDIZATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis* 2005;3(4):692-4.

(59) Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004 Sep;126(3 Suppl):627S-44S.

(60) Anand SS, Bates S, Ginsberg JS, Levine M, Buller H, Prins M, et al. Recurrent Venous Thrombosis and Heparin Therapy: An Evaluation of the Importance of Early Activated Partial Thromboplastin Times. *Archives of Internal Medicine* 1999 Sep 27;159(17):2029-32.

(61) Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-based Clinical Practice Guidelines. (8th ed). *Chest* 2008;133:844S-86S.

(62) Patel JP, Hunt BJ. Where do we go now with low molecular weight heparin use in obstetric care? *Journal of Thrombosis and Haemostasis* 6(9)(pp 1461-1467), 2008
Date of Publication: 2008 2008;(9):1461-7.

(63) White RH, Ginsberg JS. Low-Molecular-Weight Heparins: Are they all the Same? *British Journal of Haematology* 2003;121(1):12-20.

- (64) Stratta P, Canavese C, Cena T, Quaglia M, Pergolini P, Bellomo G, et al. Low-molecular-weight-heparin and pregnancy, when the dose does it: a nephrologist's opinion: a rebuttal. *J Thromb Haemost* 2011 Oct;9(10):2127-9.
- (65) Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet* 1960;1:1309-12.
- (66) Chan WS, Anand SS, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves. *Arch Intern Med* 2000;160(2):191-6.
- (67) Wesseling J, Van DD, Heymans HSA, Rosendaal FR, Geven-Boere LM, Smrkovsky M, et al. Coumarins during pregnancy: Long-term effects on growth and development of school-age children. *Thrombosis and Haemostasis* 85(4)(pp 609-613), 2001 Date of Publication: 2001 2001;(4):609-13.
- (68) Wesseling J, Van DD, Heymans HS, Van D, V, Sauer PJ, Touwen BC, et al. Behavioural outcome of school-age children after prenatal exposure to coumarins. *Early Hum Dev* 2000 Jun;58(3):213-24.
- (69) Wesseling J, Van DD, Smrkovsky M, Van D, V, Geven-Boere LM, Sauer PJ, et al. Neurological outcome in school-age children after in utero exposure to coumarins. *Early Hum Dev* 2001 Jul;63(2):83-95.
- (70) Dempfle CE. Minor transplacental passage of fondaparinux in vivo. *N Engl J Med* 2004 Apr 29;350(18):1914-5.
- (71) Bates SM, Greer I, Middeldorp S, Prabalos A, Vandvik PO. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest Suppl*, e691S-e736S. 7-2-2012.

Ref Type: Journal (Full)

- (72) Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk P, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2008 Sep;29(18):2276-315.
- (73) Snow V, Qaseem A, Barry P, Hornbake ER, Rodnick JE, Tobolic T, et al. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med* 2007 Feb 6;146:204-10.
- (74) Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. [Review] [108 refs]. *Blood* 2005 Jul 15;106(2):401-7.
- (75) Bates SM, Ginsberg JS. 5 Anticoagulants in pregnancy: fetal effects. *Baillière's Clinical Obstetrics and Gynaecology* 1997 Sep;11(3):479-88.

- (76) Dimitrakakis C, Papageorgiou P, Papageorgiou I, Antzaklis A, Sakarelou N, Michalas S. Absence of transplacental passage of the low molecular weight heparin enoxaparin. *Haemostasis* 30(5)(pp 243-248), 2000 Date of Publication: 2000 2000;(5):243-8.
- (77) Boutitie F, Pinede L, Schulman S, Agnelli G, Raskob G, Julian J, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. *BMJ* 2011;342:d3036.
- (78) Che Yaakob CA, Dzarr AA, Ismail AA, Zuky Nik Lah NA, Ho JJ. Anticoagulant therapy for deep vein thrombosis (DVT) in pregnancy. *Cochrane Database Syst Rev* 2010;6:CD007801.
- (79) Greer I, Thompson J. THE ACUTE MANAGEMENT OF THROMBOSIS AND EMBOLISM DURING PREGNANCY AND THE PUERPERIUM. 2010.

Ref Type: Internet Communication

- (80) McLintock C, Brighton T, Chunilal S, Dekker G, McDonnell N, McRae S, et al. Recommendations for the diagnosis and treatment of deep venous thrombosis and pulmonary embolism in pregnancy and the postpartum period. *Aust N Z J Obstet Gynaecol* 2011 Oct 6.
- (81) Knight M, UKOSS. Antenatal pulmonary embolism: risk factors, management and outcomes. *BJOG: An International Journal of Obstetrics & Gynaecology* 2008 Mar;115(4):453-61.
- (82) Voke J, Keidan J, Pavord S, Spencer NH, Hunt BJ, British Society for Haematology Obstetric Haematology Group. The management of antenatal venous thromboembolism in the UK and Ireland: a prospective multicentre observational survey. *British Journal of Haematology* 2007 Nov;139(4):545-58.
- (83) Greer IA. The acute management of venous thromboembolism in pregnancy. *Curr Opin Obstet Gynecol* 2001 Dec;13(6):569-75.
- (84) Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997;337(10):688-98.
- (85) Sanson BJ, Lensing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost* 1999 May;81:668-72.
- (86) Monreal M, Lافoz E, Olive A, del Rio L, Vedia C. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. *Thromb Haemost* 1994 Jan;71:7-11.
- (87) Pettila V, Leinonen P, Markkola A, Hiilesmaa V, Kaaja R. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. *Thromb Haemost* 2002 Feb;87:182-6.

- (88) Crowther MA, Spitzer K, Julian J, Ginsberg JS, Johnston M, Crowther R, et al. Pharmacokinetic profile of a low-molecular weight heparin (Reviparin) in pregnant patients: a prospective cohort study. *Thromb Res* 2000;98(2):133-8.
- (89) Wells PS, Anderson DR, Rodger MA, Forgie MA, Florack P, Touchie D, et al. A randomized trial comparing 2 low-molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. *Arch Intern Med* 2005 Apr 11;165:733-8.
- (90) Bauersachs RM. Treatment of venous thromboembolism during pregnancy. *Thromb Res* 2009;123 Suppl 2:S45-S50.
- (91) Greer IA. Venous thromboembolism and anticoagulant therapy in pregnancy. *Gend Med* 2005;2 Suppl A:S10-S17.
- (92) Arya R. How I manage venous thromboembolism in pregnancy. *Br J Haematol* 2011 Jun;153(6):698-708.
- (93) Marik PE. Venous thromboembolism in pregnancy. *Clin Chest Med* 2010 Dec;31(4):731-40.
- (94) Casele HL, Laifer SA, Woelkers DA, Venkataramanan R. Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy. *American journal of obstetrics and gynecology* 181[5], 1113-1117. 11-1-1999.

Ref Type: Abstract

- (95) Bates SM, Ginsberg JS. How we manage venous thromboembolism during pregnancy. *Blood* 2002 Nov 15;100(10):3470-8.
- (96) Sephton V, Farquharson RG, Topping J, Quenby SM, Cowan C, Back DJ, et al. A Longitudinal Study of Maternal Dose Response to Low Molecular Weight Heparin in Pregnancy. *Obstetrics & Gynecology* 2003;101(6).
- (97) Barbour LA, Oja JL, Schultz LK. A prospective trial that demonstrates that dalteparin requirements increase in pregnancy to maintain therapeutic levels of anticoagulation. *Am J Obstet Gynecol* 2004 Sep;191(3):1024-9.
- (98) Rodie VA, Thomson AJ, Stewart FM, Quinn AJ, Walker ID, Greer IA. Low molecular weight heparin for the treatment of venous thromboembolism in pregnancy: a case series. *BJOG* 2002 Sep;109(9):1020-4.
- (99) Friedrich E, Hameed AB. Fluctuations in anti-factor Xa levels with therapeutic enoxaparin anticoagulation in pregnancy. *J Perinatol* 2010 Apr;30(4):253-7.
- (100) Smith MP, Norris LA, Steer PJ, Savidge GF, Bonnar J. Tinzaparin sodium for thrombosis treatment and prevention during pregnancy. *American Journal of Obstetrics & Gynecology* 2004 Feb;190(2):495-501.

- (101) Copplestone JA, Pavord S, Hunt BJ. Anticoagulation in pregnancy: a survey of current practice. *Br J Haematol* 2004 Jan;124(1):124-5.
- (102) Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight Heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;349:146-53.
- (103) Pini M, Aiello S, Manotti C, Pattacini C, Quintavalla R, Poli T, et al. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. *Thromb Haemost* 1994;72:191-7.
- (104) Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. *World J Surg* 1996 Jun;20:521-6.
- (105) Gonzalez-Fajardo JA, Arreba E, Castrodeza J, Perez JL, Fernandez L, Agundez I, et al. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. *J Vasc Surg* 1999;30(2):283-92.
- (106) Lopaciuk S, Bielska-Falda H, Noszczyk W, Bielawiec M, Witkiewicz W, Filipecki S, et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. *Thromb Haemost* 1999;81:26-31.
- (107) Veiga F, Escriba A, Maluenda MP, Lopez Rubio M, Margalet I, Lezana A, et al. Low molecular weight Heparin (Enoxaparin) versus oral anticoagulant therapy (Acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. *Thromb Haemost* 2000;84:559-64.
- (108) Lopez-Beret P, Orgaz A, Fontcuberta J, Doblaz M, Martinez A, Lozano G, et al. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. *J Vasc Surg* 2001 Jan;33:77-90.
- (109) Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med* 2002 Aug 12;162:1729-35.
- (110) Iorio A, Guerini F, Pini M. Low-molecular-weight heparin for the long-term treatment of symptomatic venous thromboembolism: meta-analysis of the randomized comparisons with oral anticoagulants. *J Thromb Haemost* 2003;1:1906-13.
- (111) van der Heijden JF, Hutten BA, Buller HR, Prins MH. Vitamin K antagonists or low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism (Review). *Cochrane Database Syst Rev* 2009;2009(1):1-39.
- (112) Ulander VM, Stenqvist P, Kaaja R. Treatment of deep venous thrombosis with low-molecular-weight heparin during pregnancy. *Thromb Res* 2002 Apr 1;106:13-7.

- (113) Daskalakis G, Antsaklis A, Papageorgiou I, Michalas S. Thrombosis prophylaxis after treatment during pregnancy. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1997 Aug;74(2):165-7.
- (114) Lepercq J, Conard J, Borel-Derlon A, Darmon JY, Boudignat O, Francoual C, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. *BJOG* 2001 Nov;108(11):1134-40.
- (115) Daskalakis G, Antsaklis A, Papageorgiou I, Michalas S. Thrombosis prophylaxis after treatment during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1997;74(2):165-7.
- (116) Sanson BJ, Lensing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost* 1999 May;81(5):668-72.
- (117) Yaakob CAC, Dzarr AA, Ismail AA, Lah NAZN, Ho JJ. Anticoagulant therapy for deep vein thrombosis (DVT) in pregnancy. *Cochrane Database of Systematic Reviews* (2), 2009 Article Number: CD007801 Date of Publication: 2009 2009;(2).
- (118) Huo MH, Spyropoulos AC. The eighth American college of chest physicians guidelines on venous thromboembolism prevention: implications for hospital prophylaxis strategies. *J Thromb Thrombolysis* 2010 Aug 5.
- (119) Caprini JA, Tapson VF, Hyers TM, Waldo AL, Wittkowsky AK, Friedman R, et al. Treatment of venous thromboembolism: adherence to guidelines and impact of physician knowledge, attitudes, and beliefs. *J Vasc Surg* 2005 Oct;42:726-33.
- (120) de Monye W, Sanson BJ, Mac Gillavry MR, Pattynama PM, Buller HR, Berg-Huysmans AA, et al. Embolus location affects the sensitivity of a rapid quantitative D-dimer assay in the diagnosis of pulmonary embolism. *Am J Respir Crit Care Med* 2002 Feb 1;165(3):345-8.
- (121) Burrows RF, Gan ET, Gallus AS, Wallace EM, Burrows EA. A randomised double-blind placebo controlled trial of low molecular weight heparin as prophylaxis in preventing venous thrombotic events after caesarean section: a pilot study. *BJOG* 2001 Aug;108(8):835-9.
- (122) Pettila V, Kaaja R, Leinonen P, Ekblad U, Kataja M, Ikkala E. Thromboprophylaxis with low molecular weight heparin (dalteparin) in pregnancy. *Thromb Res* 1999 Nov 15;96(4):275-82.
- (123) Ellison J, Walker ID, Greer IA. Antenatal use of enoxaparin for prevention and treatment of thromboembolism in pregnancy. *BJOG* 2000 Sep;107(9):1116-21.
- (124) Jacobsen AF, Qvigstad E, Sandset PM. Low molecular weight heparin (dalteparin) for the treatment of venous thromboembolism in pregnancy. *BJOG* 2003 Feb;110(2):139-44.
- (125) Rey E, Rivard GE. Prophylaxis and treatment of thromboembolic diseases during pregnancy with dalteparin. *Int J Gynaecol Obstet* 2000 Oct;71(1):19-24.

- (126) Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000 Jun 22;342(25):1887-92.
- (127) D'Agostino RB, Sr., Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues - the encounters of academic consultants in statistics. *Stat Med* 2003 Jan 30;22(2):169-86.
- (128) Brandjes DPM, Heijboer Ht, B++ller HR, de Rijk M, Jagt Ht, ten Cate JW. Acenocoumarol and Heparin Compared with Acenocoumarol Alone in the Initial Treatment of Proximal-Vein Thrombosis. *N Engl J Med* 1992 Nov 19;327(21):1485-9.
- (129) Hull R, Delmore T, Genton E, Hirsh J, Gent M, Sackett D, et al. Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. *N Engl J Med* 1979 Oct 18;301(16):855-8.
- (130) Nielsen HK, Husted SE, Krusell LR, Fasting H, Charles P, Hansen HH, et al. Anticoagulant therapy in deep venous thrombosis. A randomized controlled study. *Thrombosis Research* 1994 Feb 15;73(3GÇô4):215-26.
- (131) EMA. Guideline on the choice of the non-inferiority margin. [2005 Available from: www.ema.europa.eu/pdfs/human/ewp/215899en.pdf.
- (132) Fleming TR, Odem-Davis K, Rothmann MD, Li Shen Y. Some essential considerations in the design and conduct of non-inferiority trials. *Clinical Trials* 2011 Aug 1;8(4):432-9.
- (133) Huitfeldt B, Hummel J. The draft FDA guideline on non-inferiority clinical trials: a critical review from European pharmaceutical industry statisticians. *Pharm Stat* 2011 Sep;10(5):414-9.
- (134) Julious SA. Time to end the non-inferiority complex? *Pharm Stat* 2011 Sep;10(5):393-4.
- (135) Julious SA. The ABC of non-inferiority margin setting from indirect comparisons. *Pharm Stat* 2011 Sep;10(5):448-53.
- (136) Kaul S, Diamond GA, Weintraub WS. Trials and tribulations of non-inferiority: the ximelagatran experience. *J Am Coll Cardiol* 2005 Dec 6;46(11):1986-95.
- (137) Schumi J, Wittes J. Through the looking glass: understanding non-inferiority. *Trials* 2011;12(1):106.
- (138) Ellenberg SS, Temple R. Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments. Part 2: Practical Issues and Specific Cases. *Annals of Internal Medicine* 2000 Sep 19;133(6):464-70.
- (139) Temple R, Ellenberg SS. Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments. Part 1: Ethical and Scientific Issues. *Annals of Internal Medicine* 2000 Sep 19;133(6):455-63.

- (140) Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010 Dec 23;363(26):2499-510.
- (141) Camm AJ, Bounameaux H. Edoxaban: A New Oral Direct Factor Xa Inhibitor. *Drugs* 2011;71(12).
- (142) Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009 Dec 10;361(24):2342-52.
- (143) Erkens PM, Prins MH. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev* 2010;(9):CD001100.
- (144) Carrier M, Righini M, Wells PS, Perrier A, Anderson DR, Rodger MA, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. *J Thromb Haemost* 2010 Aug;8(8):1716-22.
- (145) Donato AA, Khoche S, Santora J, Wagner B. Clinical outcomes in patients with isolated subsegmental pulmonary emboli diagnosed by multidetector CT pulmonary angiography. *Thromb Res* 2010 Oct;126(4):e266-e270.
- (146) HOLMGREN KAJ, ANDERSSON GUNN, FAGRELL BENG, JOHNSON HANS, LJUNGBERG BENG, NILSSON ERLI, et al. One-Month versus Six-Month Therapy with Oral Anticoagulants after Symptomatic Deep Vein Thrombosis. *Acta Medica Scandinavica* 1985;218(3):279-84.
- (147) Lagerstedt CI, Olsson CG, Fagher BO, Oqvist BW, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. *Lancet* 1985 Sep 7;2(8454):515-8.
- (148) Hull RD, Raskob GE, Hirsh J, Jay RM, Leclerc JR, Geerts WH, et al. Continuous Intravenous Heparin Compared with Intermittent Subcutaneous Heparin in the Initial Treatment of Proximal-Vein Thrombosis. *N Engl J Med* 1986 Oct 30;315(18):1109-14.
- (149) Brandjes DP, Heijboer H, Buller HR, de RM, Jagt H, Ten Cate JW. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1992 Nov 19;327(21):1485-9.
- (150) Raschke R, Hertel G. Clinical Use of the Heparin Nomogram. *Archives of Internal Medicine* 1991 Nov 1;151(11):2318-b.
- (151) Levine MN, Hirsh J, Gent M, Turpie AG, Weitz J, Ginsberg J, et al. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. *Thromb Haemost* 1995 Aug;74(2):606-11.

- (152) Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Lärffars G, Nicol P, et al. A Comparison of Six Weeks with Six Months of Oral Anticoagulant Therapy after a First Episode of Venous Thromboembolism. *N Engl J Med* 1995 Jun 22;332(25):1661-5.
- (153) van Dongen CJ, MacGillavry MR, Prins MH. Once versus twice daily LMWH for the initial treatment of venous thromboembolism. *Cochrane Database Syst Rev* 2005;(3):CD003074.
- (154) Narin C, Reyhanoglu H, Tulek B, Onoglu R, Ege E, Sarigul A, et al. Comparison of different dose regimens of enoxaparin in deep vein thrombosis therapy in pregnancy. *Adv Ther* 2008 Jun;25(6):585-94.
- (155) Holmström M, Berglund MC, Granquist S, Bratt G, Thrombohm E, Lockner D. Fragmin once or twice daily subcutaneously in the treatment of deep venous thrombosis of the leg. *Thrombosis Research* 1992 Jul 1;67(1):49-55.
- (156) Partsch H. Therapy of deep vein thrombosis with low molecular weight heparin, leg compression and immediate ambulation. *Vasa* 2001 Jul;30(3):195-204.
- (157) Siegbahn A, Hassan S, Boberg J, Bylund H, Neerstrand HS, Östergaard P, et al. Subcutaneous treatment of deep venous thrombosis with low molecular weight heparin. A dose finding study with LMWH-Novo. *Thrombosis Research* 1989 Sep 15;55(6):767-78.
- (158) Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, et al. Subcutaneous Enoxaparin Once or Twice Daily Compared with Intravenous Unfractionated Heparin for Treatment of Venous Thromboembolic Disease. *Annals of Internal Medicine* 2001 Feb 6;134(3):191-202.
- (159) Charbonnier BA, Fiessinger JN, Banga JD, Wenzel E, d'Azemar P, Sagnard L. Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis. FRAXODI group. *Thromb Haemost* 1998 May;79(5):897-901.
- (160) Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: practical issues and specific cases. *Ann Intern Med* 2000 Sep 19;133(6):464-70.
- (161) Blackwelder WC. "Proving the null hypothesis" in clinical trials. *Control Clin Trials* 1982 Dec;3(4):345-53.
- (162) Food and Drug Administration DoHaHS. International Conference on Harmonisation. Guidance on choice of control group and related design and conduct issues in clinical trials (ICH E 10) (2000). <http://www.fda.gov/cder/guidance/index.htm>. 2010.
Ref Type: Internet Communication
- (163) WOMBAT. Women's & families' preferences & attitudes. <http://www.wombatcollaboration.net/doc/Women's%20and%20families%20preferences%20and%20attitudes%20to%20recruitment%20pd%202011%20September%203> Available from: URL:

<http://www.wombatcollaboration.net/doc/Women's%20and%20families%20preferences%20and%20attitudes%20to%20recruitment.pdf>

- (164) Goldkind SF, Sahin L, Gallauresi B. Enrolling Pregnant Women in Research GÇö Lessons from the H1N1 Influenza Pandemic. *N Engl J Med* 2010 Jun 16;362(24):2241-3.
- (165) Fletcher R, Fletcher S. *Clinical Epidemiology: The Essentials*. Fourth ed. Wolters Kluwer Health; 2015.
- (166) Benson K, Hartz AJ. A Comparison of Observational Studies and Randomized, Controlled Trials. *N Engl J Med* 2000 Jun 22;342(25):1878-86.
- (167) Ioannidis JPA, Haidich AB, Pappa M, Pantazis N, Kokori SI, Tektonidou MG, et al. Comparison of Evidence of Treatment Effects in Randomized and Nonrandomized Studies. *JAMA: The Journal of the American Medical Association* 2001 Aug 15;286(7):821-30.
- (168) Concato J, Lawler EV, Lew RA, Gaziano JM, Aslan M, Huang GD. Observational methods in comparative effectiveness research. *Am J Med* 2010 Dec;123(12 Suppl 1):e16-e23.
- (169) Horwitz RI, Viscoli CM, Clemens JD, Sadock RT. Developing improved observational methods for evaluating therapeutic effectiveness. *Am J Med* 1990 Nov;89(5):630-8.
- (170) Hannan EL. Randomized Clinical Trials and Observational Studies: Guidelines for Assessing Respective Strengths and Limitations. *J Am Coll Cardiol Intv* 2008 Jun 1;1(3):211-7.
- (171) Eliopoulos GM, Harris AD, Bradham DD, Baumgarten M, Zuckerman IH, Fink JC, et al. The Use and Interpretation of Quasi-Experimental Studies in Infectious Diseases. *Clinical Infectious Diseases* 2004 Jun 1;38(11):1586-91.
- (172) Pocock SJ. The combination of randomized and historical controls in clinical trials. *Journal of Chronic Diseases* 1976 Mar;29(3):175-88.
- (173) A primer on before-after studies: evaluating a report of a "successful" intervention. *Eff Clin Pract* 2002 Mar;5(2):100-1.
- (174) Brody T. Chapter 2 - Introduction to Regulated Clinical Trials. *Clinical Trials*. Boston: Academic Press; 2012. p. 17-50.
- (175) Wells PS, Anderson DR, Rodger MA, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: Management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. *Ann Intern Med* 2001;135:98-107.
- (176) Wells PS, Ginsberg JS, Anderson DR, Kearon C, Gent M, Turpie AGG, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med* 1998;129:997-1005.

- (177) van Belle A, Buller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 2006 Jan 11;295:172-9.
- (178) Musset D, Parent F, Meyer G, Maitre S, Girard P, Leroyer C, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. *Lancet* 2002 Dec 14;360:1914-20.
- (179) Perrier A, Roy P-M, Aujesky D, Chagnon I, Howarth N, Gourdier A-L, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-Dimer measurement, venous ultrasound, and helical computed tomography: A multicenter management study. *Am J Med* 2004;116:291-9.
- (180) Perrier A, Bounameaux H, Morabia A, de Moerloose P, Slosman D, Didier D, et al. Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. *Arch Intern Med* 1996 Mar 11;156:531-6.
- (181) Stein PD, Beemath A, Goodman LR, Hales CA, Hull RD, Sostman HD, et al. Outcome studies of pulmonary embolism versus accuracy: they do not equate. *Thromb Haemost* 2006 Aug;96(2):107-8.
- (182) Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding Pulmonary Embolism at the Bedside without Diagnostic Imaging: Management of Patients with Suspected Pulmonary Embolism Presenting to the Emergency Department by Using a Simple Clinical Model and d-dimer. *Annals of Internal Medicine* 2001 Jul 17;135(2):98-107.
- (183) Qaseem A, Snow V, Barry P, Hornbake ER, Rodnick JE, Tobolic T, et al. Current Diagnosis of Venous Thromboembolism in Primary Care: A Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians*. *Annals of Internal Medicine* 2007 Mar 20;146(6):454-8.
- (184) Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7(27):iii-173.
- (185) Kumar A, Brooks SS, Cavanaugh K, Zuckerman B. FDA perspective on objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. *Journal of Vascular Surgery* 2009 Dec;50(6):1474-6.
- (186) Grunkemeier GL, Jin R, Starr A. Prosthetic Heart Valves: Objective Performance Criteria Versus Randomized Clinical Trial. *The Annals of Thoracic Surgery* 2006 Sep;82(3):776-80.
- (187) McKee M, Britton A, Black N, McPherson K, Sanderson C, Bain C. Methods in health services research. Interpreting the evidence: choosing between randomised and non-randomised studies. *BMJ* 1999 Jul 31;319(7205):312-5.
- (188) Dawson B, Trapp G. *Basic & Clinical Biostatistics*. Fourth ed. McGraw-Hill; 2012.

- (189) Chin R, Lee BY. Chapter 1 - Overview of Clinical Research Medicine. Principles and Practice of Clinical Trial Medicine. New York: Academic Press; 2008. p. 1-16.
- (190) Ulander VM, Lehtola A, Kaaja R. Long-term outcome of deep venous thrombosis during pregnancy treated with unfractionated heparin or low molecular weight heparin. *Thrombosis Research* 2003;111(4-5):239-42.
- (191) Li H, Yue LQ. Statistical and Regulatory Issues in Nonrandomized Medical Device Clinical Studies. *Journal of Biopharmaceutical Statistics* 2007 Dec 10;18(1):20-30.
- (192) Brody T. Chapter 9 - Biostatistics. *Clinical Trials*. Boston: Academic Press; 2012. p. 165-90.
- (193) Whitley E, Ball J. Statistics review 5: Comparison of means. *Critical Care* 2002;6(5):424-8.
- (194) Taylor JM, Braun TM, Li Z. Comparing an experimental agent to a standard agent: relative merits of a one-arm or randomized two-arm Phase II design. *Clinical Trials* 2006 Aug 1;3(4):335-48.
- (195) Palesch YY, Tilley BC, Sackett DL, Johnston KC, Woolson R. Applying a Phase II Futility Study Design to Therapeutic Stroke Trials. *Stroke* 2005 Nov 1;36(11):2410-4.
- (196) Campbell* G. Statistics in the World of Medical Devices: The Contrast with Pharmaceuticals. *Journal of Biopharmaceutical Statistics* 2007 Dec 10;18(1):4-19.
- (197) Kovacs MJ, Kearon C, Rodger M, Anderson DR, Turpie AGG, Bates SM, et al. Single-Arm Study of Bridging Therapy With Low-Molecular-Weight Heparin for Patients at Risk of Arterial Embolism Who Require Temporary Interruption of Warfarin. *Circulation* 2004 Sep 21;110(12):1658-63.
- (198) Perrier A, Roy PM, Sanchez O, Le Gal Gg, Meyer G, Gourdier AL, et al. Multidetector-Row Computed Tomography in Suspected Pulmonary Embolism. *N Engl J Med* 2005 Apr 28;352(17):1760-8.
- (199) MALATO A, SACCULLO G, LO COCO L, CARAMAZZA D, ABBENE I, PIZZO G, et al. Patients requiring interruption of long-term oral anticoagulant therapy: the use of fixed sub-therapeutic doses of low-molecular-weight heparin. *Journal of Thrombosis and Haemostasis* 2010;8(1):107-13.
- (200) Pengo V, Cucchini U, Denas G, Erba N, Guazzaloca G, La Rosa L, et al. Standardized Low-Molecular-Weight Heparin Bridging Regimen in Outpatients on Oral Anticoagulants Undergoing Invasive Procedure or Surgery. *Circulation* 2009 Jun 9;119(22):2920-7.
- (201) Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. *Journal of Vascular Surgery* 2009 Dec;50(6):1462-73.

- (202) Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. *Cathet Cardiovasc Intervent* 2007;69(6):910-9.
- (203) O'Malley AJ, Normand SI, Kuntz RE. Application of models for multivariate mixed outcomes to medical device trials: coronary artery stenting. *Statist Med* 2003;22(2):313-36.
- (204) Levin B. The Utility of Futility. *Stroke* 2005 Nov 1;36(11):2331-2.
- (205) Paul G, Iain C, Michael R, Peter M. When are randomised trials unnecessary? Picking signal from noise. *BMJ* 2007 Feb 15;334.
- (206) Gordon CSS, Jill PP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003 Dec 18;327.
- (207) Colebrook L, Kenny M+, the members of the HONORARY STAFF OF QUEEN CHARLOTTE'S HOSPITAL. TREATMENT WITH PRONTOSIL OF PUERPERAL INFECTIONS: DUE TO H+âMOLYTIC STREPTOCOCCI. *The Lancet* 1936 Dec 5;228(5910):1319-22.
- (208) Sacks H, Chalmers TC, Smith J. Randomized versus historical controls for clinical trials. *The American Journal of Medicine* 1982 Feb;72(2):233-40.
- (209) Pond GR, Abbasi S. Quantitative evaluation of single-arm versus randomized phase II cancer clinical trials. *Clinical Trials* 2011 Jun 1;8(3):260-9.
- (210) Sharma MR, Stadler WM, Ratain MJ. Randomized Phase II Trials: A Long-term Investment With Promising Returns. *Journal of the National Cancer Institute* 2011 Jul 20;103(14):1093-100.
- (211) Tang H, Foster NR, Grothey A, Ansell SM, Goldberg RM, Sargent DJ. Comparison of Error Rates in Single-Arm Versus Randomized Phase II Cancer Clinical Trials. *Journal of Clinical Oncology* 2010 Apr 10;28(11):1936-41.
- (212) Kitsios GD, Dahabreh IJ, Abu Dabrh AM, Thaler DE, Kent DM. Patent Foramen Ovale Closure and Medical Treatments for Secondary Stroke Prevention. *Stroke* 2012 Feb 1;43(2):422-31.
- (213) Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al. Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale. *N Engl J Med* 2012 Mar 14;366(11):991-9.
- (214) Fernald DH, Coombs L, DeAlleaume L, West D, Parnes B. An Assessment of the Hawthorne Effect in Practice-based Research. *The Journal of the American Board of Family Medicine* 2012 Jan;25(1):83-6.

- (215) Bland JM, Altman DG. Statistics Notes: Some examples of regression towards the mean. *BMJ* 1994 Sep 24;309.
- (216) Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692-4.
- (217) Miller S, Lester F, Hensleigh P. Prevention and treatment of postpartum hemorrhage: new advances for low-resource settings. *J Midwifery Womens Health* 2004 Jul;49(4):283-92.
- (218) Higgins JPT. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. Cochrane Database Syst Rev 2009 Available from: URL: www.cochrane-handbook.org
- (219) Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2009. Report No.: Unpublished.
- (220) Miller JJ. The Inverse of the Freeman-Tukey double arcsine transformation. *The American Statistician* 1978;32(4):138.
- (221) Laird NM, Mosteller F. Some statistical methods for combining experimental results. *Int J Technol Assess Health Care* 1990;6(1):5-30.
- (222) Egger M, Davey Smith G. Principles of and procedures for systematic reviews. In: Egger M, Davey Smith G, Altman DG, editors. *Systematic Reviews in Health Care: Meta-analysis in Context*. 2nd ed ed. London: BMJ Publishing Group; 2001. p. 23-42.
- (223) Egger M, Dickersin K, Davey Smith G. Problems and limitations in conducting systematic reviews. In: Egger M, Davey Smith G, Altman DG, editors. *Systematic Reviews in Health Care: Meta-analysis in Context*. 2nd ed ed. London: BMJ Publishing Group; 2001. p. 43-68.
- (224) Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002 Jun 15;21:1539-58.
- (225) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003 Sep 6;327(7414):557-60.
- (226) Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000 Jun;56(2):455-63.
- (227) Nelson-Piercy C, Powrie R, Borg JY, Rodger M, Talbot DJ, Stinson J, et al. Tinzaparin use in pregnancy: an international, retrospective study of the safety and efficacy profile. *Eur J Obstet Gynecol Reprod Biol* 2011 Dec;159(2):293-9.
- (228) Lyall H, Myers B. Incidence and management of 82 cases of pregnancy-associated venous thromboembolism occurring at a single centre--comparison with Voke et al. *Br J Haematol* 2008 Jun;142(2):309-11.

- (229) Bauersachs RM, Dudenhausen J, Faridi A, Fischer T, Fung S, Geisen U, et al. Risk stratification and heparin prophylaxis to prevent venous thromboembolism in pregnant women. *Thrombosis & Haemostasis* 2007 Dec;98(6):1237-45.
- (230) Blanco-Molina A, Trujillo-Santos J, Criado J, Lopez L, Lecumberri R, Gutierrez R, et al. Venous thromboembolism during pregnancy or postpartum: findings from the RIETE Registry. *Thrombosis & Haemostasis* 2007 Feb;97(2):186-90.
- (231) Priollet P, Roncato M, Aiach M, Housset E, Poissonnier MH, Chavinie J. Low-molecular-weight heparin in venous thrombosis during pregnancy. *British Journal of Haematology* 1986 Jul;63(3):605-6.
- (232) Barbour LA, Oja JL, Schultz LK. A prospective trial that demonstrates that dalteparin requirements increase in pregnancy to maintain therapeutic levels of anticoagulation. *American Journal of Obstetrics & Gynecology* 2004 Sep;191(3):1024-9.
- (233) Kinori M, Saar N, Justo D, Almog R. Determination of anti-Xa levels in pregnant women treated with low molecular weight heparins for prevention of recurrent venous thromboembolism: a case report and review of the literature. *Thrombosis Research* 122(2):289-90.
- (234) Panni JK, Panni MK. Obstetric patient on Lovenox therapy: evidence of heparin activity at 24 hours. *Journal of Obstetrics & Gynaecology* 2010 Jan;30(1):62-4.
- (235) Tawes RL, Jr., Kennedy PA, Harris EJ, Brown WH, Scribner RG, Sydorak GR, et al. Management of deep venous thrombosis and pulmonary embolism during pregnancy. *American Journal of Surgery* 1982 Jul;144(1):141-5.
- (236) Armour R, Schwedler M, Kerstein MD. Current assessment of thromboembolic disease and pregnancy. *American Surgeon* 2001 Jul;67(7):641-4.
- (237) Kominiarek MA, Angelopoulos SM, Shapiro NL, Studee L, Nutescu EA, Hibbard JU. Low-molecular-weight heparin in pregnancy: peripartum bleeding complications. *Journal of Perinatology* 2007 Jun;27(6):329-34.
- (238) Witlin AG, Mattar FM, Saade GR, Van Hook JW, Sibai BM. Presentation of venous thromboembolism during pregnancy. *American Journal of Obstetrics & Gynecology* 1999 Nov;181(5:Pt 1):t-21.
- (239) Bauersachs RM, Dudenhausen J, Faridi A, Fischer T, Fung S, Geisen U, et al. Risk stratification and heparin prophylaxis to prevent venous thromboembolism in pregnant women. *Thromb Haemost* 2007 Dec;98(6):1237-45.
- (240) Davies CW, Wimperis J, Green ES, Pendry K, Killen J, Mehdi I, et al. Early discharge of patients with pulmonary embolism: a two-phase observational study. *European Respiratory Journal* 2007 Oct;30(4):708-14.
- (241) Schneider DM, von Tempelhoff GF, Heilmann L. Retrospective evaluation of the safety and efficacy of low-molecular-weight heparin as thromboprophylaxis during pregnancy. *American Journal of Obstetrics & Gynecology* 1997 Dec;177(6):1567-8.

- (242) Huxtable LM, Tafreshi MJ, Ondreyco SM. A protocol for the use of enoxaparin during pregnancy: results from 85 pregnancies including 13 multiple gestation pregnancies. *Clinical & Applied Thrombosis/Hemostasis* 2005 Apr;11(2):171-81.
- (243) Santoro R, Iannaccaro P, Prejano S, Muleo G. Efficacy and safety of the long-term administration of low-molecular-weight heparins in pregnancy. *Blood Coagulation & Fibrinolysis* 2009 Jun;20(4):240-3.
- (244) Lambert JR, Austin SK, Peebles D, Cohen H. Audit of the peri-delivery use of unfractionated heparin in women on therapeutic low-molecular weight heparin. *British Journal of Haematology* 2008 Jul;142(3):453-6.
- (245) Sorensen HT, Johnsen SP, Larsen H, Pedersen L, Nielsen GL, Moller M. Birth outcomes in pregnant women treated with low-molecular-weight heparin. *Acta Obstetrica et Gynecologica Scandinavica* 2000 Aug;79(8):655-9.
- (246) Pillny M, Sandmann W, Luther B, Muller BT, Tutschek B, Gerhardt A, et al. Deep venous thrombosis during pregnancy and after delivery: indications for and results of thrombectomy. *Journal of Vascular Surgery* 2003 Mar;37(3):528-32.
- (247) Tornngren S, Hjertberg R, Rosfors S, Bremme K, Eriksson M, Swedenborg J. The long-term outcome of proximal vein thrombosis during pregnancy is not improved by the addition of surgical thrombectomy to anticoagulant treatment. *European Journal of Vascular and Endovascular Surgery* 12(1)(pp 31-36), 1996 Date of Publication: 1996 1996;(1):31-6.
- (248) Ratiu A, Motoc A, Pascut D, Crisan DC, Anca T, Pascut M. Compression and walking compared with bed rest in the treatment of proximal deep venous thrombosis during pregnancy. *Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din Iasi* 2009 Jul;113(3):795-8.
- (249) Rosfors S, Noren A, Hjertberg R, Persson L, Lillthors K, Tornngren S. A 16-year haemodynamic follow-up of women with pregnancy-related medically treated iliofemoral deep venous thrombosis. *European Journal of Vascular and Endovascular Surgery* 22(5)(pp 448-455), 2001 Date of Publication: 2001 2001;(5):448-55.
- (250) Myers B, Westby J, Strong J. Prophylactic use of danaparoid in high-risk pregnancy with heparin-induced thrombocytopenia-positive skin reaction. *Blood Coagulation & Fibrinolysis* 2003 Jul;14(5):485-7.
- (251) O'Connor DJ, Scher LA, Gargiulo NJ, III, Jang J, Suggs WD, Lipsitz EC. Incidence and characteristics of venous thromboembolic disease during pregnancy and the postnatal period: a contemporary series. *Ann Vasc Surg* 2011 Jan;25(1):9-14.
- (252) Clark NP, Delate T, Witt DM, Parker S, McDuffie R. A descriptive evaluation of unfractionated heparin use during pregnancy. *Journal of Thrombosis & Thrombolysis* 2009 Apr;27(3):267-73.

- (253) Andersen AS, Berthelsen JG, Bergholt T. Venous thromboembolism in pregnancy: prophylaxis and treatment with low molecular weight heparin. *Acta Obstetrica et Gynecologica Scandinavica* 2010;89(1):15-21.
- (254) Blanco-Molina A, Rota LL, Di MP, Brenner B, Trujillo-Santos J, Ruiz-Gamietea A, et al. Venous thromboembolism during pregnancy, postpartum or during contraceptive use. *Thromb Haemost* 2010 Feb;103(2):306-11.
- (255) Aburahma AF, Stickler DL, Robinson PA. A prospective controlled study of the efficacy of short-term anticoagulation therapy in patients with deep vein thrombosis of the lower extremity. *J Vasc Surg* 1998;28(4):630-7.
- (256) Bergqvist A, Bergqvist D, Hallbook T. Deep vein thrombosis during pregnancy. A prospective study. *Acta Obstet Gynecol Scand* 1983;62:443-8.
- (257) Deiter RW. Thromboembolic disease in pregnancy: a prospective trial of intermittent heparin therapy during the antepartum period. *Journal of the American Osteopathic Association* 1985 Apr;85(4):247-51.
- (258) Deruelle P, Denervaud M, Hachulla E, Ducloy-Bouthors AS, Valat AS, Puech F, et al. Use of low-molecular-weight heparin from the first trimester of pregnancy: a retrospective study of 111 consecutive pregnancies. *European Journal of Obstetrics, Gynecology, & Reproductive Biology* 2006 Jul;127(1):73-8.
- (259) Dulitzky M, Pauzner R, Langevitz P, Pras M, Many A, Schiff E. Low-molecular-weight heparin during pregnancy and delivery: preliminary experience with 41 pregnancies. *Obstet Gynecol* 1996 Jan 3;87(3):380-3.
- (260) Ellison J, Walker ID, Greer IA. Antenatal use of enoxaparin for prevention and treatment of thromboembolism in pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology* 2000 Sep;107(9):1116-21.
- (261) Ainle FN, Wong A, Appleby N, Byrne B, Regan C, Hassan T, et al. Efficacy and safety of once daily low molecular weight heparin (tinzaparin sodium) in high risk pregnancy. *Blood Coagulation and Fibrinolysis* 19(7)(pp 689-692), 2008 Date of Publication: October 2008 2008;(7):689-92.
- (262) Ginsberg JS, Kowalchuk G, Hirsh J, Brill-Edwards P, Burrows RF. Heparin therapy during pregnancy. Risks to the fetus and mother. *Arch Intern Med* 1989 Oct;149:2233-6.
- (263) Jacobsen AF, Qvigstad E, Sandset PM. Low molecular weight heparin (dalteparin) for the treatment of venous thromboembolism in pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology* 2003 Feb;110(2):139-44.
- (264) Lykke JA, Gronlykke T, Langhoff-Roos J. Treatment of deep venous thrombosis in pregnant women. *Acta Obstetrica et Gynecologica Scandinavica* 2008;87(11):1248-51.
- (265) Mitic G, Povazan L, Lucic AM. [Treatment of pregnancy related venous thromboembolism]. *Med Pregl* 2009 Jul;62(7-8):346-51.

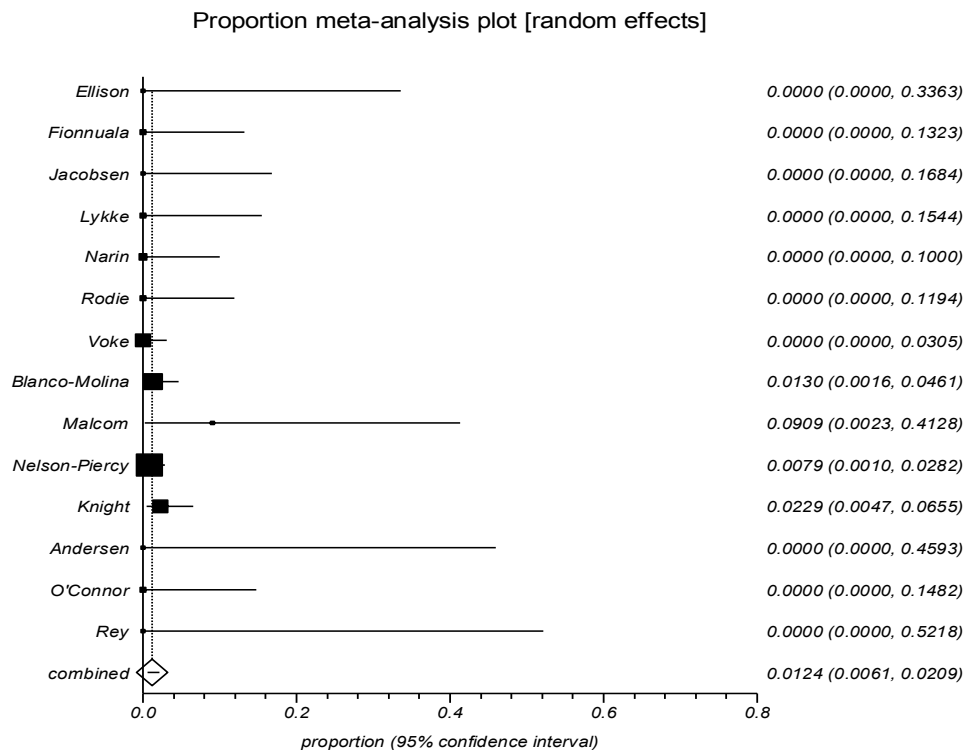
- (266) Rey E RG. Prophylaxis and treatment of thromboembolic diseases during pregnancy with dalteparin. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2000 Oct;(1):19-24.
- (267) Rodie VA, Thomson AJ, Stewart FM, Quinn AJ, Walker ID, Greer IA. Low molecular weight heparin for the treatment of venous thromboembolism in pregnancy: a case series. *BJOG: An International Journal of Obstetrics & Gynaecology* 2002 Sep;109(9):1020-4.
- (268) Rowan JA, McLintock C, Taylor RS, North RA. Prophylactic and therapeutic enoxaparin during pregnancy: indications, outcomes and monitoring. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 2003 Apr;43(2):123-8.
- (269) Ulander VM, Stenqvist P, Kaaja R. Treatment of deep venous thrombosis with low-molecular-weight heparin during pregnancy. *Thrombosis Research* 2002 Apr 1;106(1):13-7.
- (270) Malcolm JC, Keely EJ, Karovitch AJ, Wells PS. Use of low molecular weight heparin in acute venous thromboembolic events in pregnancy. *Journal of Obstetrics & Gynaecology Canada: JOGC* 2002 Jul;24(7):568-71.
- (271) Bergqvist A, Bergqvist D, Hallbook T. Deep vein thrombosis during pregnancy. A prospective study. *Acta Obstetrica et Gynecologica Scandinavica* 1983;62(5):443-8.
- (272) Lepercq J, Conard J, Borel-Derlon A, Darmon JY, Boudignat O, Francoual C, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. *BJOG: An International Journal of Obstetrics & Gynaecology* 2001 Nov;108(11):1134-40.
- (273) Aburahma AF, Boland JP. Management of deep vein thrombosis of the lower extremity in pregnancy: a challenging dilemma. *American Surgeon* 1999 Feb;65(2):164-7.
- (274) Clark NP, Delate T, Cleary SJ, Witt DM. Unfractionated heparin dose requirements targeting intermediate intensity antifactor Xa concentration during pregnancy. *Pharmacotherapy* 2010 Apr;30(4):369-74.
- (275) Friedrich J, Adhikari N, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. *BMC Medical Research Methodology* 2007;7(1):5.
- (276) Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Statist Med* 2007;26(1):53-77.
- (277) Sweeting J, Sutton J, Lambert C. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Statist Med* 2004;23(9):1351-75.
- (278) Einarson TR. Pharmacoeconomic applications of meta-analysis for single groups using antifungal onychomycosis lacquers as an example. *Clinical Therapeutics* 1997 May;19(3):559-69.

- (279) Mosteller F, Youtz C. Tables of the Freeman-Tukey Transformations for the Binomial and Poisson Distributions
Selected Papers of Frederick Mosteller. In: Fienberg S, Hoaglin D, editors. Springer New York; 2006. p. 337-47.
- (280) Musiol G. An Introduction to Categorical Data Analysis: Agresti, A. (1996) New York: Wiley & S Sons, ISBN 0-471-11338-7, XI + 290 pages, \$ 90.00. Computational Statistics & Data Analysis 1997 Feb 6;23(4):565.
- (281) Juni P, Holenstein F, Sterne J, Bartlett C, Egger M. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. *Int J Epidemiol* 2002 Feb;31(1):115-23.
- (282) Egger M, Juni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technol Assess* 2003;7(1):1-76.
- (283) van Walraven C, Mahon JL, Moher D, Bohm C, Laupacis A. Surveying physicians to determine the minimal important difference: implications for sample-size calculation. *J Clin Epidemiol* 1999 Aug;52(8):717-23.
- (284) Dane A. Active controlled studies in antibiotic drug development. *Pharm Stat* 2011 Sep;10(5):454-60.
- (285) Naylor CD, Llewellyn-Thomas HA. Can there be a more patient-centred approach to determining clinically important effect sizes for randomized treatment trials? *Journal of Clinical Epidemiology* 1994 Jul;47(7):787-95.
- (286) Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. *Ann Intern Med* 2006 Jul 4;145(1):62-9.
- (287) Columbus Investigators, ten Cate JW. Low molecular weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;337:657-62.
- (288) Barrett B, Brown R, Mundt M. Comparison of anchor-based and distributional approaches in estimating important difference in common cold. *Quality of Life Research* 2008;17(1):75-85.
- (289) Kaplowitz MD, Hadlock TD, Levine R. A Comparison of Web and Mail Survey Response Rates. *Public Opinion Quarterly* 2004 Mar 1;68(1):94-101.
- (290) Sills SJ, Song C. Innovations in Survey Research. *Social Science Computer Review* 2002;20(1):22-30.
- (291) Strabac Z, Aalberg T. Measuring Political Knowledge in Telephone and Web Surveys: A Cross-National Comparison. *Social Science Computer Review* 2011 May 1;29(2):175-92.

- (292) VISSER PS, KROSNICK JA, MARQUETTE JESS, CURTIN MICH. MAIL SURVEYS FOR ELECTION FORECASTING? Public Opinion Quarterly 1996 Jun 20;60(2):181-227.
- (293) Keeter S, Kennedy C, Dimock M, Best J, Craighill P. Gauging the Impact of Growing Nonresponse on Estimates from a National RDD Telephone Survey. Public Opinion Quarterly 2006 Jan 1;70(5):759-79.
- (294) Zucker DM, Wittes JT, Schabenberger O, Brittain E. Internal pilot studies II: comparison of various procedures. Stat Med 1999 Dec 30;18(24):3493-509.
- (295) Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol 2010;10:1.

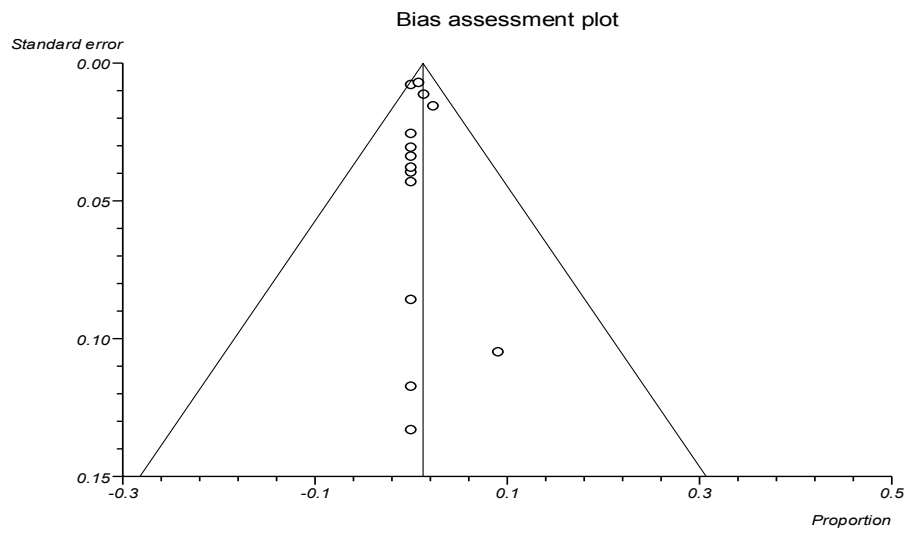
Appendix 3 Publication bias analysis

Analysis 1 Recurrent VTE in patients treated with full dose LMWH

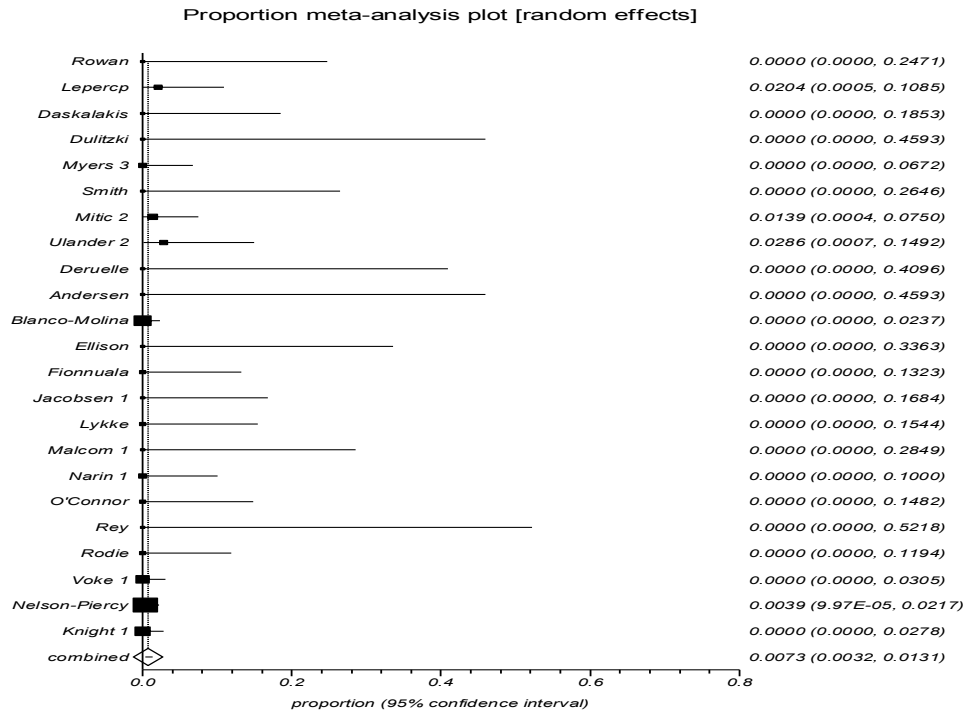


Bias indicators

Egger: bias = 0.05221 (95% CI = -0.376698 to 0.481118) P = 0.7953



Analysis 2 Acute treatment failure with LMWH



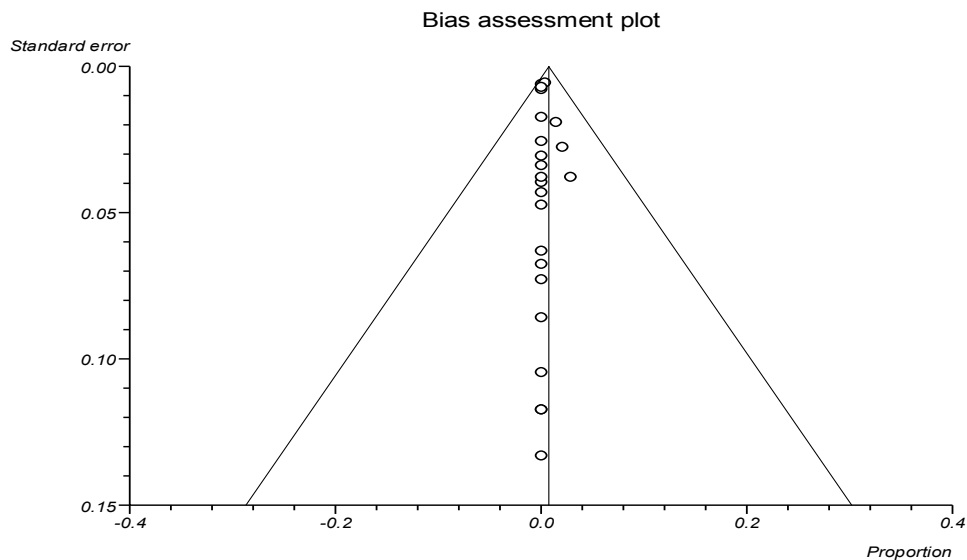
Non-combinability of studies

Cochran Q = 9.734362 (df = 22) P = 0.9886

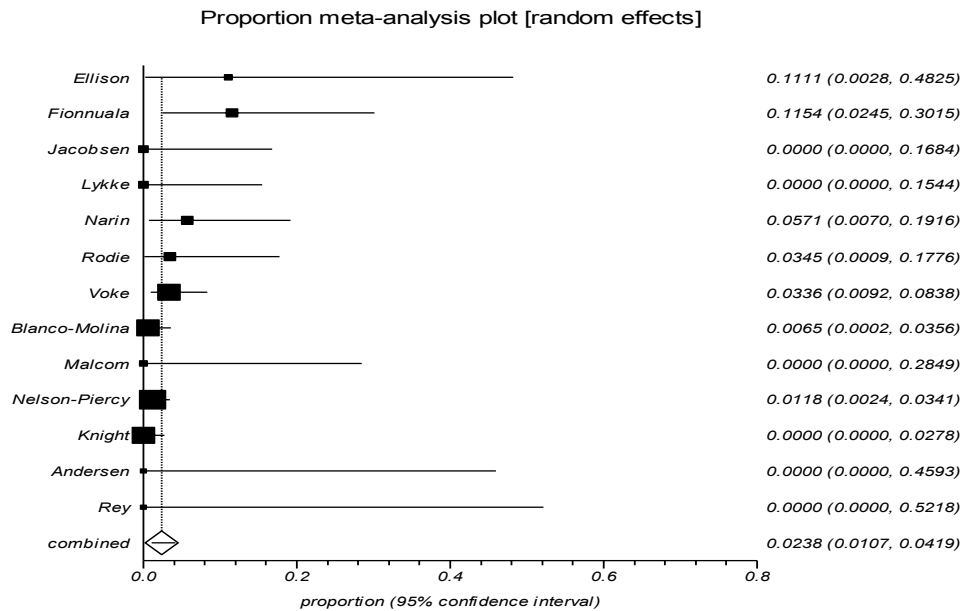
I² (inconsistency) = 0% (95% CI = 0% to 40.2%)

Bias indicators

Egger: bias = 0.069076 (95% CI = -0.096997 to 0.235148) P = 0.3968



Analysis 3 Major bleeding using a full dose LMWH strategy



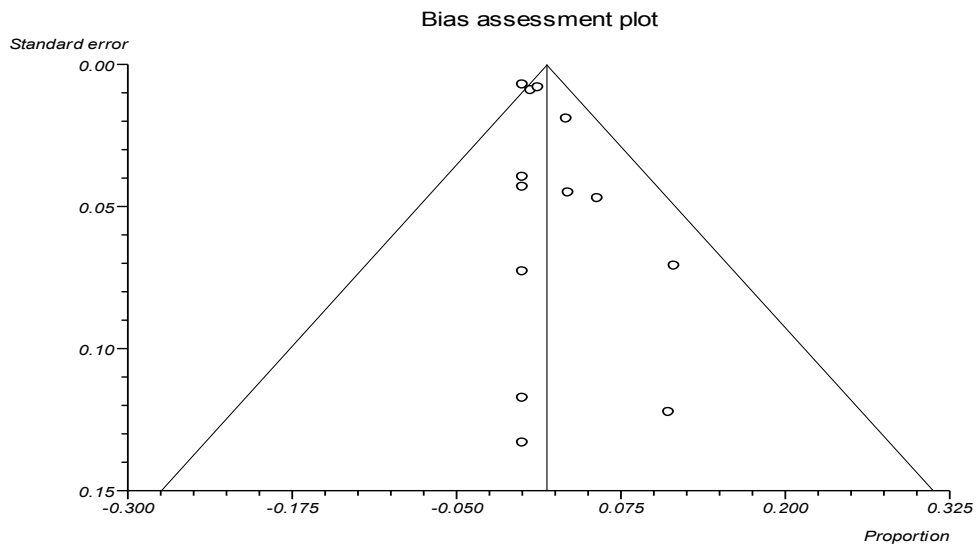
Non-combinability of studies

Cochran Q = 19.56273 (df = 12) P = 0.0758

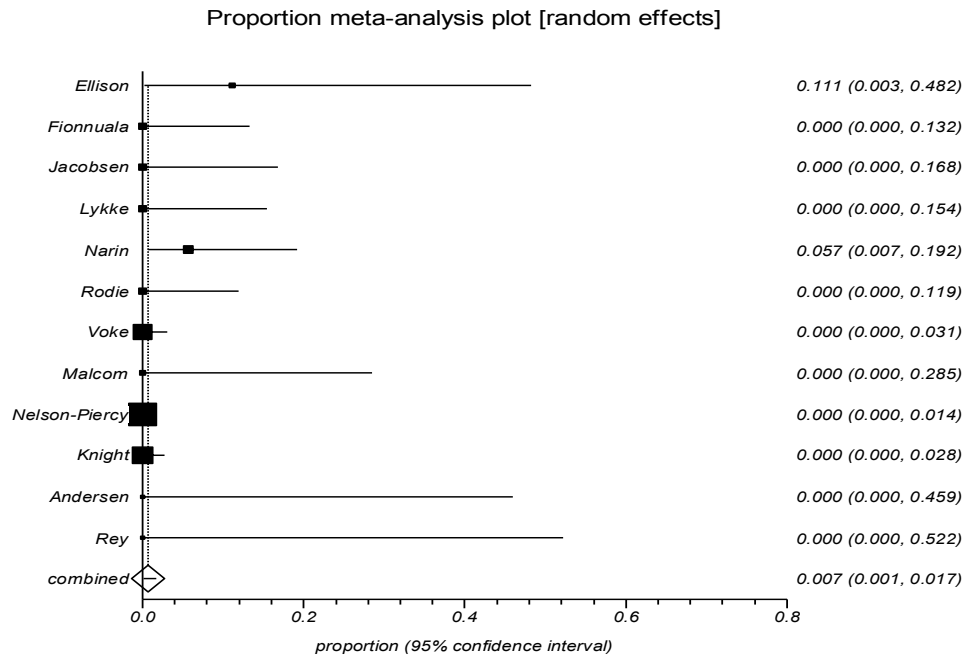
I² (inconsistency) = 38.7% (95% CI = 0% to 66.9%)

Bias indicators

Egger: bias = 0.565967 (95% CI = -0.041104 to 1.173038) P = 0.0648



Analysis 4 Major ante-partum bleeding using full dose LMWH



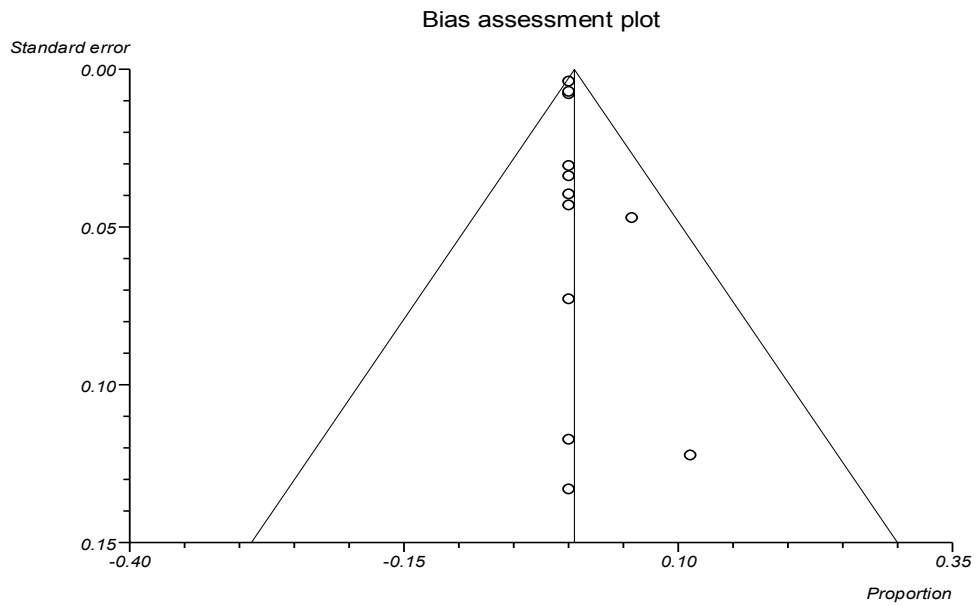
Non-combinability of studies

Cochran Q = 13.403074 (df = 11) P = 0.2678

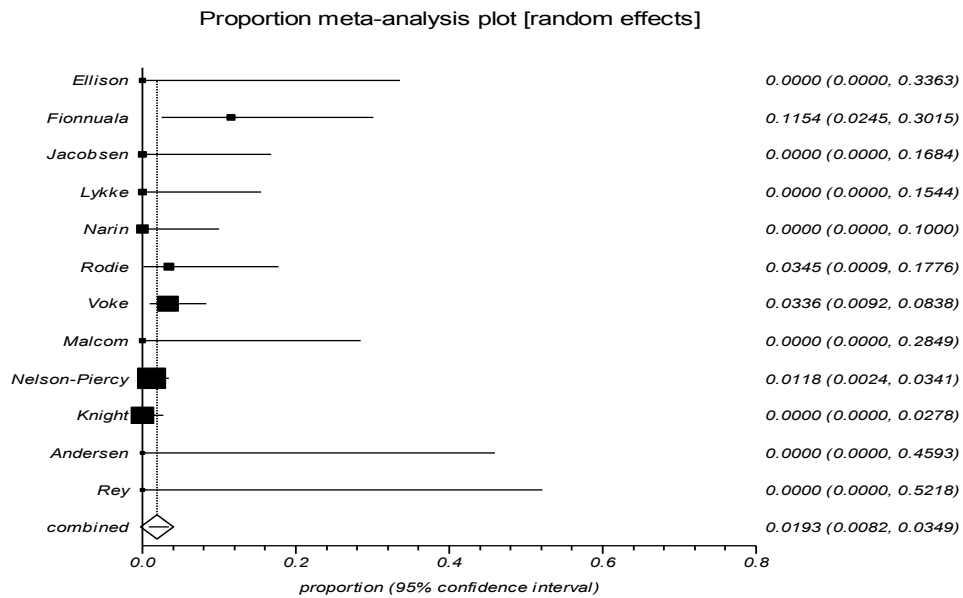
I² (inconsistency) = 17.9% (95% CI = 0% to 58.4%)

Bias indicators

Egger: bias = 0.253028 (95% CI = -0.090894 to 0.59695) P = 0.1322



Analysis 5 Major post-partum bleeding with full dose LMWH



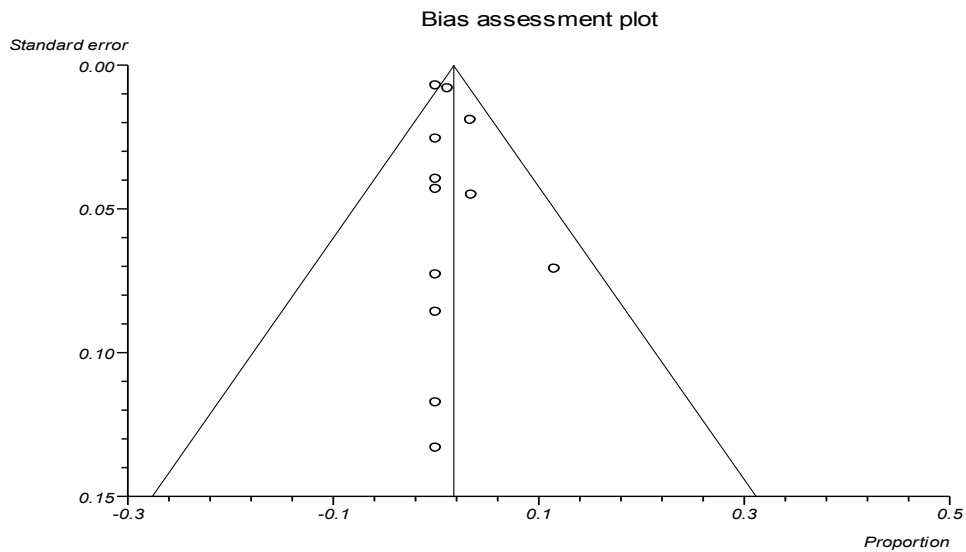
Non-combinability of studies

Cochran Q = 13.942432 (df = 11) P = 0.2362

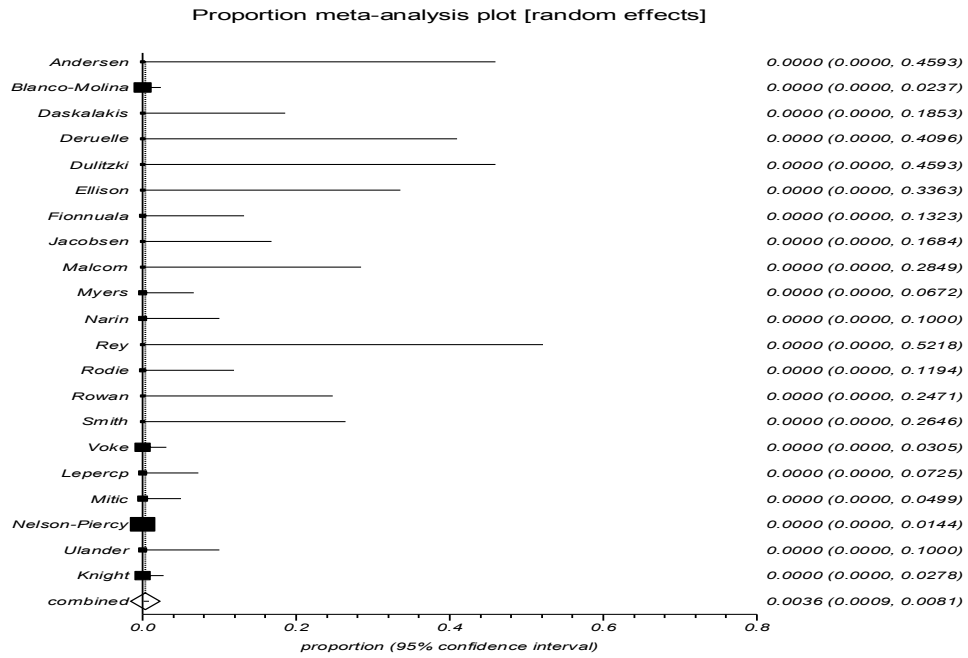
I² (inconsistency) = 21.1% (95% CI = 0% to 59.8%)

Bias indicators

Egger: bias = 0.312096 (95% CI = -0.341471 to 0.965663) P = 0.3123



Analysis 6 Incidence of HIT in patients treated with LMWH



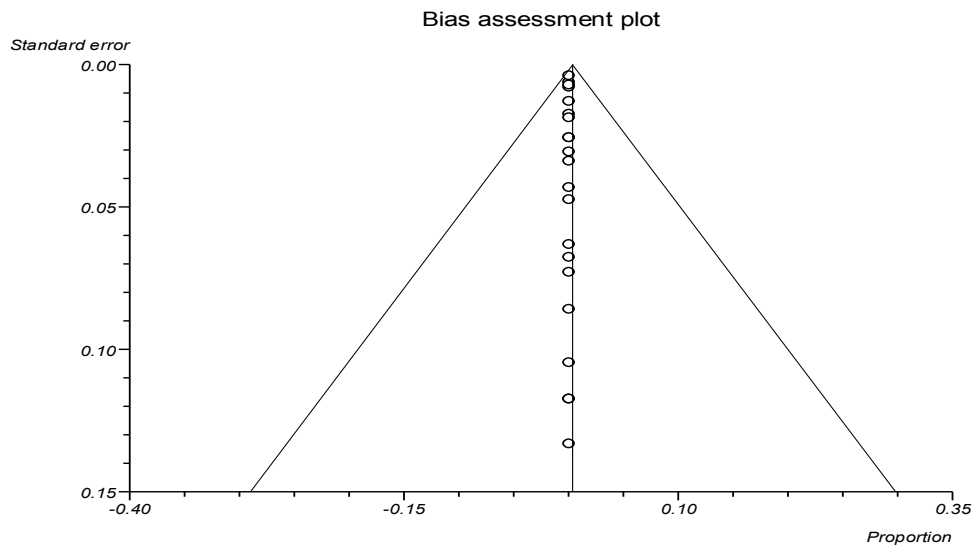
Non-combinability of studies

Cochran Q = 5.66717 (df = 20) P = 0.9993

I² (inconsistency) = 0% (95% CI = 0% to 41.5%)

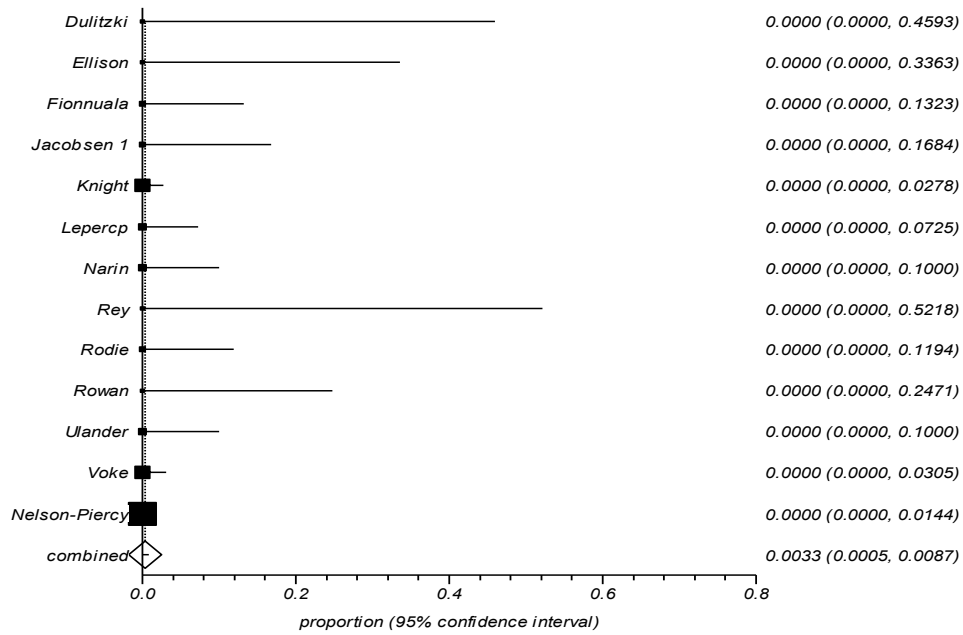
Bias indicators

Egger: bias = 0 (95% CI = 0 to 0) P = *



Analysis 7 Heparin induced osteoporosis in patients treated with LMWH

Proportion meta-analysis plot [random effects]



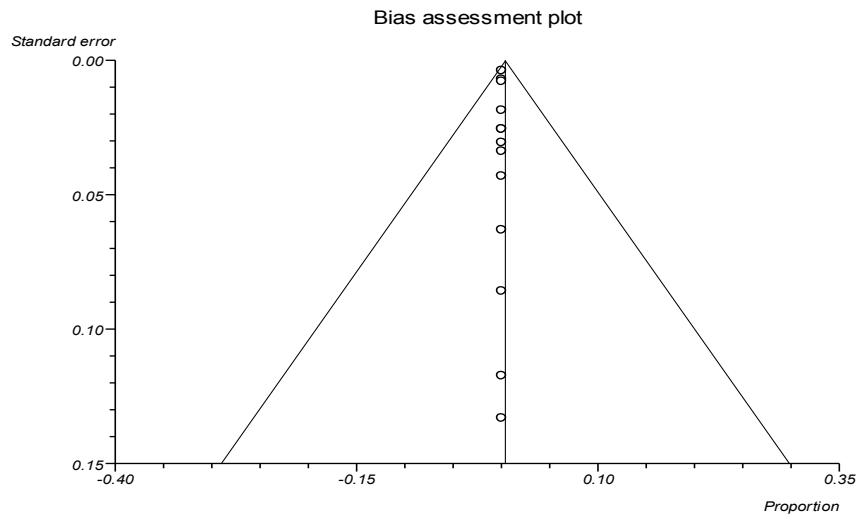
Non-combinability of studies

Cochran Q = 3.487863 (df = 12) P = 0.991

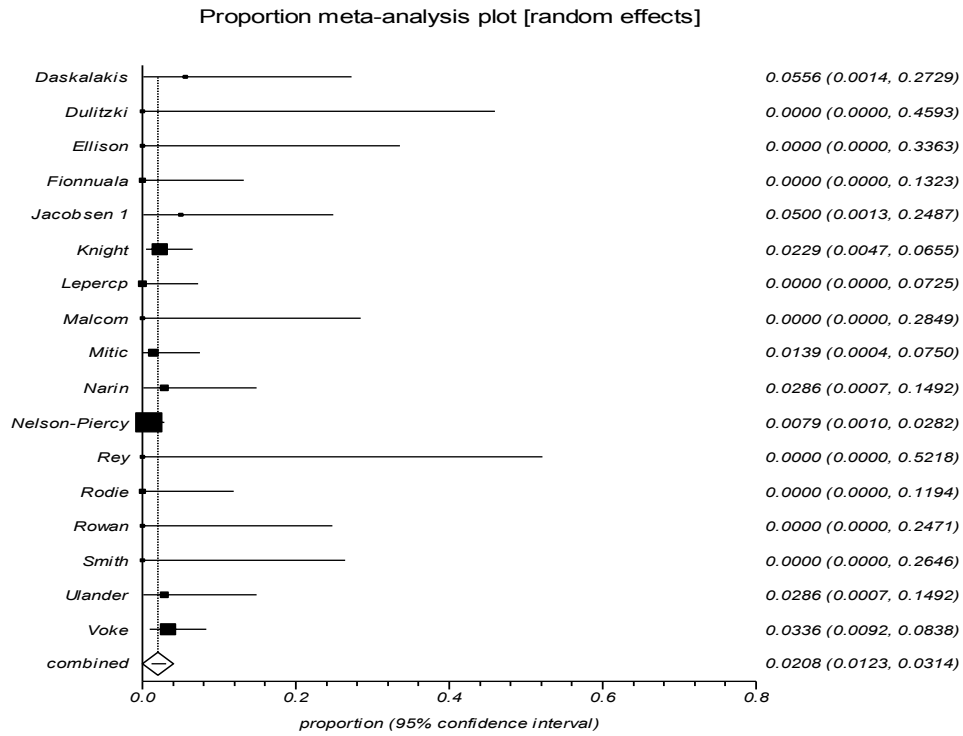
I² (inconsistency) = 0% (95% CI = 0% to 48.6%)

Bias indicators

Egger: bias = 0 (95% CI = 0 to 0) P = *



Analysis 8 Miscarriage or stillbirth during treatment with LMWH



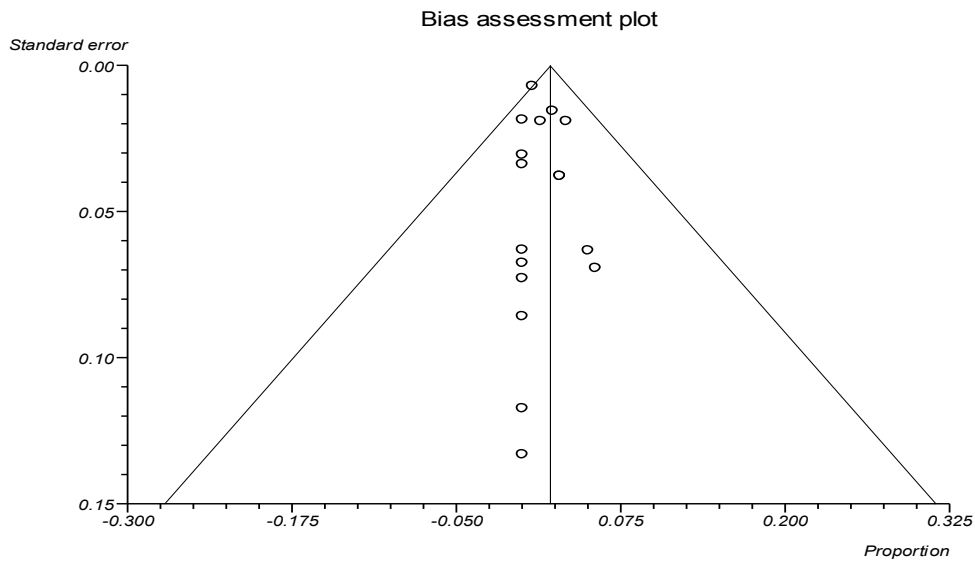
Non-combinability of studies

Cochran Q = 9.02843 (df = 16) P = 0.9122

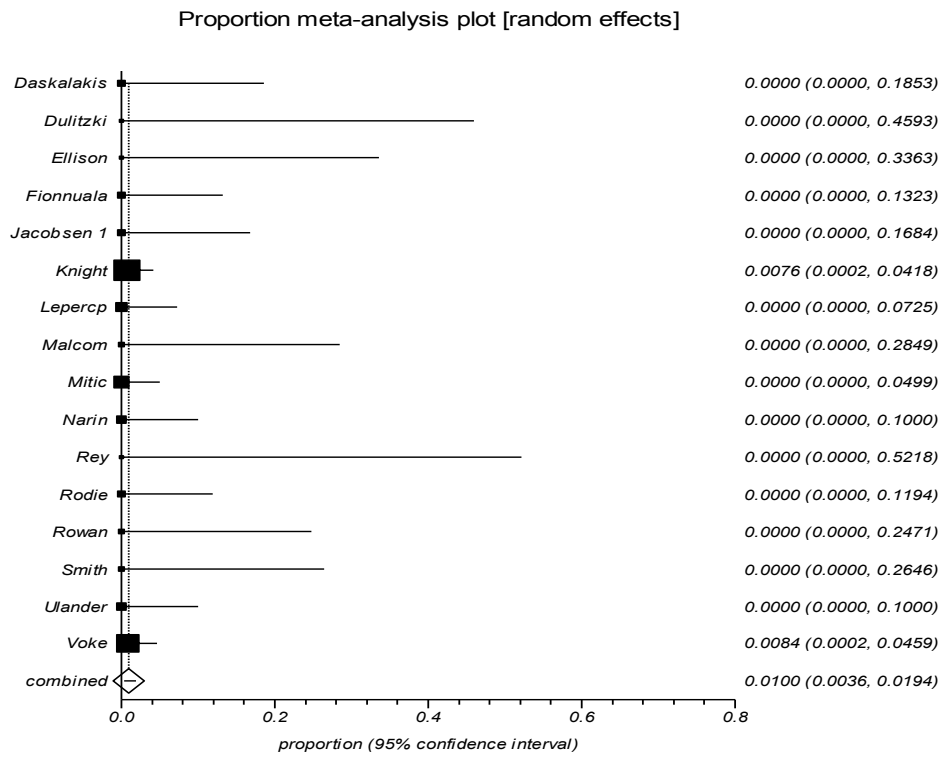
I² (inconsistency) = 0% (95% CI = 0% to 44.5%)

Bias indicators

Egger: bias = 0.154461 (95% CI = -0.231285 to 0.540206) P = 0.4068



Analysis 9 Incidence of fetal malformation in patients treated with LMWH



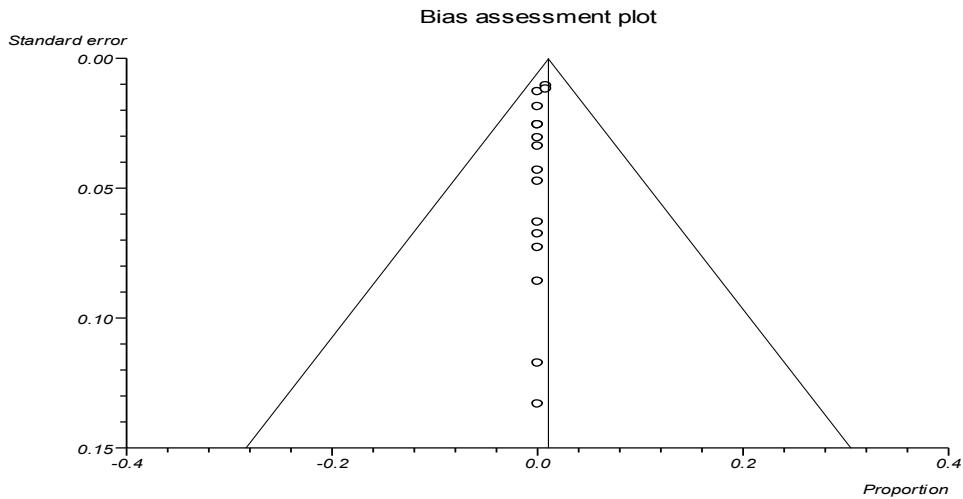
Non-combinability of studies

Cochran Q = 1.792475 (DF = 15) P > 0.9999

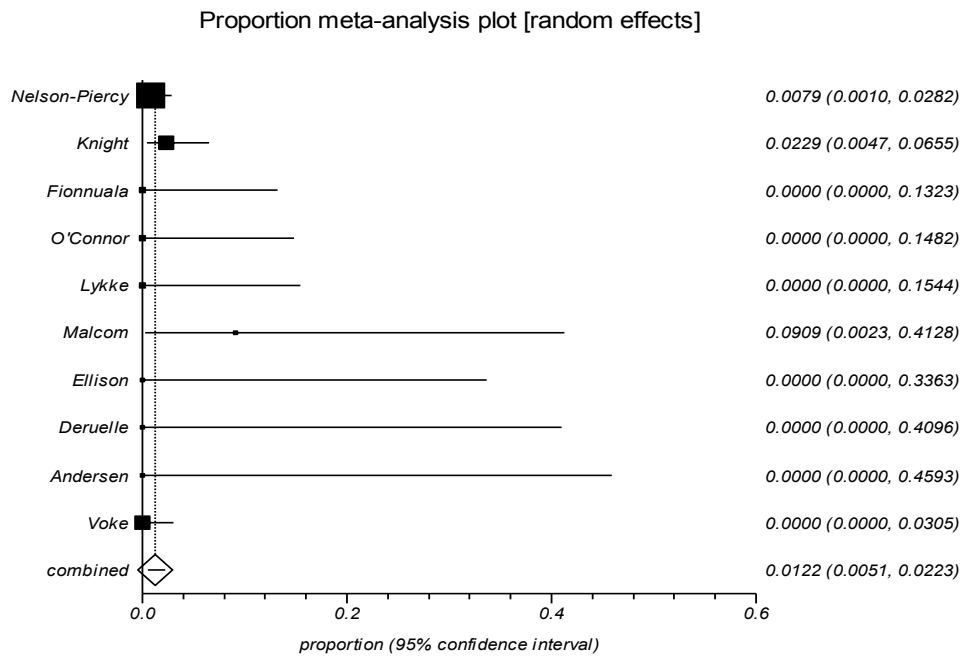
I² (inconsistency) = 0% (95% CI = 0% to 45.4%)

Bias indicators

Egger: bias = -0.143225 (95% CI = -0.291069 to 0.004619) P = 0.0566



Analysis 10 Recurrent VTE in patients treated with full dose LMWH in retrospective studies



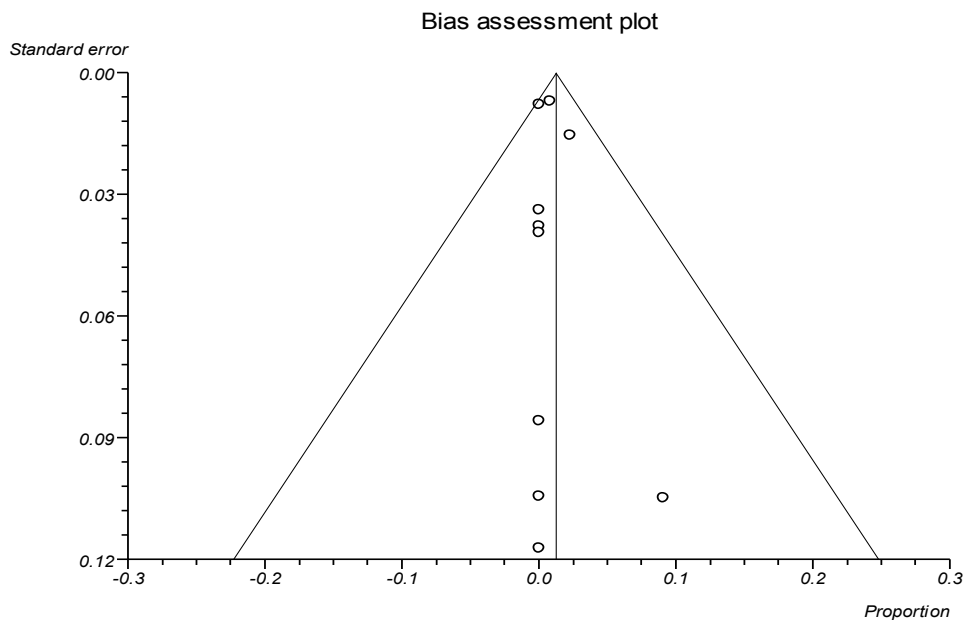
Non-combinability of studies

Cochran Q = 7.012557 (df = 9) P = 0.6358

I² (inconsistency) = 0% (95% CI = 0% to 52.7%)

Bias indicators

Egger: bias = 0.134103 (95% CI = -0.430293 to 0.698499) P = 0.5987



Appendix 2 Survey instrument

Treatment of pregnancy related VTE

1.

Dear Dr,

You are being asked to participate in a survey designed to elicit preferences for the therapeutic management of pregnancy associated venous thromboembolism. We also seek to determine the non inferiority margin for a study evaluating a quarter dose reduction in the dose of low molecular weight heparin used after 30 days of full dose treatment in pregnant patients diagnosed with venous thromboembolism.

Completing this survey will take you less than 10 minutes. By completing this survey, consent is implied.

AT THE END OF THE SURVEY, YOU WILL BE OFFERED TO PARTICIPATE IN A RAFFLE FOR FOUR 50 DOLLARS GIFT CARDS FOR AMAZON

Participating in this study is completely voluntary and anonymous (NO PERSONAL DATA WILL BE COLLECTED). You may choose not to participate.

This survey is not sponsored by any pharmaceutical company and is conducted in the context of a thesis project.

All data provided will remain anonymous and the survey has been approved by the Ottawa Hospital Research Ethics Board. The Ottawa Hospital Research Ethics Board and the Ottawa Hospital Research Institute may review your relevant study records for audit purposes. The study records will be kept for 15 years after termination of the study and then destroyed.

If you have any questions about this study, you may contact Dr. Esteban Gandara at egandara@ohri.ca. If you have any questions about your rights as a research participant, you may contact the Chairman of the Ottawa Hospital Research Ethics Board at 613-798-5555, ext. 14902.

Thanks in advance for your collaboration,

Dr Esteban Gandara and Dr Marc Rodger
Thrombosis Program, Department of Medicine
University of Ottawa
Ottawa Hospital Research Institute

Treatment of pregnancy related VTE

2.

***1. On average do you manage one or more cases of pregnancy associated venous thromboembolism per year ?**

Yes

No

Treatment of pregnancy related VTE

3.

***2. The average rate of recurrent VTE in pregnant patients during pregnancy and the post-partum period treated with monitored split q12 h full dose LMWH (given twice a day and monitored with Anti-Xa levels) appears to be approximately 1.15% (Greer et al. Blood 2005). The rate of significant bleeding during the antepartum period appears to be 0.6%, and 1.1% during the postpartum period (Greer et al. Blood 2005).**

After the initial 30 days of treatment, some experts recommend reducing the dose to 75% without monitoring and administering the drug once a day. The efficacy and safety of this practice in the context of pregnancy awaits confirmation.

Assuming that a $\frac{1}{4}$ dose reduction strategy LEADS TO A POTENTIAL REDUCTION IN SIGNIFICANT BLEEDING, is given once a day and needs no monitoring, what is the maximum potential increase in the absolute rate of recurrence during pregnancy and the post-partum period that you would accept to consider the $\frac{1}{4}$ dose reduction strategy non-inferior to ongoing monitored twice daily full-dose treatment?

In the box below please provide the increase in absolute rate of recurrent VTE that is acceptable (suggested range 0 to 10%):

Treatment of pregnancy related VTE

4.

***3. The average rate of recurrent VTE in pregnant patients during pregnancy and the post-partum period treated with monitored split q12 h full dose LMWH (given twice a day and monitored with Anti-Xa levels) appears to be approximately 1.15% (Greer et al. Blood 2005). The rate of significant bleeding during the antepartum period appears to be 0.6%, and 1.1% during the postpartum period (Greer et al. Blood 2005).**

After the initial 30 days of treatment, some experts recommend reducing the dose to 75% without monitoring and administering the drug once a day. The efficacy and safety of this practice in the context of pregnancy awaits confirmation.

Assuming that a $\frac{1}{4}$ dose reduction strategy LEADS TO A POTENTIAL REDUCTION IN SIGNIFICANT BLEEDING, is given once a day and needs no monitoring, what is the maximum potential increase in the absolute rate of recurrence during pregnancy and the post-partum period that you would accept to consider the $\frac{1}{4}$ dose reduction strategy non-inferior to ongoing monitored twice daily full-dose treatment?

- 0%
- 0.05%
- 0.1%
- 0.3%
- 0.5%
- 1%
- 2%
- 3%
- 4%
- 5%
- 10%

Treatment of pregnancy related VTE

5.

***4. Please assume that a $\frac{1}{4}$ dose reduction strategy DOES NOT REDUCE SIGNIFICANT BLEEDING, is given once a day and needs no monitoring, what is the maximum potential increase in the absolute rate of recurrence during pregnancy and the post-partum period that you would accept to consider the $\frac{1}{4}$ dose reduction strategy non-inferior to ongoing monitored twice daily full-dose treatment?**

Please check one of the following:

0%

0.05%

0.1%

0.3%

0.5%

1%

2%

3%

4%

5%

10% In other words an increase in absolute rate of recurrent VTE during pregnancy and the post-partum period of 10% (i.e. an increase from 1.15% with full dose to 11.15% with dose reduction is acceptable). The number needed to harm with $\frac{1}{4}$ dose reduction is 10 i.e. you would need to treat 10 patients with $\frac{1}{4}$ dose reduction to increase by one the number of recurrent VTE compared to full dose treatment

Treatment of pregnancy related VTE

6.

***5. Now, assuming that a ¼ dose reduction strategy DOES NOT REDUCE SIGNIFICANT BLEEDING AND NEEDS ANTI-Xa MONITORING, but is given once a day, what is the maximum potential increase in the absolute rate of recurrence during pregnancy and the post-partum period that you would accept to consider the ¼ dose reduction strategy non-inferior to ongoing monitored twice daily full-dose treatment?**

Please check one of the following:

0%

0.05%

0.1%

0.3%

0.5%

1%

2%

3%

4%

5%

10% In other words an increase in absolute rate of recurrent VTE during pregnancy and the post-partum period of 10% (i.e. an increase from 1.15% with full dose to 11.15% with dose reduction is acceptable). The number needed to harm with ¼ dose reduction is 10 i.e. you would need to treat 10 patients with ¼ dose reduction to increase by one the number of recurrent VTE compared to full dose treatment

Treatment of pregnancy related VTE

7.

***6. Finally, assume the ¼ dose reduction strategy DOES NOT HAVE ANY BENEFITS (does not reduce significant bleeding, needs monitoring and is given twice a day), what is the maximum potential increase in the absolute rate of recurrence during pregnancy and the post-partum period that you would accept to consider the ¼ dose reduction strategy non-inferior to ongoing monitored twice daily full-dose treatment?**

Please check one of the following:

0%

0.05%

0.1%

0.3%

0.5%

1%

2%

3%

4%

5%

10% In other words an increase in absolute rate of recurrent VTE during pregnancy and the post-partum period of 10% (i.e. an increase from 1.15% with full dose to 11.15% with dose reduction is acceptable). The number needed to harm with ¼ dose reduction is 10 i.e. you would need to treat 10 patients with ¼ dose reduction to increase by one the number of recurrent VTE compared to full dose treatment

Treatment of pregnancy related VTE

8. Treatment preferences

***7. In pregnant patients diagnosed with DVT, during the first and second trimester, your initial option for acute treatment (0 to 30 days) is:**

- Unfractionated heparin IV
- Unfractionated heparin SC twice a day
- Low molecular weight heparin full dose split twice a day
- Low molecular weight heparin full dose SC once a day
- Vena cava filter and; either Low molecular weight heparin or Unfractionated heparin
- Other

Other (please specify)

Treatment of pregnancy related VTE

9.

***8. After the initial acute treatment phase (7 to 30 days) for DVT, and still during the first or second trimester, you continue therapy with:**

- Unfractionated heparin SC, full dose twice a day, monitored
- Low molecular weight heparin SC, full dose twice a day
- Low molecular weight heparin SC, full dose once a day
- Low molecular weight heparin SC, 75% dose twice a day
- Low molecular weight heparin SC, 75% dose once a day
- Other

Other (please specify)

Treatment of pregnancy related VTE

10.

***9. In pregnant patients diagnosed with hemodynamically stable PE, during the first or second trimester, your initial option for acute treatment (0 to 30 days) is:**

- Unfractionated heparin IV
- Unfractionated heparin SC twice a day
- Low molecular weight heparin full dose SC split twice a day
- Low molecular weight heparin full dose SC once a day
- Vena cava filter and; either Low molecular weight heparin or Unfractionated heparin
- Other

Other (please specify)

Treatment of pregnancy related VTE

11.

*** 10. After the initial acute treatment phase (7 to 30 days) for PE, still during the first or second trimester, you continue therapy with:**

- Unfractionated heparin SC, full dose twice a day, monitored
- Low molecular weight heparin SC, full dose twice a day
- Low molecular weight heparin SC, full dose once a day
- Low molecular weight heparin SC, 75% dose twice a day
- Low molecular weight heparin SC, 75% dose once a day
- Other

Other (please specify)

Treatment of pregnancy related VTE

12.

*** 11. In pregnant patients diagnosed with venous thromboembolism during the first and second trimester, how do you manage the peri-partum period (provided that is a planned delivery induction or cesarean section)?**

- IVC filter, and low molecular weight heparin split full dose to be stopped 12 hours before delivery and restarted 12 hours after delivery
- IVC filter, and SC unfractionated heparin twice daily to be stopped 12 hours before delivery and restarted 12 hours after delivery
- IVC filter, and IV unfractionated heparin to be stopped 3 hours before delivery and restarted 6 hours after delivery
- NO IVC filter, and low molecular weight heparin split full dose to be stopped 12 hours before delivery and restarted 12 hours after delivery
- NO IVC filter, and SC unfractionated heparin twice daily to be stopped 12 hours before delivery and restarted 12 hours after delivery
- NO IVC filter, and IV unfractionated heparin to be stopped 3 hours before delivery and restarted 6 hours after delivery
- Other

Other (please specify)

Treatment of pregnancy related VTE

13.

***12. In patients diagnosed with PE or DVT, within four weeks (BUT NOT TWO WEEKS) of the expected due date(provided that is a planned delivery induction or cesarean section), your treatment strategy is:**

- IVC filter, and low molecular weight heparin split full dose to be stopped 12 hours before delivery and restarted 12 hours after delivery
- IVC filter, and SC unfractionated heparin twice daily to be stopped 12 hours before delivery and restarted 12 hours after delivery
- IVC filter, and IV unfractionated heparin to be stopped 3 hours before delivery and restarted 6 hours after delivery
- NO IVC filter, and low molecular weight heparin split full dose to be stopped 12 hours before delivery and restarted 12 hours after delivery
- NO IVC filter, and SC unfractionated heparin twice daily to be stopped 12 hours before delivery and restarted 12 hours after delivery
- NO IVC filter, and IV unfractionated heparin to be stopped 3 hours before delivery and restarted 6 hours after delivery
- Other

Other (please specify)

Treatment of pregnancy related VTE

14.

***13. In patients diagnosed with PE or DVT, within two weeks of the expected due date, your treatment strategy is:**

- IVC filter, and low molecular weight heparin split full dose to be stopped 12 hours before delivery and restarted 12 hours after delivery
- IVC filter, and SC unfractionated heparin twice daily to be stopped 12 hours before delivery and restarted 12 hours after delivery
- IVC filter, and IV unfractionated heparin to be stopped 3 hours before delivery and restarted 6 hours after delivery
- NO IVC filter, and low molecular weight heparin split full dose to be stopped 12 hours before delivery and restarted 12 hours after delivery
- NO IVC filter, and SC unfractionated heparin twice daily to be stopped 12 hours before delivery and restarted 12 hours after delivery
- NO IVC filter, and IV unfractionated heparin to be stopped 3 hours before delivery and restarted 6 hours after delivery
- Other

Other (please specify)

Treatment of pregnancy related VTE

15.

***14. In pregnant patients treated with low molecular weight heparin for venous thromboembolism, DURING the acute initial period (0 to 30 days) do you monitor Anti-Xa levels?**

- Yes, weekly in all patients
- Yes, once during the first month
- Yes, weekly but only in special groups
- Yes, once during the first month but only in special groups
- No, never
- Other

Other (please specify)

Treatment of pregnancy related VTE

16.

***15. In pregnant patients treated with low molecular weight heparin for venous thromboembolism, AFTER the acute initial period (0 to 30 days) and for the duration of pregnancy, do you monitor Anti-Xa levels?**

- Yes, weekly in all patients
- Yes, monthly in all patients
- Yes, weekly in special groups
- Yes, monthly in special groups
- No, never
- Other

Other (please specify)

Treatment of pregnancy related VTE

17. Demographics

***16. Your medical specialty is:**

- Hematology
- Internal Medicine
- Obstetrics
- Cardiology or cardiovascular medicine
- Respirology
- Other

17. How many years have you practiced medicine?

- Less than five
- Five to ten
- Ten to fifteen
- Fifteen or more

***18. Do you have any formal training in research methods?**

- Yes
- No

Treatment of pregnancy related VTE

18. Study Feasibility

*** 19. Experts recommend the use of a 3/4 treatment dose (likely without monitoring) after 3 to 4 weeks of full treatment in pregnant patients with VTE, but call for more clinical evidence.**

Do you agree that a well design study is needed?

Yes

No

20. If that study was conducted, would you be willing to participate?

Yes

No