VENOUS THROMBOEMBOLISM PREVENTION IN THE BARIATRIC SURGICAL PATIENT: ARE WE DOING ENOUGH?

By

Kimberley Eden Steele, M.D., F.A.C.S
Associate Professor of Surgery
The Johns Hopkins Center for Bariatric Surgery

A dissertation submitted to the Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, MD
April, 2014

Abstract

Bariatric surgery has become an accepted, safe and durable method of weight loss for the obese patient. Despite this success, venous thromboembolism (VTE) continues to be one of the top two causes of mortality in bariatric surgery. Most bariatric surgeons today use a combination of non-invasive and pharmacologic techniques, including sequential compression devices, anti-embolic stockings, anticoagulation, and early ambulation, to prevent VTE. Despite these interventions, the incidence of VTE after bariatric surgery has been reported to be widely variable ranging from 0.3 to 3.8%. (1-11) The most recent study published to date reported an incidence of pulmonary emboli (PE) of 0.9%, deep venous thrombosis (DVT) without PE to be 1.3% and VTE (DVT + PE) to be 2.2% within the perioperative period. (12) Little data has been collected to evaluate the long term risk (greater than 30 days post-op) of VTE following bariatric surgery. Furthermore, the prevalence of asymptomatic deep venous thrombosis (DVT) in this population is unknown and is sure to be higher.

Our main goal for this thesis was to study the effectiveness of current and future practices of venous thromboembolism prophylaxis in the bariatric surgical population. To do so, we first completed a narrative summary of the current agents and techniques used to prevent VTE in this population (Chapter one). We then analyzed a large administrative database to determine the long term risk and predictors for VTE in patients undergoing bariatric surgery using current VTE prophylaxis (Chapter two). We identified a history of previous VTE events as being the strongest predictor of development of a VTE post-surgery. This high rate of recurrence has led to the recommendation that patients with

prior VTE or other high risk groups should be considered for prophylactic vena cava filter insertion before surgery. This finding motivated us to specifically assess the efficacy and risks of IVC filters in the bariatric surgery population. We completed a retrospective analysis of a large administrative database to determine these risks and benefits (Chapter three). The body habitus of a bariatric surgical patient presents technical challenges in the detection of VTE, especially asymptomatic DVT in the pelvis and lower limbs. Because of the limited sensitivity and specificity of ultrasound in the detection of DVT in the obese patient, we performed a systematic review and meta-analysis to determine the diagnostic accuracy of magnetic resonance venography in the detection of DVT in the obese (Chapter four). Based on these results above, we then designed a randomized double blinded controlled trial (RCT) to study the incidence of asymptomatic deep venous thrombosis in this special population. We compared two different anticoagulation regimens in the prevention of VTE in bariatric surgical patients:enoxaparin 40 mg subcutaneously twice daily (our standard regimen), and fondaparinux 5 mg subcutaneously once daily (a non-standard dose in the obese population, used under an IND obtained by Dr. Steele). We used MRV as a novel non-invasive diagnostic tool to detect asymptomatic DVT in our patient population (Chapter five). In the final chapter, Chapter six, we discuss public health-based approaches and future work in the prevention of VTE in this special population.

Readers:

Dr. Timothy Moran

Dr. Dorry Segev

Dr. Jodi Segal

Dr. Larry Cheskin

Dr. Michael Streiff (alternate for Dr. Julie Freischlag)

Preface and Acknowledgements

This work was supported by an NIH KL2 training grant awarded by the Clinical Scholar Program to the thesis author during 2011-13 period. Protected time to complete this thesis was also supported by a Clinician Scientist Award 2013-15. Funding for the retrospective analyses was provided by the Hariri Family Foundation and Mr. and Mrs. Chad and Nissa Richinson. The dataset used for this thesis work was originally created for a different research project on patterns of obesity care within selected Blue Cross/Blue Shield (BCBS) plans. The previous research project (but not the current study) was funded by unrestricted research grants from Ethicon Endo-Surgery, Inc (a Johnson & Johnson company); Pfizer, Inc.; and GlaxoSmithKline. The data and database development support and guidance were provided by the BCBS Association, BCBS of Tennessee, BCBS of Hawaii, BCBS of Michigan, BCBS of North Carolina, Highmark, Inc. of Pennsylvania, Independence Blue Cross of Pennsylvania, Wellmark BCBS of Iowa, and Wellmark BCBS of South Dakota. The randomized controlled trial work was made possible by an investigator initiated grant from GlaxoSmithKline. Study materials (drug) and/or additional financial support were provided by GlaxoSmithKline. Financial supporters had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

I am incredibly grateful to all of my thesis committee members for their mentorship, continued support, guidance and advice. My progress and work would not have been possible without their insightfulness, guidance, input and availability. Through the GTPCI program and my committee's mentorship, I have learned how to conduct quality

research and how to be a productive clinical researcher despite having countless clinical, research and personal responsibilities. Finally, I would like to thank most of all, my husband Greg Prokopowicz and our sons Michael and Matthew. This could never have been accomplished without their patience, unconditional love and continued support. "Thanks guys for letting mommy have the time to get this done!"

Table of Contents

List of Tables

List of Figures

Abbreviations

ASMBS	American Society of Metabolic and Bariatric Surgery
ACCP	American College of Chest Physicians
aPTT	Activated Partial Thromboplastin Time
AT	Antithrombin III
aOR	Adjust Odds Ratio
BC/BS	Blue Cross Blue Shield
BL	Baseline
BMI	Body Mass Index
CC	Case-control
CPT	Current Procedural Terminology
CS	Cohort study
CV	Contrast Venography
CT	Computed Tomography
DVT	Deep Vein Thrombosis
DM	Diabetes Mellitus
DSMB	Data Safety Monitoring Board
ED	Emergency Department
FDA	Food and Drug Administration
GERD	Gastroesophaeal Reflux Disease
GI	Gastrointestinal
GTPCI	Graduate Training in Clinical Investigation
GU	General Urology

HIT	Heparin Induced Thrombocytopenia
HTN	Hypertension
IND	Investigational New Drug
INR	International Normalization Ratio
IPC	Intermittent pneumatic compression
IVC Filter	Inferior Vena Cava Filter
LMWH	Low molecular weight heparin
LOS	Length of stay
MRV	Magnetic Reasonance Venography
NIH	National Institute of Health
NR	Not reported
OR	Odds Ratio
PE	Pulmonary Embolism (Emboli)
PECO	Population, exposure, comparison and outcome
QUADAS-2	Quality Assessment for Diagnostic Accuracy Studies tool -2
RCT	Randomized Controlled Trial
SCD	Sequential compression device
SRMA	Systematic Review and Meta-analysis
SOC	Standard of Care
T	Telsa
TED hose	Thromboembolism-Deterrent hose
UFH	Unfractionated heparin
U/S	Ultrasound

VSG	Vertical Sleeve Gastrectomy
VTE	Venous Thromboembolism

Chapter 1 Introduction

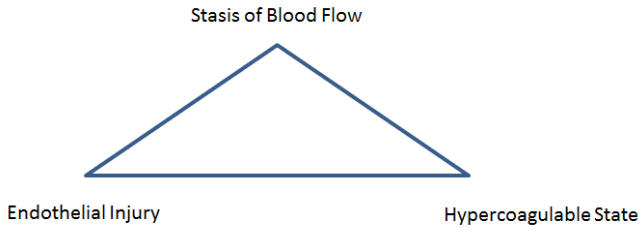
1.1 Defining Venous Thromboembolism

VTE includes both deep vein thrombosis (DVT), blood clots that form in the deep veins of the body, and pulmonary emboli (PE), blood clots that form in the deep veins of the body and then break free and enter the arteries of the lungs. VTE affects all races, ethnicities, both genders and all age groups.(13)

There is a fine balance between clot formation and fibrinolysis. Normally these two physiologic states are in dynamic equilibrium preventing patients from bleeding or clotting excessively. Numerous factors affect this delicate balance. These factors can be grouped into three broad categories, also known as Virchow's triad (after the German physician Rudolf Virchow) (14):

1. Vascular injury (endothelial damage)
2. Activation of blood coagulation (hypercoagulability)
3. Venous stasis

Figure 1 Virchow's Triad



1.2 Burden of Venous Thromboembolism in the Bariatric Surgical Patient

VTE and its sequelae constitute one of the most significant causes of morbidity and mortality in hospitalized and post-operative surgical patients. In the United States alone, an estimated 300,000 to 600,000 (1 to 2 per 1,000) patients each year are diagnosed with

VTE, and 60,000 to 100,000 die of VTE. (15) Among people who have had a DVT, one-half will have long-term complications such as swelling, pain, discoloration, and scaling in the affected limb (post-thrombotic syndrome). (15, 16) Spyrpoulos et al completed a healthcare claims analysis on the economic burden of VTE and found that the cost of VTE ranges from $7594 to $16, 644 per patient.(17) This equates to a total annual cost of 2 to 10 billion dollars. VTE is one of the top two causes of morbidity and mortality in the bariatric surgical patient. In the ninth edition of the Antithrombotic Therapy and Prevention of Thrombosis guideline published by the American College of Chest Physicians (2012), it is reported that virtually all bariatric surgical patients have at least a moderate risk of VTE, with many patients at high risk. (18, 19) Despite these impressive figures, there exists no FDA-approved or universally accepted protocol for pharmacologic VTE prophylaxis in morbidly obese patients.

1.3 Etiology and Risk Factors for Developing Venous Thromboembolism

As with many conditions, VTE is a multifactorial condition that involves genetic factors as well as acquired risk factors. Genetic factors include family history, factor V Leiden, protein C, S, and antithrombin deficiencies, prothrombin G20210A, and sickle cell trait. Acquired risk factors may be transient, such as pregnancy, use of birth control pills or hormonal therapy, trauma, immobilization, or surgery. Acquired risk factors may also be relatively immutable, such as advanced age, cancer, chronic disease, or obesity. (13) Patients undergoing bariatric surgery for the treatment of morbid obesity often have three or more risk factors (20, 21) and are therefore at high risk for a VTE event. In our retrospective analysis we identified male sex, advanced age, previous VTE, smoking, and long length of stay (>5 days) as risk factors for VTE. In a systematic review of venous

thromboembolism prophylaxis in obese patients, the authors concluded that "obese patients undergoing bariatric surgery have an increased risk for VTE that is greater than the risk of surgical procedure itself."(22)

The choice of open versus laparoscopic approach to bariatric surgery also affects the risk of VTE. Characteristics of the laparoscopic approach that increase the risk of VTE includes increased intra-abdominal pressure and decreased femoral venous flow, and characteristics that decrease the risk include milder derangement of the coagulation pathways, early ambulation, and faster recovery. (23)

1.4 Prophylaxis of Venous Thromboembolism in Bariatric Surgical Patients

To date, there remains no consensus as to the optimal regimen for prevention of VTE in the bariatric surgical patient. The approach to VTE prophylaxis used by most bariatric surgeons today is a combination of non-invasive and pharmacologic techniques, including sequential compression devices, anti-embolic stockings, anticoagulation, and early ambulation. In 2000, Wu and colleagues surveyed members of the American Society of Metabolic and Bariatric Surgery (ASMBS) and found that while virtually all of those who completed the survey practiced some form of DVT prophylaxis, nearly half nonetheless experienced patient mortality due to PE. They found considerable variation among surgeons with respect to preferred means of prophylaxis, and because of the relative infrequency of VTE they concluded that a multi-center, randomized trial would be needed to settle the issue. Unfortunately, such a trial would be very expensive, requiring a very large number of subjects. Furthermore, the existing protocol required by the FDA to assess the efficacy of prophylactic anticoagulation requires the use of lower extremity venography, which is very difficult to perform on morbidly obese patients due

to the difficulty of obtaining venous access in the lower extremities. Various investigators have attempted to use duplex ultrasound in place of venography to document adequacy of DVT prophylaxis. However, the sensitivity of duplex ultrasound in the general population is only 43% (with 97% specificity) and it is likely that the performance of this test is worse in the morbidly obese due to the technical challenges presented by the large lower extremities and abdominal pannus overlying the inguinal region. (24)

In April 2004, a roundtable meeting sponsored by The Johns Hopkins University School of Medicine, in conjunction with Princeton Media Associates, was held to discuss the state of the art in prevention of VTE. This meeting involved 5 experts in the field including Dr. Michael Schweitzer, Johns Hopkins, Dr. Giselle Hamad, University of Pittsburgh, Dr. Raul Rosenthal, Cleveland Clinic, Dr. Eric DeMaria, Duke University, and Dr. Julio Teixeira, St. Luke's Roosevelt Hospital. (25) A review of the meeting demonstrated significant inter-institution variability in the approach to VTE prophylaxis. Four out of the five surgeons used sequential compression devices plus anticoagulation. Two out of the five administered the first dose of anticoagulation before the start of the case. All five were in agreement that VTE prophylaxis should be continued in all patients at least until hospital discharge. The use of inferior vena cava filters (IVC filters) was also assessed, and four of the five surgeons strongly believed that a history of PE warranted the use of an IVC filter, while three of the five would also consider the device in patients with a history of DVT, obesity hypoventilation syndrome, severe leg edema, severe chronic venous stasis disease, or wheelchair bound status.

Because of this, best practices for VTE prophylaxis in bariatric surgical patients are unfortunately based not on evidence but on the experience and opinion of experts in the field.

1.5 Narrative Summary of Methods of VTE Prophylaxis

1.5.1 Non-pharmacologic VTE Prophylaxis

According to the American College of Chest Physicians VTE guideline for non-orthopedic surgical patients, non-pharmacologic prophylaxis includes early and frequent ambulation or mobilization, and mechanical prophylaxis such as graduated compression stockings (GCS), intermittent pneumatic compression (IPC), or sequential compression devices (SCDs). (26) IPC devices are designed to decrease venous stasis, improve blood flow, and increase the level of circulating fibrinolysins (proteolytic enzymes derived from blood plasminogen that cause breakdown of the fibrin in blood clots). The advantage of IPC devices over chemoprophylaxis is that there is no monitoring involved, with no increase in bleeding and they are in general well tolerated. (27) The disadvantage of IPC devices is that one size does not fit all and in patients with extremely large lower limbs there may not be an IPC device that fits correctly. In addition, their use is contraindicated in patients with lower limb DVT or injury.

Most studies of bariatric surgical patients in the literature recommend some form of mechanical prophylaxis in combination with chemoprophylaxis. When there is an increased risk of bleeding complications, most would favor the use of mechanical prophylaxis, preferably IPC, over no prophylaxis until the risk of bleeding decreases and pharmacologic prophylaxis may be resumed. Several studies have questioned the need for chemoprophylaxis at all when mechanical prophylaxis has been used properly. Gagner et

al. completed a prospective observational study utilizing the Longitudinal Assessment of Bariatric Surgery (LABS) data which includes a cohort of 10 clinical sites within the United States between 2005 and 2007. (28) The authors compared bariatric surgical patients who received anticoagulation therapy during their index hospitalization to those who received only mechanical prophylaxis. Of the 4416 patients, 396 received SCDs alone, and the remaining 4020 received anticoagulation therapy. Interestingly, the incidence of VTE within 30 days was higher in the anticoagulation group than in the mechanical prophylaxis group.(28) Clements et al. had similar outcomes in their prospective study of 957 consecutive patients undergoing laparoscopic Roux-en Y gastric bypass by a single surgeon. The authors concluded that adequate VTE prophylaxis can be achieved using calf-length IPC devices with early ambulation and short operative times. They further went on to state that pharmacologic anticoagulation is not mandatory when the above conditions are met and the patient has no previous history of VTE.(7) While these studies have promoted the use of mechanical prophylaxis alone, it should be noted that both of these studies did not include high-risk bariatric surgical patients and there are far more studies with stronger evidence that recommend the use of mechanical prophylaxis in conjunction with chemoprophylaxis.

1.5.2 Chemoprophylactic VTE Prevention

To date there remains no class 1 evidence to formulate specific recommendations regarding the use of anticoagulation medication. The American College of Chest Physicians recognizes three main drug classes: heparin, including low-dose unfractionated heparin (UFH) and low-molecular weight heparin (LMWH), fondaparinux (anti-factor Xa inhibitor), and aspirin.

Aspirin acts as an effective platelet inhibitor at low doses (50-100mg daily). It acts on the cyclooxygenase-1 and prevents thrombosis. Scientists and physicians have considered aspirin for possible VTE prophylaxis. Unfortunately, the results have not measured up (29) and the American College of Chest and Physicians Guidelines do not recommend the use of aspirin alone as prophylaxis for VTE for any patient population.(26)

Unfractionated Heparin (UFH) was first discovered by Mclean (a second year medical student at Johns Hopkins University) in 1916. (30) It is a naturally occurring polysaccharide and is derived from either porcine intestine or bovine lung. UFH binds to antithrombin (AT) III and enhances AT to inactivate factors IIa, Xa, IXa, and XIIa. This then prevents the conversion of prothrombin to thrombin and fibrinogen to fibrin. (31) UFH consists of polysaccharide molecular chains of varying lengths (5000 to 40,000 Daltons). Heparin is administered intravenously or subcutaneously but is inactivated in the GI tract. It binds non-specifically to various plasma proteins and therefore causes an unreliable dose-response. It has a rapid onset of action and a short half-life. Intravenous administered heparin is measured by the activated partial thromboplastin time (aPTT).

Low Molecular Weight Heparins (LMWH) are obtained by fractionating or depolymerizing unfractionated heparin through various chemical or enzymatic processes creating short chains of polysaccharides that have an average molecular weight of less than 8000 Daltons (32). LMWH also binds to and enhances the activity of AT, but has a preferential and longer lasting effect on factor Xa and does not selectively bind to specific proteins like heparin. As a result this drug is more predictable and has less inter-patient variability, and has a longer duration of action when compared to heparin and the

risk of developing DVT is significantly reduced. (33-35) LMWHs do not require monitoring of either aPTT or INR.

There are numerous varieties of LMWH based on their molecular weight and include Enoxaparin, Dalteparin, Nadroparin, Parnaparin, Certoparin. Bemiparin, Reviparin and Tinzaparin. Enoxaparin is the most commonly used and studied LMWH in the bariatric literature. It is derived from the intestinal mucosa of pigs.

Fondaparinux is a synthetic pentasaccharide factor Xa inhibitor. Fondaparinux inhibits factor Xa by selectively binding to antithrombin III (AT), a blood protein responsible for inactivating enzymes in the clotting cascade. When fondaparinux sodium is introduced into the circulatory system it binds to AT and effectively neutralizes its activity. This in turn disrupts the blood coagulation cascade and prevents thrombin formation. (36) Fondaparinux has no direct effect on thrombin. It is administered subcutaneously and has a long half-life. While this medication cannot be used in patients with renal impairment, a potential advantage of fondaparinux over LMWH or unfractionated heparin is a greatly reduced risk for heparin-induced thrombocytopenia (HIT).(37)

Whereas fondaparinux *directly* prevents DVT formation by selective binding to a specific protein, enoxaparin *indirectly* prevents DVT formation by prolonging the natural lag phase of thrombin formation in the body. (38)

New Oral Anticoagulants (NOACs) are currently available for prophylaxis against venous thromboembolism in patients undergoing total hip or knee replacement surgery. Dabigatran etexilate (*Pradaxa*) is a direct thrombin inhibitor which inhibits both free and fibrin-bound thrombin. Randomized controlled trials have shown that dabigatran is as effective in the prevention of VTE in total hip replacement.(39) Rivaroxaban (*Xarelto*) is

an orally activated direct factor Xa inhibitor (4 hours after the dose is taken and the factor Xa activity does not return to normal for 24 hours thus once daily dosing is possible). (40) This drug has FDA approval for the initial treatment of DVT and PE and for the prevention of recurrent DVT and PE. Apixaban (*Elquis*): Like Rivaroxaban, Apixaban is a direct factor Xa inhibitor. Apixaban first became available in Europe in 2011 and is used there for preventing venous thromboembolism in hip and knee surgery. This drug is used in the United States presently for reducing the risk of stroke and PE in patients with atrial fibrillation. (41)

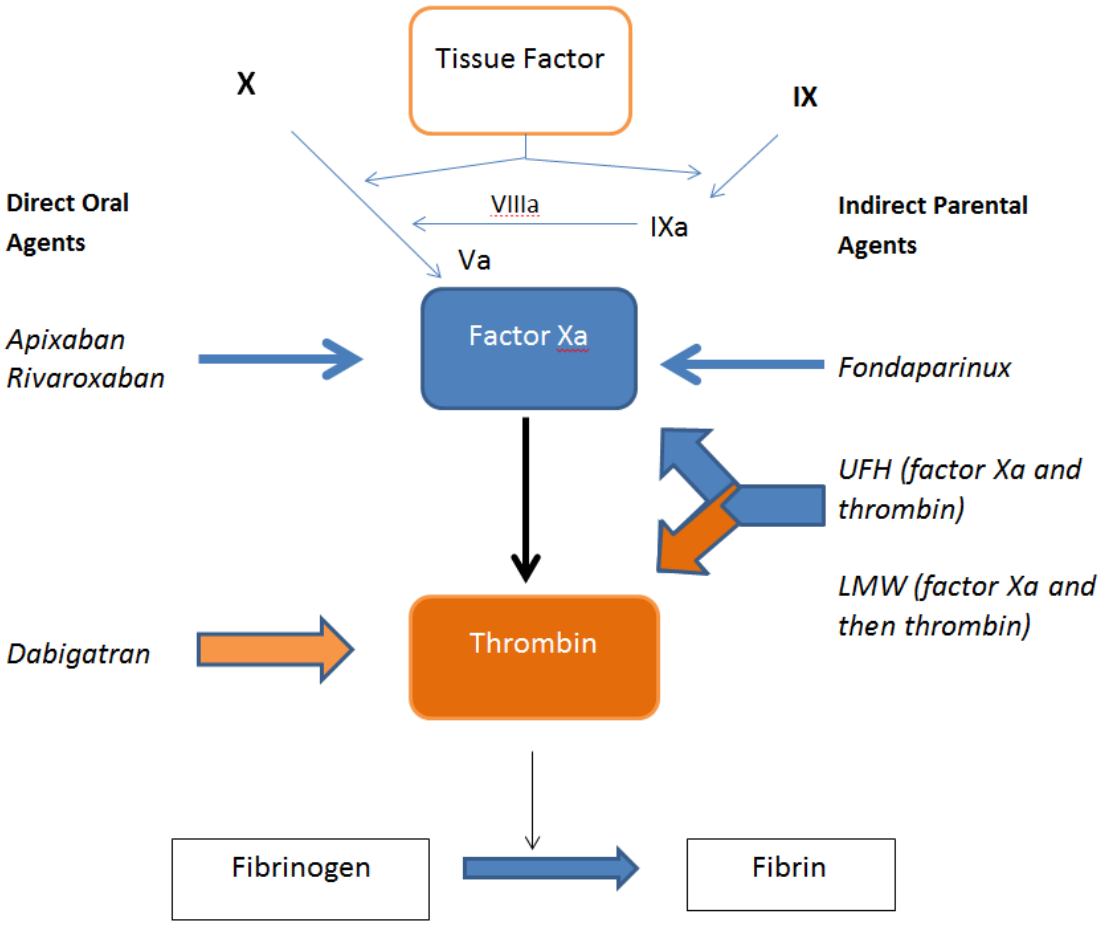
A recent review and meta-analysis of these new oral anticoagulants has concluded that they were equally as good as enoxaparin but did have a higher bleeding tendency. The drugs did not differ significantly for efficacy and safety.(42) NOACs do not require routine coagulation monitoring and seem to be the way of the future for ease of administration efficacy and tolerability. Additional research is needed to determine how these new oral anticoagulants should be used in special populations such as the obese medical or surgical patient. (See Chapter 6 for future projects proposed)

Table 1. Comparison of Anticoagulation Agents

	Unfractionated Heparin (UFH)	**Low Molecular Weight Heparin (LMWH)**	**Fondaparinux**	**Aspirin**
Derived from	Porcine intestine or bovine cow	Porcine intestine	Synthetic	Willow bark
Drug Characteristic and Mechanism of Action	1) Binds to AT and accelerates its effects on Factor Xa and Thrombin 2) Binds non-specifically to plasma proteins 3) unpredictable dose response 4) Can be reversed if super therapeutic	1) Binds to AT and accelerates its effects more specifically on Factor Xa than on thrombin 2) Has minimal binding to plasma proteins 3) predictable dose response	1) Increases anti-Xa activity on AT 2) Has great specificity for AT 3) Does NOT bind to other plasma proteins 3) predictable dose response	1) Platelet inhibitor 2) Inhibits cyclooxygenase 1 and 2 (therefore blocks the formation of thromboxane in platelets producing an inhibitory effect on platelet aggregation)
Reversal Antidotes	Protamine Sulfate	Protamine Sulfate (not complete reversal ≈60% of activity reversed	No reversal known	None
Half-life	1 to 2 hours	4.5 to 7 hours	17 to 21 hours	2 hours
Monitoring of Drug Levels	aPTT for IV drips	None (can monitor with Factor Xa levels)	None (can monitor with Factor Xa levels)	None
Clearance	Hepatic and RES No need for renal adjustment	Renal (must adjust for CrCl < 30 mL/min)	Renal (contraindicated for Cr < 30 mL/min	Hepatic
Heparin Induced Thrombocytopenia	Yes	Yes	No (*may use when suspect HIT)	No
Established use in Bariatric Patients/Recommended by the ASMBS	Yes 5000 IU three times daily subcutaneously	Yes 40mg twice daily subcutaneously	*** No studies have studied optimal dosing to date	No

AT- Antithrombin III
RES-Reticuloenodthelial System
HIT-Heparin Induced Throbocytopenia
aPTT-activated partial thromboplastin time
*CHEST guidelines has suggested the use of fondaparinux in the treatment of HIT, but not FDA approved indication to date
** The EFFORT Trial a RCT which is presented in this thesis studied 5mg once daily dosing subcutaneously and showed equivalent results to enoxaparin 40 mg twice daily

Figure 2 Mechanism of Action of Anticoagulants



*Derived from Dwek et al 2012 (43)

The most widely used agents for the prevention of VTE in the bariatric surgical population include UFH and LMWH, more specifically enoxaparin.(21, 22, 44, 45) Currently, there are no direct comparative studies (RCTs) to evaluate these anticoagulants in the prophylaxis of bariatric surgical patients. There is one recent RCT which randomized 258 patients to two different doses (4250 vs. 6400 IU subcutaneous daily) of parnarparin (a drug not used within the United States). They concluded that 4250 IU daily was preferable for use in the prevention of VTE in bariatric patients, as the higher dose caused excessive bleeding.(46) Several cohort studies have compared heparin to

enoxaparin.(47, 48) Kothari et al compared enoxaparin 40 mg twice daily to UFH 5000 units every 8 hours. One PE event occurred in the UFH group and none in the LMWH group. However, there was significantly more bleeding within the LMWH group, and the authors concluded that heparin was the safer choice. Birkmeyer et al used a state-wide registry and found similar results (48) but concluded that enoxaparin was safe and effective for use of VTE prevention. The ASMBS has recommended either UFH or LMWH as suitable choices for VTE prevention. (11)

A large systematic review, which included 30 published papers that reported various combinations of UFH, LMWH and mechanical prophylaxis, concluded that the most effective regimen in the bariatric surgical population was either UFH 5000 IU every 8 hours or enoxaparin 30 to 40 mg every 12 hours, and that the dosing should start pre-operatively in combination with sequential compression devices. (49)

Controversy exists regarding the use of anti-factor Xa levels in obese patients, as varying doses and frequencies of administration of enoxaparin, including 0.5 mg/kg once-daily (3), 60 mg twice daily vs. 40 mg twice daily (4), and 40 mg twice daily, have yielded inconsistent results.(50) These discrepancies may be due to the indirect nature of enoxaparin on thrombin activity. The inter-subject variability of factor Xa and platelet levels in obese patients may affect the mechanism of action of enoxaparin, as more or less drug may be needed to achieve prolongation of the lag phase of thrombin production. With this in mind the general consensus at this time is that weight-adjusted dosing of UFH or LMWH provides no clear advantage with respect to VTE prevention and may increase the incidence of bleeding. (51, 52)

Limited data have been published on extended prophylaxis in the bariatric population. In 2008, Raftopoulos et al. reported a 4.5 % VTE rate in patients receiving perioperative VTE prophylaxis only, vs. with no VTE observed in patients who received extended prophylaxis. (53) In 2010, a study carried out in England reported a 0% VTE rate in patients who received extended prophylaxis with dalteparin (LMWH).(54) The question as to what the long term risk of VTE is in the bariatric population had not been determined and this is what motivated the aims for Chapter 2.

1.5.3 Inferior Vena Cava Filters

The first IVC filters to be used were permanent and included the Mobin Udin filter. (55) In the 1980s, Dr. Lazar Greenfield and engineers developed the Greenfield IVC filter. (56) Today, technically better filters are available that are retrievable, and are deployed by interventional radiologists and vascular surgeons to prevent life threatening PEs in high risk patients. The American College of Chest Physicians recommends the use of retrievable filters for patients in whom anticoagulation is contraindicated. There remains great controversy in the bariatric surgical literature and with the ASMBS as to the indications for IVC filter use in the bariatric surgical patient. This was a motivations for our research described in Chapter 3.

1.6 Duration of Prophylaxis

The optimal duration of anticoagulation has been addressed in a clinical trial: the ENOXACAN II study. (57) This was not a study in bariatric patients but was conducted in patients with cancer undergoing abdominal or pelvic surgery. Using venography, the study found that 6 to 10 days of enoxaparin therapy resulted in a VTE rate of 12 percent, while an additional 21 days of therapy reduced the rate to 4.8 percent. While this study

was both randomized and blinded, it is of questionable applicability as the patients studied had cancer and were not morbidly obese.

1.7 Summary

Currently there is no high level of evidence to guide our management of perioperative venous thromboembolism prophylaxis in the morbidly obese patient population. There is a general consensus among experts in the field that some form of anticoagulation therapy should be given for the duration of the hospital stay. However, the specific agents and dosing vary depending on the surgeon, the institution, and his or her experience. Special considerations should be given to patients with additional risk factors. In 2013, the ASMBS issued a consensus statement with recommendations for VTE prophylaxis. This included: 1) all bariatric patients are at moderate risk for VTE and prophylaxis should be used, 2) factors that place patients into a high risk category include high BMI, advanced age, immobility, prior VTE, known hypercoagulable conditions, obesity hypoventilation syndrome, pulmonary hypertension, venous stasis disease, hormonal therapy, expected long operative time or open approach and male gender, 3) individual practices should adhere to a standard VTE protocol, 4) mechanical prophylaxis is recommended for all bariatric patients, 5) early ambulation is recommended, 6) the combination of mechanical and chemoprophylaxis should be considered based on clinical judgment and risk of bleeding, 7) there is conflicting data regarding the type of chemoprophylaxis, though the highest level of evidence available suggests that low molecular weight heparin (LMWH) offers better VTE prophylaxis than unfractionated heparin (UFH) without increased bleeding risk, 8) most postdischarge VTE events occur within the first 30 days after surgery, so extended VTE prophylaxis should be considered despite insufficient data to

recommend a specific dose or duration, and 9) the use of IVC filters as the only method of prophylaxis before bariatric surgery is not recommended, though filter placement may be considered in combination with chemical and mechanical prophylaxis for selected high risk patients in whom the risks of VTE are determined to be greater than the risks of filter-related complications. (11)

1.8 Specific Aims and Outline of Thesis Content

Chapter 2

1. To estimate the risk of late VTE, defined as greater than 30 days post-operatively in bariatric surgical patients.

2. To identify specific characteristics that predicts an increased risk of VTE in bariatric surgical patients.

Hypothesis: The risk of VTE in bariatric surgical patients will remain significantly elevated beyond the 30 day post-operative period. Certain demographic characteristics and pre-existing medical conditions will predict an increased risk of VTE in the bariatric surgical patient.

Brief Methodology: We will perform a retrospective analysis based on a large administrative data base to determine the long term risk of VTE and predictors for VTE in patients undergoing bariatric surgery.

Chapter 3

1. To determine the incidence of post-operative complications related to the use of IVC filter placement in the bariatric surgical patient.

Hypothesis: Patients who undergo IVC filter placement prior to having bariatric surgery will have an increased risk of post-operative complications including post-operative bleeding and extended length of stay.

Brief Methodology: To perform a retrospective analysis based on a large administrative data base to determine the incidence of post-operative complications related to the use of IVC filter placement in the bariatric surgical patient.

Chapter 4

1. To determine whether MRV is an effective diagnostic tool in the detection of suspected (symptomatic or asymptomatic) lower limb and pelvic DVT.

Hypothesis: MRV is an underutilized non-invasive diagnostic tool for the detection of DVT. It should be considered for use in special populations such as the obese patient.

Brief Methodology: We performed a systematic review and meta-analysis of all previously published observational studies that compared MRV to modalities used in the detection of VTE utilizing the Cochrane guidelines.

Chapter 5

1. To compare the effectiveness and safety of enoxaparin versus fondaparinux in the prevention of perioperative VTE in the bariatric surgical patient.

2. To conduct a pilot study using magnetic resonance venography to estimate the incidence of asymptomatic DVT in bariatric surgical patients receiving enoxaparin versus fondaparinux during their perioperative hospitalization.

Hypothesis: Once daily dosing of fondaparinux will be as effective and safe to use as twice daily enoxaparin in the peri-operative prevention of VTE in the bariatric surgical patient. The incidence of asymptomatic DVT, especially within the pelvis of bariatric surgical patients (obese patients) will be higher than previous recorded studies have revealed.

Brief Methodology: We performed a randomized double blinded controlled trial comparing 40 mg of subcutaneous enoxaparin twice daily with 5mg of subcutaneous fondaparinux sodium once daily during bariatric surgical patient's initial hospitalization. Two weeks following surgery the bariatric surgical patient underwent MRV to detect the presence of absence of asymptomatic DVT.

Chapter 2 Long Term Risk of Venous Thromboembolism in the Bariatric Surgical Patient

2.1 Abstract

Background: Venous thromboembolism (VTE) is a leading cause of morbidity and mortality following bariatric surgery. The exact duration and magnitude of post-surgery risk for VTE, however, is unclear. We analyzed a large administrative database to determine the long term risk and predictors for VTE in patients undergoing bariatric surgery.

Methods: A private insurance claims database was used to identify 17,434 patients who underwent bariatric surgery. Longitudinal data were available for each patient for up to 12 months post-surgery. We used logistic regression to identify independent predictors for VTE events.

Results: The incidence of VTE during the index surgical hospitalization was .88%. This rate rose to 2.17% at one month and 2.99% by 6 months post-surgery. Over 74% of VTE events occurred after discharge. Risk factors identified for VTE developing by 6 months post-surgery included male sex (odds ratio (OR) = 1.68; confidence limits (CL) = 1.37-2.07), age $\geq$ 55 years (OR = 2.18; CL =1.56-3.03), smoking (OR = 1.86; CL = 1.06-3.27), and previous VTE (OR = 7.48; CL = 5.78-9.67). The laparoscopic adjustable gastric band (LAGB) was less likely to result in VTE compared to open or laparoscopic gastric bypass (OR = .31; CL = .13-.75).

Conclusions: The period of increased risk for VTE following bariatric surgery extends well beyond the initial hospital discharge and 30 days post-surgery. The high frequency

of VTE up to 6 months following bariatric surgery suggests that more aggressive extended prophylaxis should be considered in patients at higher risk for VTE.

2.2 Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolus (PE) is a significant cause of morbidity and mortality in hospitalized and postoperative patients (20). An estimated 900,000 fatal and nonfatal VTE events occur in the United States per year, representing a leading cause of preventable death in hospitalized patients (58). An increasing awareness of the public health implications of VTE has led to numerous initiatives aimed at primary prevention. In 2008, the Acting Surgeon General of the United States issued a "Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism"(59). The Surgical Care Improvement Project (SCIP), a nationwide initiative to improve perioperative outcomes, includes appropriate VTE prophylaxis and routine VTE risk stratification as key quality of care indicators (60). Traditional risk factors for VTE in patients undergoing surgery include previous VTE, advancing age (> 40 years old), general anesthesia/major surgery, relative immobility, malignancy, tobacco use, oral contraceptive agents, and coagulation disorders (20).

Obesity has also been noted to be an independent risk factor for venous thrombosis. Accordingly, patients undergoing bariatric surgery for the treatment of morbid obesity often have three or more risk factors (20, 21) and are considered to be at high risk for a VTE event. The clinical significance of VTE is underscored by several reports suggesting that pulmonary embolus is the leading cause of death after bariatric surgery (61-63). The incidence of VTE after bariatric surgery has been reported to range from 0.2 to 3.8

percent (1-6, 8-10, 39, 44, 53, 64). This wide variation in rates may be due to the fact that most studies represent single institution series with relatively small study populations and with variable follow up and study design. Large population based studies using administrative data sets have reported overall VTE rates of less than one percent (1, 2, 64). Most of these reports, however, lack longitudinal follow up and focus only on the surgical admission or a short time period after discharge. Several investigators (3, 21, 44, 53) have noted that the majority of VTE events may occur after the initial hospital discharge and therefore may not be accounted for in studies that lack or have variable extended follow up. Understanding the timing of VTE events after surgery and duration of risk is critical to help guide measures to prevent VTE occurrence.

We hypothesized that the risk for VTE after bariatric surgery extends well beyond the initial hospitalization and traditional thirty day postoperative window. Using a large administrative database, our aim was to define the prevalence and timing of VTE events after bariatric surgery and identify risk factors for VTE events.

2.3 Materials and Methods

2.3.1 Study Design

We performed a retrospective cohort study in which we measured the cumulative incidence of VTE occurring over a one year period after bariatric surgery utilizing a private insurance claims database.

2.3.2 Dataset

The data were provided by Blue Cross/ Blue Shield (BCBS) of Tennessee, Highmark, Inc.(of Pennsylvania), BCBS of Michigan, BCBS of North Carolina, Independence Blue Cross (of Pennsylvania), Wellmark BCBS of Iowa, Wellmark BCBS of South Dakota,

and BCBS of Hawaii. All individuals with one of these seven plans as their primary insurer were eligible for inclusion in the dataset. The claims data used in this study were de-identified in accordance with the Health Information Portability and Accountability Act definition of a limited dataset. The dataset includes approximately 3.4 million insured lives over a five year period (2002-2006) and includes information on enrollee age, sex, enrollment dates, and inpatient and outpatient claims for reimbursement for billable health care services. These data include patient diagnoses as identified by ICD-9 codes and Diagnosis Related Groups, and medical procedures classified by CPT and ICD-9 procedure codes.

2.3.3 Study Cohort

All patients in the dataset who had gastric bypass or LAGB surgery from 2002-2005 were eligible for inclusion in the study, as identified by diagnostic and procedural codes. Additional criteria for inclusion were patient age 18-65 years and continuous insurance coverage for at least 6 months prior to and 6 months after bariatric surgery. Prior to 2005, no specific CPT code for laparoscopic gastric bypass was available. Laparoscopic cases were identified by the appropriate bariatric surgery code as well as an associated laparoscopic procedure code and diagnostic code for morbid obesity. Patients were excluded if they had a diagnosis of gastrointestinal or pancreatic malignancy in the setting of a bariatric procedure code since these operations were more likely performed for the treatment of cancer rather than obesity.

2.3.4 Statistical Analysis

Our main outcome measure was the occurrence of VTE at various time points after bariatric surgery (during the index surgical admission as well as 1, 6, and 12 months after

surgery). The ICD-9 codes utilized for PE included 415.1-.19 and codes for DVT included 453, 453.0-.9. At 6 months after surgery, various demographic and surgical variables were evaluated as potential risk factors for VTE including age, sex, type of bariatric procedure, previous history of VTE, preoperative history of smoking or oral contraceptive use, and length of stay (LOS) during the index surgical admission. Data were compared using chi-square analysis and multivariate logistic regression analysis. All statistical analyses were performed using SAS Software version 9.1 (SAS Inc., Cary, North Carolina).

2.4 Results

A total of 17,434 patients were identified who had gastric bypass or LAGB surgery and met all inclusion criteria for the study. These patients make up the study cohort. A subset of this group (16,929 patients) also had continuous insurance coverage up to 12 months after surgery and was used for data analysis at this time point. The overall group was predominately female (82%) with a mean age of 43 years and an average LOS for the index surgical admission of 2.91 days. Open gastric bypass was the most common procedure (n=11,123), followed by laparoscopic bypass (n=5695) and LAGB (n=616). Cumulative rates for VTE as well as the subgroup of patients developing a PE are presented in Table 2. During the index surgical admission, 153 patients (0.88 %) developed a VTE event. When analyzed by type of VTE, 91 patients developed DVT only, 55 developed PE only, and 7 developed both DVT and PE by the time of hospital discharge. By 6 months after surgery, a total of 522 patients (2.99%) were coded as having had a VTE event (DVT only = 324; PE only = 127; DVT and PE = 71). Of the 579 patients developing a VTE event in the first year after surgery, only 26% occurred

during the index surgical admission. The majority of VTEs occurred after hospital discharge with 64% developing by one month and 88% by 6 months after surgery.

Risk factors for a VTE occurring by 6 months post-surgery are presented in Table 3. Patients experiencing a VTE were significantly more likely to be male, age 55 years or older, have had a previous VTE, smoke, or have a long length of stay after surgery compared to patients without a VTE event. Oral contraceptive agent use among female patients was similar in the VTE and no-VTE groups; data on post-menopausal estrogen replacement were not available.

We also analyzed the data by looking at the incidence of VTE for each risk factor. By 6 months after surgery, men were significantly more likely to develop a VTE compared to women (4.7% vs. 2.6%; $p<.001$). Advancing age was also a risk factor for VTE (Fig. 3) with a VTE rate in patients 55 years or older of 4.7% (<55 years=2.7%; $p<.001$). All age groups had significantly higher VTE rates compared to the <24-year old group ($p<.05$). Long length of stay during the index admission (5 days or greater = 5.6% vs. <5 days=2.5%) and a history of previous VTE (previous VTE=21% vs. no previous VTE=2.4%) were also significantly associated with VTE occurrence after surgery ($p<.001$). Although relatively few patients were coded as smoking tobacco, this was associated with higher rates of VTE at 6 months (5.1% vs. 2.9%; $p<.05$).

Type of bariatric procedure also appeared to impact the rate of VTE (Table 4). LAGB surgery was associated with a lower rate of VTE (0.8%) compared to laparoscopic (2.7%) and open (3.3%) gastric bypass ($p< .01$). No significant difference in VTE rates was found when open and laparoscopic gastric bypass procedures were compared.

On multivariate logistic regression analysis, the likelihood of a VTE by 6 months after surgery was associated with male sex (odds ratio (OR) = 1.69; 95% confidence interval (CI) = 1.37-2.07), long LOS (OR = 1.82; CI = 1.51-2.18), previous VTE (OR = 7.48; CI =5.78-9.67), smoking (OR = 1.86; CI = 1.06-3.27), and advancing age (OR = 2.18; CI = 1.56-3.03). Patients undergoing LAGB were less likely to develop a VTE (OR = .31; CI = .13-.75).

2.5 Discussion

In this study, utilizing a large insurance claims database we demonstrated that the risk for VTE after bariatric surgery extends well beyond the initial hospitalization. Only 26% of VTE events occurring in the first 12 months after surgery were evident by the time of hospital discharge. Over one third of VTEs occurred after 30 days post-bariatric surgery, a traditional time point for reporting perioperative complications. We identified male sex, advancing age, previous VTE, smoking, and long length of stay as risk factors increasing the likelihood of VTE. LAGB appeared to lower the likelihood of VTE when compared to gastric bypass.

Previous studies examining the incidence of VTE post-bariatric surgery have reported rates ranging from .2 to 3.8 percent (1-6, 8-10, 39, 44, 53, 64). Our observed incidence of VTE by 6 months (2.99%) and 12 months (3.42%) after surgery is similar to rates reported by others (3, 8, 10) of 3.4 - 3.8%. Many studies, however, have reported VTE rates of less than 1%. The reason for this wide variation may be related to relatively small patient numbers in some single institution series as well as incomplete follow up. Studies utilizing large administrative datasets such as the National Inpatient Sample (NIS) (1), University Health Consortium (UHC) (2), and National Surgical Quality

Improvement Program (NSQIP) (64) have reported VTE rates of .35%, .43%, and .59% respectively. These studies, however, lack longitudinal follow up beyond the index surgical admission (NIS and UHC) or 30 days post-surgery (NSQIP) and therefore fail to account for VTE events after these short time periods. The strengths of our study include a large study cohort of over 17,000 patients and complete longitudinal follow up of each patient for at least 6 months post-surgery. Interestingly, a recent study by Encinosa et al (4) using a similar insurance claims based dataset involving 7060 patients reported a VTE rate at 6 months post-bariatric surgery of 2.5%, similar to our observed rate.

Our finding that the majority of VTE events occur after hospital discharge has important clinical implications. Pharmacologic thromboprophylaxis with low-molecular-weight or unfractionated heparin has been recommended during the index hospitalization after bariatric surgery in order to prevent VTE (20, 65). In a survey of members of the American Society for Metabolic and Bariatric Surgery, Barba et al (66) found that 95% of surgeons used some form of pharmacologic prophylaxis perioperatively during the initial hospital admission. There is little consensus, however, on the role of extended thromboprophylaxis after discharge. Our observation of the continued risk for VTE after discharge has been reported by others. In a study by Hamad and Choban (21), seven of 668 patients undergoing bariatric surgery developed a VTE, all occurring post discharge. Other studies have also noted that the majority of thrombotic events after bariatric surgery occurred post discharge (once pharmacologic prophylaxis had been stopped).(3, 6, 44, 53) These findings suggest that extended pharmacologic thromboprophylaxis for up to 4 weeks after discharge may be warranted in certain high risk patients undergoing bariatric surgery. Randomized controlled trials in other high risk groups for VTE such as

patients undergoing cancer surgery (57) suggest that 30 days of extended thromboprohylaxis can significantly reduce VTE events.

We identified several risk factors impacting the likelihood of VTE after bariatric surgery. Males were at significantly higher risk for VTE, a finding which has been noted by others.(6) This may be related, in part, to the relative increased central and intra-abdominal deposition of fat in males which may lead to venous stasis and impaired venous return. Advancing age was also noted to be a risk factor for VTE. This was evident in all age groups compared to patients less than 24 years old. Age greater than 40 years is a traditional risk factor for VTE and our data suggest this relative risk extends to patients age 30 to 40 years as well. Because estrogen use has been associated with VTE risk (20), we examined the risk of VTE in subjects reporting and not reporting oral contraceptive use. While no difference in risk was found, we were unable to determine whether contraceptive agents had been stopped prior to surgery. Furthermore, we were unable to obtain data on postmenopausal estrogen use.

The type of bariatric surgery performed also appeared to influence VTE risk, with LAGB lowering the odds of VTE compared to gastric bypass. This was not surprising since the LAGB is in general a less invasive procedure with shorter operating times, shorter length of stay, and quicker return to full activity. We found no difference in VTE rates comparing laparoscopic and open gastric bypass. Some investigators have noted less VTE risk with laparoscopic bypass (2, 67), while others have found no difference between the open and laparoscopic techniques.(5, 21, 64) The laparoscopic approach involves steep reverse trendelenburg positioning and pneumoperitoneum, both of which may impede venous return and increase the potential for venous thrombosis. This may be

offset, however, by the association of open surgery with increased tissue trauma and inflammatory cytokine production as well as slower return to full activity, potentially increasing the risk for VTE.(2)

In the present study, we identified a history of a previous VTE event as being the strongest predictor of development of a VTE post-surgery. Patients with a history of a prior VTE were over eight times more likely to develop another VTE (21%) compared to those with no prior VTE events (2.5%). Consistent with our findings, Prystowsky et al (3) and Gonzalez et al (8) reported VTE rates of 33% and 19%, respectively following bariatric surgery in patients with a previous history of VTE. This high rate of recurrence has led to the recommendation that patients with prior VTE or other high risk groups should be considered for prophylactic vena cava filter insertion before surgery. (68) It is unclear, however, whether vena cava filters provide adequate protection against PE and DVT. It is also unclear how long such filters should be kept in place to maximize anti-embolic benefit. Lower extremity venous duplex screening prior to discharge has been proposed to better select those patients most likely to benefit from extended thromboprophylaxis or vena cava filter placement. However, most clinical VTE events occurring after discharge appear to arise from clots that occurred de novo following discharge.(3)

Our study is one of the largest to date reporting on VTE rates after bariatric surgery with longitudinal post-surgery follow up of 12 months. We recognize, however, several important limitations. This was a retrospective review utilizing an insurance claims database with the potential for errors in diagnostic and procedural coding. We were unable to account for potential variations in the use, duration, and type of

thromboprophylaxis after surgery, which could impact VTE occurrence. The number of laparoscopic gastric bypass procedures is likely underestimated in this study due to the lack of a specific procedural code prior to 2005. In addition, body mass index (BMI) data were not reliably available in the database and therefore we are unable to comment if increasing BMI above 40 is an independent risk factor for VTE. Previous studies have reported that increasing BMI or "super obesity" increases the likelihood of VTE (5, 6), while others have not found this relationship. (8) Finally, our data did not show whether the VTE events in our population resulted in clinically significant outcomes, such as death or prolonged disability. Nonetheless, we feel that the morbidity accompanying VTE is sufficiently well established that such events can be assumed to have significant consequences for many patients.

2.6 Significance

Patients undergoing bariatric surgery are at significant risk for VTE. Previous studies may have underestimated this risk by focusing primarily on the immediate perioperative period. We have found that the risk of VTE extends well beyond the initial hospitalization with the majority of VTE events occurring after discharge, with over one-third occurring more than four weeks post-surgery. Risk factors identified on multivariate analysis for VTE after bariatric surgery include male sex, advancing age, smoking, long length of stay and history of prior VTE. LAGB was associated with lower incidence of VTE compared to gastric bypass. Extended post discharge thromboprophylaxis or vena cava filter placement may be considered in high risk patients to help minimize the risk of VTE.

Table 2 Cumulative Incidence of VTE and PE at 1,6 and 12 months after Bariatric Surgery

		Months Post-Surgery		
	During Index Surgery Admission n (%)	1 Month n (%)	6 Months n (%)	12 Months* n (%)
VTE (DVT and/or PE)	153 (0.88%)	379 (2.17%)	522 (2.99%)	579 (3.42%)
PE	62 (0.36%)	144 (0.83%)	198 (1.14%)	209 (1.23%)

VTE = Venous thromboembolism

DVT = Deep vein thrombosis

PE = Pulmonary embolism

* - The total n at admission, 1 month, and 6 months was 17434. The total n at 12 months was 16929.

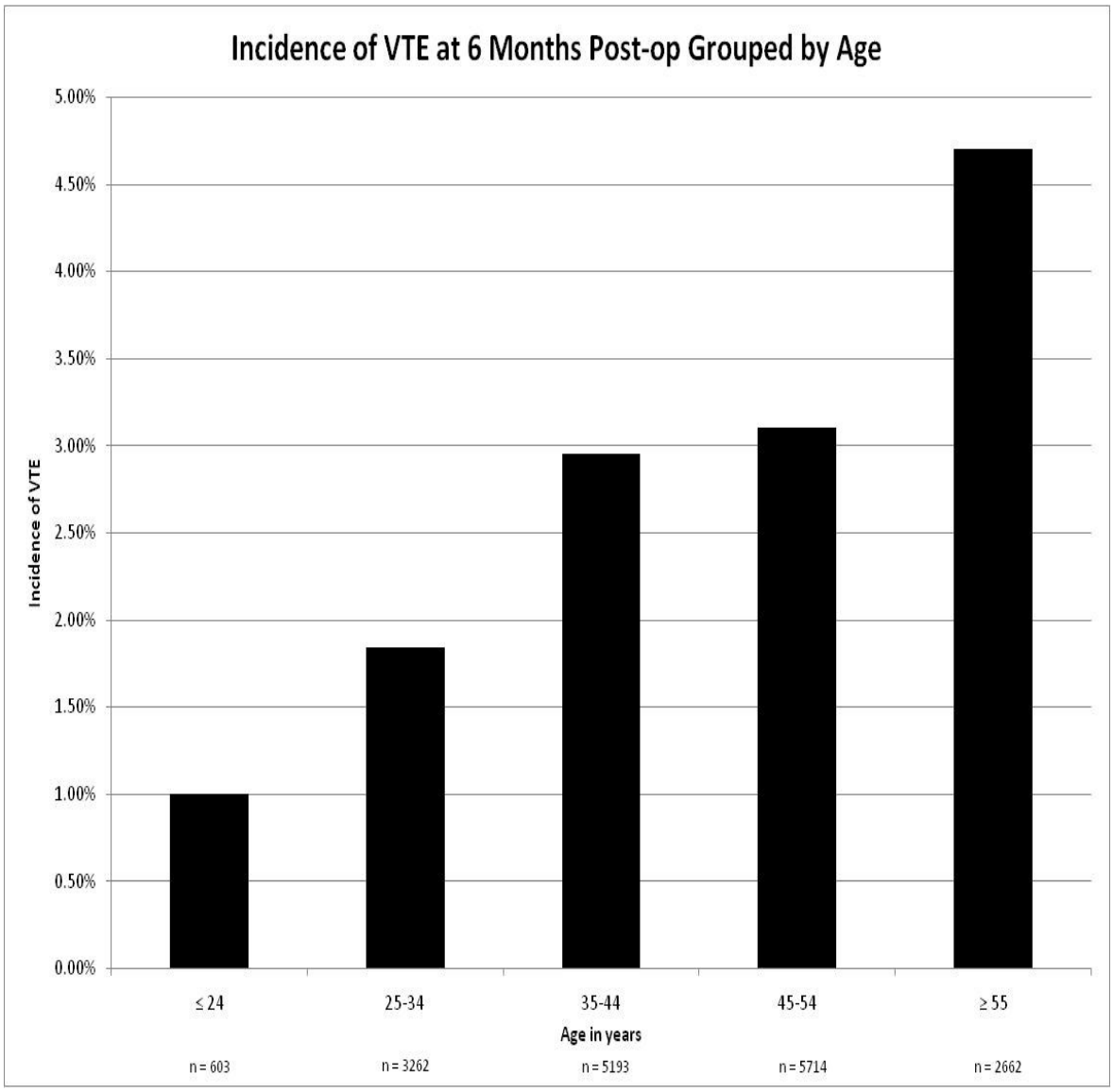
Table 3 Characteristics of Patients with and without VTE at 6 Months after Surgery

Variables	VTE n = 522 n (%)	No VTE n = 16912 n (%)	Total Group n = 17434 n (%)	p value
Male	146 (28%)	2977 (18%)	3123 (18%)	p < .001
Age ≥ 55 years	126 (24%)	2536 (15%)	2662 (15%)	p < .001
LOS ≥ 5 days	147 (28%)	2458 (14%)	2605 (15%)	p < .001
Previous VTE	106 (20%)	389 (2.3%)	495 (2.8%)	p < .001
Oral contraceptives	34 (9%)	1231 (8.6%)	1265 (8.8%)	NS
Smoking	14 (2.7%)	260 (1.5%)	274 (1.6%)	p < .05

Table 4 Cumulative Incidence of VTE by Procedure Type

Procedure	n	Incidence of VTE at 6 Months	
Laparoscopic Adjustable Gastric Band	616	0.8%	p < .01 vs. other procedures
Laparoscopic Gastric Bypass	5695	2.7%	
Open Gastric Bypass	11123	3.3%	

Figure 3 Incidence of VTE at 6 Months Post-op Grouped by Age



Chapter 3 Prophylactic Inferior Vena Cava Filters in Patients Undergoing Bariatric Surgery: Does the Benefit Outweigh The Risk?

3.1 Abstract

Background: Pulmonary embolism remains a major risk after bariatric surgery. Current practice is to identify patients who are at high risk for VTE and place an inferior vena cava (IVC) filter preoperatively to prevent postoperative pulmonary embolism. The purpose of this study is to analyze postoperative complications in bariatric surgical patients receiving a preoperative IVC filter.

Methods: Retrospective data from 2002 to 2008 was queried from the national BC/BS bariatric surgery database. 972 patients were identified as having an IVC filter placed prior to bariatric surgery. These patients were case-matched by age, gender, and type of surgery to non-IVC filter patients. A multivariate logistic regression analysis was performed using the SAS statistical package.

Results: Seven hundred and eighty-nine of the 972 IVC filter patients were case matched to 1,578 non-IVC filter patients. Seventy-one percent of all patients underwent open gastric bypass, 22% underwent laparoscopic gastric bypass, and 7% underwent laparoscopic adjustable band. Forty-two percent of patients who received a pre-operative IVC filter had a history of VTE within one year prior to bariatric surgery. The risk of postoperative VTE in the IVC filter group was 16.7% and in the non-IVC filter group was 10.7%. The length of stay for IVC filter patients was greater (3.12 days vs. 2.77 days; $p=0.0198$). Post-operative bleeding (29% vs. 13.6%; $p=0.0001$) was significantly higher in the filter group. All postoperative complications combined were higher in the filter group (84% vs. 76.6%; $p < 0.0002$), but mortality within one year of surgery was statistically equivalent in the filter and non-filter groups (0.38% vs. 0.25%, $p=1.0$).

Conclusions: This study is one of the largest retrospective analyses to date of bariatric patients who underwent preoperative IVC filter placement. While complication rates were higher in those who underwent a preoperative IVC filter, mortality rates for both groups were nearly equivalent. Interestingly, the presence of an IVC filter is strongly associated with development of VTE within one year postoperatively.

3.2 Introduction

Roux-en-Y gastric bypass, vertical sleeve gastrectomy, and laparoscopic adjustable gastric banding have become established as safe and effective surgical procedures for morbid obesity. The overall mortality rate is low at 1% or less in many series, with pulmonary embolism and anastomotic leak as the first and second leading causes of death.(69, 70) Despite widespread use of perioperative prophylaxis for venous thromboembolism with sequential compression devices, anti-embolic stockings, anticoagulation, and early ambulation, the incidence of symptomatic pulmonary embolism remains between 0% and 6.4%. (71, 72) A systematic review that included 19 studies of VTE rates following bariatric surgery reported the incidence of pulmonary emboli to be 0.5%. (51) Birkmeyer et al. and Finks et al. utilized the Michigan Bariatric Surgery Collaborative Database and reported VTE rates of less than 0.5% in average risk bariatric surgical patients. (48) While the incidence of symptomatic VTE appears to be low, a post-mortem study of gastric bypass patients showed that while only 20% had been clinically diagnosed with pulmonary emboli prior to death, 80% had evidence of pulmonary emboli that were thought to have contributed to their morbidity and mortality.(73) This finding suggests that venous thromboembolism remains an underappreciated complication. Patients undergoing bariatric surgery are classified as

moderate to high risk for having a thrombotic complication according to American Chest Physicians guidelines.(26) Despite its importance, to date there exists no consensus regarding agent, dose, and duration of chemoprophylaxis for the prevention of VTE.

To reduce rates of death from pulmonary embolism after bariatric surgery, other prophylactic modalities have been tried, including mechanical compression devices combined with early ambulation and chemoprophylaxis. A less commonly used modality is preoperative placement of an inferior vena cava filter those patients deemed at highest risk. Among trauma patients, a significant reduction in the incidence of pulmonary emboli from 17 to 2.5 % has been demonstrated with the use of prophylactic IVC filter placement in patients with three or more risk factors.(74) A recent systematic review in 2013 confirmed these findings, supporting the association of IVC filter placement with a lower incidence of PE and fatal PE in trauma patients. (75) However, the evidence for benefit of inferior vena cava filters in the bariatric surgical population is less clear. Keeling et al reviewed their experience with IVC filter placement in 14 gastric bypass patients and reported no filter-related complications or pulmonary emboli. Based on this very small series, the authors recommended routine preoperative filter placement in all bariatric patients with prior pulmonary embolus, prior deep venous thrombosis, evidence of venous stasis, or a known hypercoagulable state. (76) More recent studies including a systematic review reported less favorable results with regards to using IVC filters in the bariatric surgical population.(52, 77) The aim of this study was to determine the incidence of post-operative complications related to the use of IVC filter placement in the bariatric surgical patient.

3.3 Methods

3.3.1 Study Design

We performed a retrospective cohort study using administrative claims data.

3.3.2 Data

We accessed claims data from seven Blue Cross Blue Shield health plans providing coverage in Western Pennsylvania, Philadelphia, South Dakota, Iowa, Hawaii, Michigan, North Carolina, and Tennessee. All individuals with one of these seven plans as their primary insurer were eligible for inclusion in the dataset. The claims data used in this study were de-identified in accordance with the Health Information Portability and Accountability Act (HIPAA) definition of a limited dataset, ensuring confidentiality of enrollee health information. The study was also approved by the Johns Hopkins Institutional Review Board. Patient diagnoses were identified by ICD-9 codes and Diagnosis Related Groups, and medical procedures by Current Procedural Terminology (CPT) and the International Classification of Diseases (ICD-9) procedure codes. We queried the data base for all bariatric surgical patients from 2002 to 2008 and identified seven hundred and eighty-nine patients as having an IVC filter placed prior to bariatric surgery. These patients were case-matched 1:1 by age group (18-24, 25-34, 35-44, 45-54 and 55-65), gender, and type of surgery to non-IVC filter bariatric surgical patients. To control for seasonality of outcomes, IVC and non-IVC filter patients were also matched by date of surgery.

3.3.3 Analytic cohort

An analytic cohort was created by restricting the above data to persons between the ages of 18 to 64 years inclusive, based on the National Institutes of Health (NIH) adult criteria

for bariatric surgery, who had at least 6 months of continuous insurance coverage prior to the date of bariatric surgery. Bariatric surgical patients were identified by the ICD-9 procedure and CPT codes listed in Appendix A.2 using methods and codes from previously published literature. (78) For four of the ICD-9 codes, we required that a code for morbid obesity (ICD-9-287.1) be present concurrently with the procedure. We excluded patients with a concurrent primary diagnosis of ulcer disease, as these patients were probably undergoing gastric bypass for ulcer disease and not obesity. Those with a diagnosis of cancer of the esophagus (ICD-9 150-150.9), stomach (ICD-9 151-151.9), small intestine (ICD-9 152-152.9) or pancreas (ICD-9 157-157.9), or malignant neoplasm without specification of site ICD-9 (199-199.2) were also excluded. We also excluded individuals with codes for gastric bypass revision procedures prior to the index bariatric surgery code (suggesting that this was not the first bariatric procedure and would put the patient at greater risk due to presumed increased operative time). (Appendix A.2) As well, we excluded patients undergoing biliopancreatic diversion with or without duodenal switch and sleeve gastrectomy procedures because of the relative infrequency of these procedures during this time period from 2002 to 2008 (<2% and <3% respectively). Laparoscopic cases were identified by the appropriate bariatric surgery code as well as an associated laparoscopic procedure code and diagnostic code for morbid obesity. Prior to 2005, no specific CPT code for laparoscopic gastric bypass was available. Patients were excluded if they had a diagnosis of gastrointestinal or pancreatic malignancy in the setting of a bariatric procedure code since these operations were more likely performed for the treatment of cancer rather than obesity.

3.3.4 Data Collection and Outcomes

Patient characteristics collected included 1) enrollment files with administrative data (date of birth, gender, state and enrollment periods); 2) benefits information that included pharmacy and medical coverage; and 3) claims records containing International Classification of Disease (ICD-9) diagnoses, and ICD-9 procedure codes. The claims were used to identify bariatric surgery cases, types of surgery, obesity related diagnoses and complications.

Our main outcome measure was post-operative VTE, defined as pulmonary embolism or deep venous thrombosis, at two time points after bariatric surgery (during the index surgical admission and up to 12 months after surgery). The ICD-9 codes utilized for PE were 415.1-415.19, and for DVT were 453 and 453.0-.9. Secondary outcome measures included other post-operative complications: bleeding (requiring > 2 units of blood), surgical site infection (wound and port site infections or wound dehiscence), cardiovascular events (myocardial infarction, arrhythmia, or stroke), respiratory events (pneumonia requiring antibiotic treatment or respiratory failure requiring 2 or more days of intubation), reoperation, and death. Various demographic and surgical variables were evaluated as potential risk factors for VTE including age, sex, type of bariatric procedure, previous history of VTE, preoperative history of diabetes, hypertension, use of anticoagulation and length of stay (LOS) during the index surgical admission.

3.3.5 Statistical Analysis

All complications were treated as binary events. Data were compared using chi-square analysis. Additionally, we used multivariate logistic regression to estimate the relative odds of the occurrence of each complication in the IVC filter group relative to the non-

IVC filter group. Models were adjusted for baseline characteristics including age, gender, type of surgery, length of stay, use of anticoagulation pre-operatively, previous VTE, and comorbidities including diabetes, hypertension and sleep apnea. All statistical analyses were performed using SAS Software version 9.1 (SAS Inc., Cary, North Carolina).

3.4 Results

From 2002 to 2008, we initially found 972 IVC filter patients. Of these, 789 had complete data and were case matched to non-IVC filter patients (n=789). Matching within the cohort resulted in fairly well balanced groups on all baseline characteristics (Table 5). The mean age of the cohort was 46.5 (IVC=46.7 and non-IVC=46.3. The majority of the cohort was female (74.4%). Seventy-one percent of patients underwent open gastric bypass, 23% underwent laparoscopic gastric bypass, and 7% underwent laparoscopic adjustable band. The length of stay for IVC filter patients was greater (3.12 days vs. 2.77 days; p=0.0198). Extended length of stay, defined as greater than 5 days for gastric bypass patients and greater than one day for band patients, was significantly more common among IVC filter patients (21.2% vs 16.5%; p=0.017). There were more patients with a diagnosis of diabetes (39% vs. 31%; p=.003), hypertension (68% vs. 62%; p=0.009) and sleep apnea (39% vs. 35%; p=0.118) in the IVC filter patients than in the non-IVC patients. Ten percent of patients who received a pre-operative IVC filter had a history of PE within one year prior to bariatric surgery (p=.002). There was no difference in the number of patients who were on anticoagulation therapy (warfarin) prior to surgery (p=0.81)

With regards to outcomes (Table 6) IVC filter patients had significantly higher rates of post-operative VTE (16.7% vs. 10.7%; p=0.0006) and DVT (13.9% vs. 8.4%; p=0.0004)

than matched controls (non-IVC filter patients). While rates of pulmonary embolism post-operatively were higher among IVC filter patients, this was not statistically significant (4.4% vs. 3.8%; p=0.08). The rates of postoperative VTE among the IVC filter and non-IVC filter groups were 16.7% and 10.7%, respectively. The occurrence of any postoperative complication was higher in the filter group than the non-filter group (84.03% vs. 76.6%; $p < 0.0002$), but mortality within one year of surgery was statistically equivalent in the two groups (0.38% vs. 0.25%, p=1.0). Bleeding post-operatively was significantly higher among IVC filter patients (29% vs. 13.6%; $p < 0.0001$). Wound infection (20.4% vs. 17.5%; p=0.157), re-operation (7.9% vs. 6.6%; p=0.33), and respiratory complications (29.9% vs. 27%; p=0.29) were also higher in the IVC filter group, but this was not statistically significant. After adjusting for patient characteristics including demographics (age, gender, type of surgery, length of stay) and medical comorbidities (diabetes, hypertension, sleep apnea, anticoagulation use, previous VTE history), patients who had an IVC filter placed prior to bariatric surgery had 2 times increased risk of developing a post-operative DVT (OR 2.01, CI 1.4-2.5; p=0.0001) and almost 3 times the increased risk of bleeding (OR 2.97, CI 2.3-2.9; p=0.0001). (Table 7)

3.5 Discussion

Bariatric surgical patients are classified as moderate to high risk for VTE by the American College of Chest Surgeons (AMCS). As such, bariatric surgeons have a low threshold when considering the approach to very high risk patients who are scheduled to undergo bariatric surgery. While there is no consensus as to the definition of a high risk patient, most of the published literature are in general agreement and include patients with a body mass index (BMI) greater than 55 kg/m^2, obesity hypoventilation syndrome,

pulmonary hypertension, venous stasis, severe lymphedema and leg swelling, history of previous VTE, hypercoagulable state (Sickle Cell anemia, Protein C, S and Factor V Leiden Deficiencies), and immobility. (79-83) The American Society for Metabolic and Bariatric Surgery (ASMBS) has recommended in their latest position statement that filter placement may be considered in combination with chemical and mechanical prophylaxis for selected high risk patients only when the risk of VTE is thought to be greater than the risk of filter related complications. (11)

3.5.1 Clinical Motivation for Study Topic

Our current study was prompted by our own Bariatric Center's experience with IVC filters. The following case in particular stands out, suggesting that further studies are needed to help form standard guidelines on VTE prophylaxis in the high risk bariatric surgical patient, more specifically on the indications for IVC filter placement.(84)

A morbidly obese 63 year old white female presented to our center for laparoscopic roux-en-Y gastric bypass. Her past medical history was significant for gastroesophageal reflux disease with Barrett's esophagus, hypertension, hypothyroidism, degenerative joint disease, urinary stress incontinence, hiatal hernia, and history of previous pulmonary embolism. At the time of her pulmonary embolus, nine years prior to the operation, an evaluation for hypercoagulability was performed and no abnormalities were found. The etiology of her pulmonary embolus was thought to be due to hormone replacement therapy and obesity.

She weighed 284 lbs and had a calculated body mass index (BMI) of 45 kg/m^2. Her cardiac and pulmonary examinations were normal, and her abdomen was notable only for obesity. Her lower extremities were warm with palpable pulses and no edema or evidence

of venous stasis. Preoperative evaluation, including laboratory investigations, electrocardiogram, and nocturnal polysomnography were all within normal limits. Her only risk factor for placement of a retrievable inferior vena cava (IVC) filter was history of previous PE. The filter was placed by our vascular surgery team on the day prior to surgery. As recommended by the ASMBS position statement, she also received chemoprophylaxis of enoxaparin 40 mg subcutaneously 2 hours prior to the procedure. Anti-embolism (TED) stockings and sequential compression devices (SCDs) were placed on her lower extremities. A laparoscopic Roux-en-Y gastric bypass and hiatal hernia repair were performed uneventfully. Postoperatively, the patient received enoxaparin 40 mg subcutaneously twice a day. TED stockings and SCDs were continued. She was encouraged to ambulate on the day of surgery. On postoperative day 2, a screening lower extremity duplex ultrasonography was completed revealing no evidence of thrombosis, and the patient was discharged to home on ursodiol 300 mg twice daily, ranitidine 150 mg orally twice daily, and levothyroxine 0.125 mg once daily.

Two weeks postoperatively the patient presented to clinic with a complaint of weakness and left lower extremity pain. Vital signs were within normal limits and physical exam revealed a benign abdomen and no lower extremity swelling nor tenderness. Laboratory studies revealed a normal chemistry panel and a hematocrit of 40.7. The patient was admitted to hospital with a working diagnosis of dehydration and possible deep venous thrombosis. Lower extremity and pelvic duplex ultrasonography was negative for thrombosis. The patient received only intravenous hydration. The following day she was feeling better and tolerating her gastric bypass diet, and she was discharged to home.

Two days following discharge the patient had a witnessed syncopal episode at home. She was found unconscious by paramedics, with a heart rate of 130 and had a systolic blood pressure of 154. On arrival to the emergency department, she was found to be bradycardic and hypotensive, and progressed to cardiac arrest. She was intubated and the Advance Cardiac Life Support protocol was initiated with atropine and epinephrine. Intravenous access could not be established, and the patient expired. Laboratory studies obtained during resuscitation were notable for a hematocrit of 29.2, creatinine of 1.5 mg/dl, and bicarbonate of 8 mEq/L. Postmortem examination revealed an IVC filter completely occluded by thrombus. Small bilateral pulmonary emboli were present but there was no saddle embolism and these emboli were too small to cause hemodynamic instability. A retroperitoneal hematoma was present, with one leg of the IVC filter protruding 1 mm through the wall of the inferior vena cava. The duplex ultrasound obtained on the previous admission was reviewed, and again no evidence of thrombosis was seen.

The above case represents the trials and tribulations that a bariatric surgeon faces when making decisions on the risk/benefit ratio of various VTE prophylactic methods. Despite the ever increasing use of IVC filters in high risk populations there is little scientific evidence to date on their safety and effectiveness. Our study assessed the incidence of post-operative complications that occur when comparing patients who had an IVC filter placed prior to bariatric surgery with those who were matched 1:1 and did not have an IVC filter pre-operatively placed. We found that patients who had an IVC filter had significantly worse outcomes (any complication, post-op DVT, and bleeding) when compared to their matched control. However, mortality was not significantly different

between the two groups. These findings were similar to those of Birkmeyer et al published in 2013. Completing a propensity-matched cohort study, the authors used the clinical registry of the Michigan Bariatric Surgery Collaborative and reported on the complications associated with 1077 bariatric surgical patients who had had a pre-operative IVC filter placed. The authors found that patients with IVC filters had significantly higher rates of VTE and DVT.(85) As in our study, rates of PE and death were higher in the filter patients but this was not statistically significant. The only systematic review published on this topic was carried out in 2010 and concluded that the evidence was insufficient to recommend IVC filters in patients undergoing bariatric surgery.(86)

Several limitations need to be defined as one interprets the findings in this study. First, this study is observational and thus is subject to confounding. While our patients were well-matched with respect to age, sex, and type of surgery, and we did control for patient risk factors such as previous VTE, diabetes, hypertension and sleep apnea, other important variables including smoking history, use of birth control pills or estrogen containing medications, hypercoagulable states, and immobility were not analyzed, as the data were missing or unable to be accessed. Second, our data also lacked height and weight data and therefore we were unable to account for BMI, which is a known increased risk factor in the development of VTE. To Birkmeyer's credit, the author used a propensity score to ensure that the IVC filter group and non-IVC filter group were better matched, and in so doing they controlled for confounding by indication. Despite our inability to account for BMI and lack of a propensity score our findings were consistent with Birkmeyer's study.(85) Thirdly, the study was limited by the use of administrative

data and the accuracy of the ICD-9 codes used to determine the exposures and outcomes. Fourth, our population was mainly female, relatively young (mean age 46.5), and well-insured and therefore may not be generalizable to males, older patients, and those with lower socioeconomic status. Fifth, the period of time in which the data was accessed (2002 to 2008) is several years old and may not accurately reflect current surgical case mix and clinical care. Today, bariatric surgeons are increasingly turning to laparoscopic procedures, and are performing fewer laparoscopic adjustable gastric bands and more vertical sleeve gastrectomies. (87, 88) As well, the safety of bariatric surgery continues to improve as techniques become ever more advanced. There is better awareness in the prevention of VTE and more standardized approaches including risk-stratified preventative measures and patient education. Finally, our data does not include specifics on the types of filters that were used in this cohort, for example retrievable vs. permanent filters. This lack of knowledge could very well influence the outcomes that were documented. In 2010, the FDA issued a warning with regard to the use of IVC filters. They cited 921 device adverse event reports including 328 occurrences of device migration, 146 device embolizations, 70 perforations into the IVC, and 56 filter fractures. The FDA recommended close surveillance, use of retrievable filters only, and removal of filters as soon as the risk of PE was gone. (89)

Strengths of this paper include the access to a large dataset, with one of the largest reported number of bariatric patients with IVC filter placement before bariatric surgery. Demographically the data drawn from the Blue Cross/Blue Shield plans closely resembles the US population and the results should be generalizable. And importantly, unlike other studies in the literature who have reported on the risks and benefits of the

IVC filters up to 30 days post bariatric surgery, our study captures events up until one year post bariatric surgery. This is a key factor to take into consideration, as venous thromboembolism and other complications that may be directly related to IVC filters have been known to occur 30 days following bariatric surgery. (90)

This study adds knowledge to the literature and provides further evidence that IVC filter use in the high risk bariatric surgical patient should be considered on an individual case basis with an understanding of the risks and benefits to their use.

3.6 Conclusion

We concur with the findings from other published literature including Birkmeyer et al (85, 91, 92) that IVC filter placement in bariatric surgical patients does not reduce the risk of PE in high risk bariatric surgical patients and may even cause more complications post-operatively. The use of IVC filter placement in high risk bariatric surgical patients should be used cautiously.

Table 5 Baseline Characteristics of the Analytic Cohort

Characteristics for 2002 to 2008 cohorts	**Inferior Vena Cava Filter Patients (n=789)**	**Non-Inferior Vena Cava Filter Patients (n=789)**	**All Bariatric Patients (n=1578)**	**P value**
Demographics/Medical History				
Mean (SE) age, in years	46.68 (0.35)	46.34 (0.35)	46.51 (0.25)	p=0.45
Age Categories, years				
18 to 24	15	15	30 (1.9%)	
24 to 34	90	90	180 (11.4%)	
35 to 44	194	194	388 (24.6%)	
45 to 54	302	302	604 (38.3%)	
55 to 64	188	188	376 (23.8%)	
Gender, % female	587 (74.4%)	202 (25.6%)	1174 (74.4%)	p=0.05
Type of Surgery				
Open Gastric Bypass	553	553	1106 (70.9%)	
Laparoscopic Gastric Bypass	180	180	360 (22.8%)	
Lap Adjustable Gastric Band	56	56	112 (7.1%)	
Comorbidities				
*Hypertension	540 (68.4%)	491 (62.2%)	1031 (65.3%)	p=0.01
*Diabetes	305 (38.6%)	248 (31.4%)	553 (35%)	p=0.003
*Sleep Apnea	308 (39.0%)	278 (35.2%)	586 (37.1%)	p=0.13

***VTE Pre-operatively**				
DVT Pre-operatively	278 (35.2%)	252 (31.9%)	530 (33.6%)	p=0.1827
PE Pre-operatively	82(10.4%)	47 (6.0%)	129 (8.2%)	p=.0017
***Anticoagulation (Warfarin) Prior to Surgery**	36 (4.6%)	33 (4.2%)	69 (4.4%)	p=0.806

*****Diagnosis or treatment within one year of bariatric surgery
DVT = Deep venous thrombosis
PE = Pulmonary Emboli

Table 6 Primary and Secondary Outcomes

Outcome	IVC Filter (n=789)	Non-IVC Filter (n=789)	Total (n=1578)	Fisher's exact p-value
Primary Outcome				
Post-op VTE	132 (16.7)	85 (10.7)	217 (13.7)	.0006
Post-op DVT (%)	110 (13.9)	66 (8.37)	176 (11.2)	0.0004
Post-op PE (%)	35 (4.4)	30 (3.8)	65 (4.1)	0.08
Secondary Outcome				
Bleeding	229 (29)	107 (13.6)	336 (21.3)	.0001
Surgical Site Infection	161 (20.4)	138 (17.5)	299 (18.9)	0.157
*Extended Length of Stay	167 (83.52	130 (16.5)	297 (18.9)	0.017
Reoperation	63 (7.9)	52 (6.6)	115 (7.3)	0.333
Cardiac Event	157 (19.9)	143 (18.1)	300 (19)	0.404
Respiratory Event	233 (29.5)	213 (27)	446 (27)	0.288
GI complication	412 (52.2)	420 (53.2)	832 (52.7)	0.724
GU complication	157 (19.9)	144 (18.3)	301 (19)	0.442
Neuro complication	5 (0.63)	4 (0.51)	9 (0.57)	0.247
Death	3 (0.38)	2 (0.25)	5 (0.32)	1.00
Any Complication	663 (84)	604 (76.6)	1267 (80.3)	0.0002

***Long length of stay = 5+ days for gastric bypass, 1+ days for laparoscopic adjustable gastric band

Table 7 Relationship between Inferior Vena Cava Filter Use and Outcomes in the Matched Analysis

Outcome	Odds Ratio	95% Confidence Interval	P Value
Primary Outcome			
Post-op VTE	1.87	1.4-2.5	0.0001
Post-op DVT (%)	2.01	1.4-2.8	0.0001
Post-op PE (%)	1.21	0.7-2.0	0.4587
Secondary Outcome			
Bleeding	2.97	2.30-3.9	0.0001
Surgical Site Infection	1.26	0.97-1.6	0.084
Reoperation	1.26	0.85-1.9	0.246
Cardiac Event	1.09	0.85-1.4	0.481
Respiratory Event	1.15	0.90-1.4	0.214
GI complication	0.98	0.81-1.2	0.886
GU complication	1.41	0.88-1.5	0.309
Any Complication	1.67	1.30-2.2	0.0001

Odd Ratio = Adjusted odds ratio controlled for age, sex, type of surgery, length of stay, diabetes, hypertension, sleep apnea

Chapter 4 The Diagnostic Accuracy of Magnetic Resonance Venography in the Detection of Deep Venous Thrombosis: A systematic review and meta-analysis

4.1 Abstract

Background: Previous studies have reported on the use of magnetic resonance venography as a possible alternative non-invasive modality in the detection of deep venous thrombosis. However, the majority of these studies have a small sample size and magnetic resonance venography's (MRV) potential significance is debated. One systematic review and meta-analysis on this topic has been published in literature in 2007. We plan to use this as our index paper and search the literature for further evidence for or against the use of MRV in the detection of DVT. In particular, we would like to consider the use of MRV in special populations for example, the morbidly obese where contrast venography may not be feasible or safe.

Objective: The aim of our systematic review and meta-analysis is to re-evaluate the accuracy of MRV in the detection of suspected (symptomatic and asymptomatic) DVT in light of recent additional data.

Methods: Pubmed, Embase, Scopus, Cochrane and Web of Science were searched to identify observational studies (case-control studies (CC) and cohort studies (CS)). We excluded case series, cross-sectional and non-human and non-English studies. Study quality and the risk of bias were evaluated using the Quality Assessment for Diagnostic Accuracy Studies tool (QUADAS 2). A random meta-analysis including subgroup and sensitivity analyses were performed.

Results: Our search resulted in 23 observational cohort studies all from academic centers. The total number of cases was 1121. Sixteen articles were included in the meta-

analysis. The summary estimates for MRV as a diagnostic non-invasive tool revealed a sensitivity of 93% [95% CI: 89% to 95%] and specificity of 96% [95% CI: 94% to 97%]. The heterogeneity of the studies was found to be high for both sensitivity and specificity. Inconsistency (I^2) for sensitivity and specificity was 80.7% and 77.9% respectively.

Conclusions: Further studies investigating the use of MRV in the detection of suspected DVT did not offer any further evidence to support the replacement of ultrasound with MRV as a first line investigation for DVT. However, MRV may offer physicians an alternative tool in the detection/diagnosis of DVT in patients for whom ultrasound is inadequate or not feasible (such as in the obese patient).

4.2 Introduction

Venous thromboembolism (VTE) is a serious condition, leading to over 50,000 deaths a year in the United States. (93-95) Venous thrombosis is defined as a blood clot (thrombus) that originates in any vein of the human venous system. These can occur in the deep veins of pelvis, thighs or legs (DVT) or part of the thrombus could detach as an embolus and lodge in the pulmonary vessels, leading to PE. (96, 97) Early detection is essential for immediate treatment to avoid significant morbidity and mortality accompanied with DVT and pulmonary emboli (PE). (98)

The clinical presentation of VTE may vary widely from being completely asymptomatic to having a lethal outcome such as PE; moreover, a diagnosis of DVT may lead to long term comorbidity such as chronic venous insufficiency. (99) One of the known risk factors for VTE is obesity.(100) Excessive abdominal fat limits the venous return and chronically raises the intra-abdominal pressure, leading to decrease in the blood velocity in the femoral veins. (100, 101) In addition to these mechanical factors, obese patients

have high levels of leptin, decreased fibrinolysis and a high activity of the coagulation cascade, which contributes to more venous thrombosis, especially in the lower limbs.(100) Other risk factors for VTE, include pregnancy, smoking, heart failure, previous DVT or PE, increased age, cancer, nephrotic syndrome, medications; including birth control pills, hormone replacement therapy and tamoxifen, surgical procedures, especially those involving the hip and pelvis, prolonged postoperative recumbency and inherited thrombophilia; such as factor V Leiden, anti-thrombin deficiency, protein C or protein S deficiency. (102)

Recently the mortality of PE caused by DVT increased in the USA, reaching 40,000–200,000 deaths annually.(103) Therefore, early detection of DVT and especially asymptomatic DVT is necessary to avoid hazardous and devastating results due to PE. The gold standard for the detection of DVT is contrast venography. While this modality is considered to be ideal it comes not without risk and comorbidity to the patient. These risks include contrast nephropathy, systemic reactions to the contrast dye, tissue necrosis due to extravasation of the contrast medium, venous thrombosis at the catheter site and pulmonary emboli as sequelae.(104) In addition, contrast venography is not ideal for pelvic originated DVT because of the wash-out effect of the contrast medium in tributaries of the deep pelvic veins. (104) Because of these obvious limitations to venography other non-invasive modalities have been developed and include duplex ultrasound (U/S), contrast enhanced computed tomography (CT) venography, and magnetic resonance venography (MRV). Each modality brings with it its own advantages and disadvantages.

Duplex U/S is a non-invasive and relatively inexpensive tool for the detection of DVT. However, it is operator dependent, with a poor anatomical view especially in the morbidly obese and might not be helpful in some situations, such as a limited available acoustic window. (99, 105) It is also not useful for pelvic veins and as such this limits its applicability to extremities only.

Unlike duplex U/S, contrast enhanced CT venography has a better anatomical view, but has high risk of ionizing radiation, in addition to the contrast material used, which makes the patient more vulnerable to allergic reactions and nephrotoxicity. (99, 105) X-ray venography is rarely used anymore, not only because it has similar limitations as contrast enhanced CT venography, including ionizing radiation and contrast material, but also because it only evaluates a single draining venous system with each acupuncture, which makes it impractical.(105, 106)

Alternatively magnetic resonance venography (MRV) has been suggested as a non-invasive diagnostic tool for confirming the presence of absence of DVT. This may be of important benefit in special populations such as uremic patients and those with inadequate venous access, as in the morbidly obese patient.(107-109) MRV has lower operator dependence and provides better venous anatomy, (98) especially in the pelvic region, allowing better visualization of the inferior vena cava and external iliac veins. This is crucial in the diagnosis of DVT for the obese patient, where thicker lower limbs and excessive fat tissue, obscuring the view of pelvic veins makes duplex ultrasound non-diagnostic. (106, 108, 109) Sampson et al. explored the accuracy and benefits of MRV in a systematic review and meta-analysis in 2007. To our knowledge this is the only literature review that has been conducted on this specific topic to date. The authors

concluded that MRV will not replace ultrasound as the first-line modality for DVT detection. However, they did suggest that MRV may offer an alternative in special populations such as the obese patient where ultrasound is not feasible or yields inconclusive results.(110) Since the systematic review and meta-analysis by Sampson and colleagues, additional studies have been published reporting the experience with MRV as compared to other non-invasive modalities and the gold standard contrast venography.

Given the limited options of non-invasive modalities available for the detection of DVT especially in special populations and the unclear benefit described in the literature, we set out to compare MRV with other non-invasive modalities (duplex ultrasound and computed tomography venography) with the gold standard contrast venography in the detection of DVT of the lower limbs.

4.3 Objective of the Review

The objective of this review is to assess whether the diagnostic accuracy of MRV for clinically suspected and asymptomatic DVT is high enough to justify its use in clinical practice and to evaluate if MRV can replace venography particularly in special populations such as the obese. Similar to our index systematic review, our hypothesis is that MRV may be very useful in special populations such as in the obese, offering an alternative modality to be used when ultrasound is not feasible or yields inconclusive results. We formulated our research question using the acronym PECO, where "E" stands for exposure, i.e. In patients with suspected DVT (symptomatic or asymptomatic) of the lower limbs does MRV when compared to other non-invasive modalities such as duplex

ultrasound and computed tomography venography accurately detect blood clots within the pelvis and lower limbs using contrast venography as the gold standard?

P In patients with suspected DVT (symptomatic or asymptomatic) of the lower limbs

E does MRV

C when compared to other non-invasive modalities such as duplex ultrasound and computed tomography venography

O accurately detect blood clots within the pelvis and lower limbs using contrast venography as the gold standard

4.4 Methods

Inclusion and exclusion criteria for studies

We included prospective and retrospective cohort studies, cross-sectional studies and case-control studies. We did not include any case series, case reports or animal studies.

4.4.1 Definition of Exposure

Adults or children who were suspected of having a DVT (symptomatic or asymptomatic) who underwent MRV for the diagnosis of blood clot in the pelvis or lower limbs were included. These same patients should have undergone another diagnostic study (duplex ultrasound, compute tomography venography and/or contrast venography) to compare the diagnostic accuracy of the MRV. We included only studies that evaluated the pelvis and lower extremities and excluded studies that only included upper extremity MRV or chest MRV. We did not exclude subjects based on age, race, ethnicity, gender geographical location, health care setting or method of MRV used.

4.4.2 Primary Outcome

The primary outcome for this review and meta-analysis was the accurate detection of blood clots in the lower limb and pelvis as compared to contrast venography (the gold standard).

4.4.3 Search Strategy

We searched MEDLINE (via PUBMED), COCHRANE, EMBASE, SCOPUS and WEB OF SCIENCE for papers containing the synonyms for both terms “deep vein thrombosis” and “magnetic resonance imaging”. Synonyms were compiled using both controlled vocabulary and free text concepts. We also searched systematic reviews and meta-analyses using the clinical queries tool in Pubmed. The specific search strings are listed in Appendix A.4.1.

Hand-searching was performed by compiling a list of the top 40 journals based on the 2013 impact factor in 3 major areas radiology (pertinent to MRV imaging), surgery/medicine and orthopedic surgery. From the list we chose the 4 most pertinent journals: Radiology, Investigative Radiology, Journal of Magnetic Resonance Imaging, JAMA surgery and Clinical Orthopedics and Related Research. Each of these journals was searched back six months for articles that were not identified in our database search. Conference proceedings were not searched for unpublished and ongoing studies. Finally, we examined the 14 articles from the Sampson review and meta-analysis (110) to ensure that they were included in our review.

The initial list of articles derived above was aggregated into EndNote X6 software. Duplicates were removed based on author, year, title, journal, volume, issue and page. Articles from Pubmed were kept in preference to those in Embase and Scopus.

4.4.4 Selection of Studies

We compiled a list of all articles identified from the search strategies outlined above. These results were merged into a common file and duplicates were deleted (as above). The articles were then divided evenly among two reviewers (KS and GA). The reviewers independently examined their assigned articles for inclusion and classified each article as "exclude" "include" or "unsure." Initial article screening began with a title screen. To be included articles needed to include the words DVT, MRV or contrast venography. Our initial title criteria were very broad in order to sufficiently capture potential studies. After title screening, abstracts were retrieved and screened to determine eligibility. Finally, full text articles were retrieved and screened for inclusion. Any discrepancy between title, abstract and text review was adjudicated by a third reviewer.

4.4.5 Data Extraction and Management

To avoid bias in the distribution of articles, we randomly shuffled the titles and abstracts using EndNote X6 and then assigned half of the articles to each reviewer (KS and GA). Titles and abstracts were then reviewed, summarized and abstracted with any relevant data compared, and any dissension was adjudicated by a third reviewer (VV). Articles were excluded if they were poster presentations, case series, case reports, review articles or editorials, animal studies or published in a language other than English. See the adapted MOOSE guidelines flow chart in Figure 4 for a numeric description of the process.

The full text of articles selected by the above procedure was retrieved. A standardized data extraction form was developed, which was pilot tested on two full text articles. (Appendix A4.2) Each team member independently reviewed the full text article,

extracted study and patients characteristics, including type of study, country of origin, origin of patients recruitment, number of cases recruited, patients status (symptomatic or asymptomatic), patients mean age, patients gender, prevalence of DVT, MRI technique used in each study, the reference standard used, MRV and the reference standard interpreted blindly, and reference standard done independently from MRV. If sensitivity and specificity were not calculated within the individual paper a 2 × 2 table was constructed to extract the number of true positives, false positives, true negatives, false negatives, for MRV study results. We also confirmed given sensitivity and specificity values of each individual study by recreating 2 x 2 tables. Any values that we found to be incorrect were corrected and used for our quantitative analysis.

The extracted data was entered in duplicate into Microsoft Excel and then transferred to our data analysis software package. We did not impute any missing values though to complete the analysis, we did correct for values of zero for sensitivity and specificity of reported for any of the individual studies Data reporting conformed to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group guidelines. (111)

4.4.6 Assessment of Methodological Quality of Included Studies

In 2003, QUADAS a validated assessment tool was developed for systematic reviews to determine the quality of primary diagnostic accuracy studies and risk of bias. QUADAS has since been modified and QUADAS-2 was developed. The QUADAS-2 tool is composed of four main domains that consider patient selection, index test, reference standard and flow of patients through the study and timing of the index tests and reference standard. (112) The tool was piloted with two reviewers (KS and GA) extracting data on 2 individual papers included in this review and agreement was found to

be good. Therefore the tool was used to rate all included studies. Two reviewers (KS and GA) independently extracted study characteristics using standardized Quadas-2 forms. (Appendix A4.3) Any disagreements were solved by consensus and if necessary, by involving a third reviewer (VV). The study was then labeled either "low bias," "high bias" or "unclear" based on each category.

4.4.7 Data Synthesis and Analysis

The unit of analysis for this study was either thrombus of the lower limb and/or pelvis or the patient. A bivariate random effects approach was used to obtain joint summary estimates of sensitivity (the proportion of patients with positive DVT, as established by contrast venography or other non-invasive modality, who have a positive MRV) and specificity (the proportion of patients who are negative for DVT by contrast venography or other non-invasive modality, who have a negative result by MRV). We used Meta-Disc (Version 1.4) dedicated and comprehensive software for meta-analysis of diagnostic data. (113) A continuity correction of 0.5 was set for any sensitivity or specificity value reported as zero. This was to ensure that we could define the calculation of sensitivity and specificity within the statistical software. Significance was set at $p < 0.05$ for all analyses. We planned to conduct stratified analyses to explore the effects of differences in the reference standard, symptomatic versus asymptomatic cohorts, and other factors that might be affecting heterogeneity.

4.4.8 Assessment of Heterogeneity

Heterogeneity was assessed qualitatively based on the individual characteristics of the studies, their methodological quality and their individual risk of bias. Specific attention was paid to participant characteristics (age, sex, hospital setting, symptomatic or

asymptomatic DVT), the type of MRV, protocol used and whether contrast or no contrast was used, criteria used to diagnose a lower limb or pelvic DVT for the index test and the reference standard. Effect size was compared using Chi-square test (Q), and by visual assessment of the point estimates of effect and degree of overlap of the confidence intervals in the forest plot. The impact of heterogeneity on the meta-analysis was quantified using I statistic (I^2). Cochran Handbook guidelines were followed with 0 to 40% defined as low heterogeneity, 30 to 60% as moderate heterogeneity, 50 to 90% as substantial heterogeneity and 75 to 100% as considerable heterogeneity. (114) To assess clinical and methodological heterogeneity we considered performing subgroup analyses of our studies according to type of reference standard performed, patient symptoms (asymptomatic versus asymptomatic), index and reference standard blinded or not, age and geographic location.

4.4.9 Qualitative Synthesis

A narrative summary of our review was completed by our two team members. This summary included a description of the quality of the studies included in our review and the degree to which individual study design might impact the quantitative results. We attempted to document and control for all potential biases that may arise while undertaking this review. We documented our reasons for exclusion of studies.

4.4.10 Subgroup Analysis

We defined our subgroup analysis a priori so as to reduce bias. These subgroups included:

1. Stratifying studies into those which included the gold standard: contrast venography as the reference standard versus those which included other reference standards such as duplex ultrasound, computed tomography venography or X-ray venography.

2. Stratifying patients as presenting with asymptomatic or symptomatic VTE.

3. Stratifying the index test as being read blindly and by two or more radiologists independently.

4.5 Sensitivity Analysis

Sensitivity analyses were performed by excluding studies that were found to have unusual variability or low methodological quality. Specifically, the following sensitivity analyses were performed:

1. Dropping individual studies that may be affecting heterogeneity (ex. those studies that extremely low sensitivities and specificities).

4.6 Results of the search

Records identified by an extensive electronic database search yielded 1062 records using the following search engines: Pubmed 228, Embase 517, Scopus 177, Cochrane Review 15 and Web of science 125. (Appendix A4.1) Two records were identified individually by hand search. All records were combined and transferred to EndNote X6. Duplicates were purged leaving 658 records for title and abstract screening. The search found all articles included in the most recent systematic review and meta-analysis; Sampson et al. 2007 (our reference article) except Pope et al. 1989 (Sampson reference 24), which was one of the two records identified by hand search. The other paper was Montgomery et al. 1994, which was found through hand searching in the reference section of Aschauer et al.

2003. We excluded 492 records based on our exclusion criteria and 166 full text articles were assessed for eligibility. Of the 166 articles, 143 articles were excluded: 85 articles did not meet our inclusion criteria, 21 were case reports, 28 were observational and systematic reviews, 8 were in foreign language; including German, Italian, Chinese and Japanese, and 1study was still pending from Weldoc. Our final date for including studies in our systematic review was March 10, 2014. After reviewing these full text articles, 23 were included in our qualitative study. All were cohort studies. Sixteen studies were included in our meta-analysis. Seven studies (Akhtar, Alnoldussen, Spuentrup, Aschauer, Evans 1996, Ono and Stover) were excluded from the meta-analysis and quantitative analysis, to be included only in qualitative analysis of the systematic review. These 7 studies were excluded because they failed to use contrast venography as the reference standard to be compared to MRV. Twenty-one out of the 23 eligible studies evaluated their cohort in a prospective fashion while the 2 remaining studies (Arnoldussen, Spritzer).were retrospective.

4.6.1 Qualitative analysis

The characteristics of these studies are summarized in Table 6. The 23 studies were performed among 3 continents, including Europe, North America and Asia. The majority (91%) of the eligible studies were done in Europe and North America. From Europe there were eleven studies, four of which were conducted in England (Fraser 2002, Fraser 2003, Montgomery, and Moody) and the remaining studies originated in seven different countries, including the Netherlands (Arnoldussen), Austria (Aschauer), Ireland (Cantwell), Italy (Catalano), Denmark (Jensen), France (Laissy) and Germany (Spuentrup). Ten studies were carried out in North America; all of which were done in

USA (Carpenter, Erdman, Evans 1996, Evans 1992, Larcom, Pope, Sica, Spritzer, Vukov, Stover). Two studies represented Asia; one was carried out in the Kingdom of Saudi Arabia (Akhtar) and one in Japan (Ono). All 23 eligible studies were conducted in an academic setting. The number of patients included in the studies ranged from 10 to 203. There were a total of 1121 cases included among all of our eligible studies. These patients were recruited from different settings that varied from either hospital inpatients (Akhtar, Arnoldussen, Erdman, Larcom, Jensen, Montgomery), a mix between inpatients and outpatients (Fraser 2003, Fraser2002, Sica, Ono, Stover) or via the Emergency Department(Cantwell, Vukov). Ten studies did not report the setting in which patients were recruited (Aschauer, Carpenter, Catalano, Evans1992, Evans1996, Laissy, Pope,Spritzer, Spuentrup, Moody). All of the 23 studies investigated suspected DVT. Fifteen of the studies recruited patients with symptomatic DVT (Akhtar , Arnoldussen, Aschauer, Cantwell, Carpenter,Catalano,Evans 1993,Evans1996,Fraser 2003,Fraser 2002,Pope,Sica,Spritzer,Vukov,Moody) (98, 105, 115-126), Laissy et al. recruited patients that had symptoms of either DVT, PE, or both. (107) Four of the studies recruited asymptomatic patients (Jensen, Larcom, Montgomery and Stover) (104, 127-129) and 2 studies recruited a mixture of both symptomatic and asymptomatic patients (Erdman,Ono). (130, 131) Spuentrup et al. did not distinguish between symptomatic or asymptomatic patients nor were any demographic or clinical details given regarding the patients recruited in their study.(132)

Fifteen of the 23 eligible studies interpreted DVT utilizing a double blinded system for both MRV and the reference standard (Akhtar, Cantwell, Carpenter, Erdman, evans1992, Evans1996, Fraser 2002,Fraser 2003, Jensen, Larcom, Laissy, Montgomery, Sica, Vukov,

Ono), while 3 of the studies did not assess DVT in a double blinded way, either for MRV or the reference standard(Arnoldussen,Aschauer, Moody). It was unclear in the remaining four studies whether the radiologic assessment of DVT was double blinded or not (Catalano, Pope, Spritzer, Spuentrup). Stover et al. interpreted DVT blinded for MRV only, while it was not clear whether it was blinded for the reference standard. The reference standard was performed independent to the results of MRV in all 23 studies, except for Ono et al. and Stover et al., for which the reference standard was only performed on patients found to be positive on MRV. All studies used non-contrast MRV, except for Aschauer et al. and Fraser et al. 2003, these studies utilized contrast enhanced MRV in the detection of DVT. In both of Evans papers (1992 and 1996) contrast enhanced MRV was used only when the non-contrast MRV studies were equivocal.
The majority of the studies used the gold standard for the detection of DVT - contrast venography (Cantwell, Catalano, Erdman, Evans 1992, Fraser 2002, Fraser 2003, Jensen, Larcom, Montgomery, Pope, Vukov, Moody). Three studies used Duplex US (Akhtar, Arnoldussen, Evans 1996), 2 studies used X ray venography (Aschauer, Ono), and 4 studies used a combination of both contrast venography and Duplex US (Carpenter, Laissy,Sica, Spritzer). Two studies incorporated computed tomography venography with other modalities: Stover et al. used computed tomography venography with contrast venography, while Spuentrup et al. used 3 imaging modalities, including computed tomography venography, X-ray venography and Duplex US.

4.6.2 Risk of Bias

We utilized predetermined criteria based on QUADAS 2 (a validated risk of bias assessment tool for diagnostic accuracy described in the methods section) to determine

the risk of bias and applicability concerns of the individual studies included in our review. These results are summarized in Table 7 and plotted in Figure 5.

In general, the studies included in this review performed well with regards to applicability. We found that the majority of the included studies were at low risk for two categories with respect to applicability, including the patient selection and index test, with an average rating of 82.6% and 78.3%, respectively. While the reference standard scored an average rating of 43.5% for low risk, 21.7% for unclear risk and 21.7% as high risk. Overall, 19 of the 23 eligible studies were rated with an average acceptable applicability of concerns, except for 3 studies (Catalano, Spritzer, Spuentrup) that were found to be unclear and 2 studies (Aschauer and Pope) were determined to be of poor quality (high risk) for applicability.

With respect to the methodological quality and risk of bias: In 14 of 23 studies, the protocol for the MRV was clearly defined, leading to low risk of bias in the index domain, with 3 studies (Aschauer, Catalano and Spuentrup) having an unclear MRV protocol and 6 studies (Arnoldussen, Jensen, Pope, Spritzer, Vukov, Moody) with MRV protocols that were ill defined and at high risk of bias. With regards to the flow and timing domain, acceptable time intervals between the index test and reference standard were found in 52.2% (12 out of 23) of the studies. Four studies (Akhtar, Catalano, Larcom, Spuentrup) were assessed as having an unclear flow and timing between the reference and index tests while 7 studies (Arnoldussen, Laissy, Montogomery, Pope, Spritzer, Ono, Stover) were found to be at high risk with time intervals between reference and index tests approaching greater than 1 week. The areas of most concern when evaluating the risk of bias in our 23 included studies were the patient selection (over 60%

of the studies were unclear or at high risk for bias because of lack of detail with respect to patient selection) and reference standard chosen (over 61% of the studies used a diagnostic modality other than the gold standard – contrast venography). Added to this, diagnostic bias (unclear whether the study included prevalent cases instead of incident cases) and confounding bias (study did not account for age, weight, race, social history (tobacco use) or patient past medical history, medications (estrogen, anticoagulants) and associated medical comorbidities such as COPD, obesity, previous VTE or predisposing risk factors of VTE) were common among the studies.

4.6.3 Quantitative analysis

Meta-analysis was performed for 16 out of the 23 eligible studies. The forest plots for sensitivity and specificity of the 16 studies using contrast venography as their reference standard are summarized in Figure 6 & 7. Sensitivities and specificities for individual studies ranged from 0 to 100% and 43% to 100% respectively. We found significant heterogeneity for both estimates ($p<0.001$). This must be considered when evaluating the pooled estimates. The pooled sensitivity was 93% [95% CI: 89% to 95%], while the pooled specificity was 96% [95% CI: 94% to 97%]. There was a large amount of heterogeneity demonstrated among the studies with regards to sensitivity (Chi-square= 77.10, I2=81.8%, p value=0.0001) and specificity (Chi-square= 59.72, I2=76.6%, p value=0.0001).

Visually, the forest plots showed that the majority of the studies tended to cluster around high estimates of sensitivity and specificity, representing a positive association between MRV and the detection of DVT in pelvis and lower limbs. (Figure 6&7)

4.6.4 Subgroup analysis

After our overall quantitative analysis was complete, we carried out our subgroup analyses to assess methodological and clinical heterogeneity. There were three planned subgroup analyses:

1. Stratifying studies into those which included the gold standard – contrast venography as the reference standard versus those which included other reference standards such as duplex ultrasound, computed tomography venography or X-ray venography.
2. Stratifying patients as presenting with asymptomatic or symptomatic VTE.
3. Stratifying the index test as being read blindly and by two or more radiologists independently.

We did not complete the third subgroup analysis. We felt that this was not necessary as the majority of the studies were blinded to the index test and were read by two or more radiologists independently.

We chose as our main meta-analysis the forest plots of sensitivity and specificity for those studies which used contrast venography as the reference standard. Contrast venography, an invasive diagnostic tool is the known gold standard for detection of DVT in the pelvis and lower limbs. Our main aim of this review was to determine if MRV, a non-invasive diagnostic tool could replace contrast venography for the detection of DVT in pelvis and lower limbs. Furthermore, we wanted to determine if MRV could be used in special populations where contrast venography is contraindicated.

The pooled sensitivity and specificity estimates of all studies in the meta-analysis: 93% [95% CI= 91 to 96%] and 96% [95% CI=95to 97%] respectively (Figure 8 & 9) was comparable to the pooled sensitivity and sensitivities of only those studies which

included contrast venography as the reference standard: 93% [95% CI=89% to 95%] and 96% [95% CI=94% to 97%] respectively (Figure 6 & 7). However, as predicted there was more heterogeneity demonstrated when all studies were included in the meta-analysis versus only studies that used contrast venography as their reference standard: sensitivity [Chi-square= 87.83 (p=0.0001), I^2=78.4%] and specificity [Chi-square= 94.48 p=0.0001), I^2=79.9%], in comparison to the studies that used contrast venography as their reference standard . [Chi-square= 77.10 (p=0.0001), I^2=80.7%] and specificity [Chi-square= 67.91(p=0.0001), I^2=77.9%].

We chose to stratify studies which reported symptomatic versus asymptomatic DVT as we felt that this may bias the interpretation of the MRV results and only 3 of the studies recruited asymptomatic only patients. We excluded Erdman et al. from this subgroup analysis because they included both asymptomatic and symptomatic patients in their recruitment. We found the pooled sensitivity of symptomatic only patients to be 97% [95% CI: 94% to 99%] versus asymptomatic only patients sensitivity pooled estimate 61% [95% CI: 41% to 78%] with an unaffected pooled specificity, symptomatic 96% [95% CI: 94% to 98%] and asymptomatic 95% [95% CI=91 to 97%]. The heterogeneity of these estimates showed a significant decrease with respect to the sensitivity estimates for the symptomatic cohort [chi-square=30.17 (p=0.0008) and I^2=66.9%] versus all patient cohorts that included symptomatic, asymptomatic and mixed cohorts [chi-square = 77.10 (p=00001) and I^2=81.8%] and pooled specificity for symptomatic cohort [chi-square=33.07 (p=0.0003) and I^2=69.8%] versus all patient cohorts that included symptomatic, asymptomatic and mixed cohorts [chi-square = 59.2 (p=00001) and I^2=76.6%] . This was not the case for the heterogeneity estimates of the asymptomatic

cohort. Heterogeneity remained high regardless of the subgroup analysis. The forest plots for sensitivity and specificity of the symptomatic and asymptomatic studies using contrast venography as their reference standard are summarized in Figure 10, Figure 11, Figure 12, and Figure 13.

4.7 Sensitivity Analysis

During our analysis, we noted several studies with measures of extreme variation and low methodological quality. We examined each individual study's effect by removing them one at a time to see if this changed the effect measures. We therefore performed sensitivity analyses:

First, on visual inspection of our index forest plot (all studies that included contrast venography as a reference standard) Jensen et al. yielded results that were markedly different then all of the other included studies and therefore we regarded this study as an obvious outlier. For this reason, we performed a sensitivity analysis by removing Jensen et al. from the main analysis. We found the results of the dropping Jensen et al. to have a slight improvement on the pooled sensitivity being 95% [95% CI= 91 to 97%], while the pooled specificity was 96% [95% CI=94to 97%], which is similar to the pooled specificity before dropping Jensen et al. However, there was a significant decrease in the heterogeneity demonstrated among the studies pooled sensitivity [Chi-square= 44.31 (p=0.0001), I^2=68.4%] and a slight decrease in the heterogeneity of the pooled specificity [Chi-square= 65.09 (p=0.0001), I^2=78.5%], when compared to the pooled estimates of all included studies in our index meta-analysis. (Figure 16 & 17)

Examining the overall forest plot of the main meta-analysis, two other studies were also found to be outliers while the majority of the studies tended to have sensitivity and

specificity estimates greater than 80%. These studies included Sica et al. and Montgomery et al. By dropping these studies one at a time we found very little change in the summary estimates for both sensitivity and specificity. However, there was an overall improvement in the I^2 score. After dropping Montgomery et al. the I^2=79.8%, then after dropping Sica et al. the I2=68.9% and finally by dropping Jensen the I^2=68.4%. Finally, when all 3 studies were dropped we found a significant improvement in heterogeneity of I^2=47.2%. (Figure 18, 19, 20, 21, 22 & 23)

For our second sensitivity analysis, we chose to exclude Jensen et al. from the asymptomatic only analysis as this study performed poorly with respect to the index test and may be a cause of the lowered sensitivity amongst the asymptomatic cohort. We found an improved pooled sensitivity of the asymptomatic cohort 77% [95% CI=55% to 92%]. The pooled specificity remained comparable at 96% (95% CI=92 to 98%). However, there was a significant decrease in the heterogeneity demonstrated among the studies with respect to pooled sensitivity [Chi-square= 2.46 (p=0.0001), I^2=59.3%] and only slight decrease in heterogeneity with respect to the pooled specificity [Chi-square= 22.85 (p=0.0001)] when compared to the pooled estimates of all asymptomatic cohort studies. The inconsistency (I^2) for specificity of MRV for the asymptomatic cohort after removing Jensen was actually higher than with all asymptomatic studies included. (Figure 14 & 15)

4.8 Discussion

4.8.1 Clinical Heterogeneity

The studies were conducted in developed countries from around the world with diverse populations including France, Germany, Italy, Denmark, The Netherlands, England,

Ireland, Japan, Austria, Saudi Arabia and several studies in the United States. Publication ranged widely from 1990 to 2012. All studies were cohort studies, were conducted at academic institutions and evaluated MRV as a diagnostic tool in the detection of DVT. Thus, none of the studies were excluded based on applicability. However, there were significant differences in the geographic location, sample size, range in patient age and almost all of the studies lacked detail with respect to patient demographics and VTE risk factors.

4.8.2 Methodological Heterogeneity

Confounding

We judged the most important confounders to be age, gender, number of cases recruited, patients status (symptomatic or asymptomatic), blind interpretation of both MRV and the reference standard in a double blinded manner, type of MRV protocol, timing and flow between studies and type of reference standard used in each study. The majority of studies accounted for sex and age, but there was great variation in the way each study recorded the patient demographics. As such, the heterogeneity we observed may be due to variations in the comorbidities. However it is impossible to control for these variations because the populations were not well described in any of the 23 included studies. Five studies (Carpenter, Catalano, Pope, Spritzer, Vukov) did not report age at all, while two studies (Jensen, Akhtar) recorded the median age of the patients rather than the mean age, three studies (Cantwell, Spuentrup, Erdman) recorded only the range without the mean ages, and two studies (Ono, Evans 1993) recorded the mean ages without the range of ages of cases. In addition, six studies (Carpenter, Catalano, Fraser 2002, Spritzer, Vukov, Spuentrup) failed to report the gender of their recruited cases.

Another confounding factor that could have affected the heterogeneity among the studies was the defined unit of analysis for each individual study. Some studies reported DVT on a patient level while others chose the unit of analysis to be on the vein level. Montgomery et al. reported DVT on both a patient level and a venous level. As well, the studies varied with regards to the anatomical areas examined. Some studies examined the entire venous system of the pelvis and lower limbs, while other studies studied only a single anatomical area. The technique and protocols used for MRV varied amongst the studies. The majority of the included studies used non-contrast MRV except for one study (Fraser 2003) which used contrast. The strength of the MRV magnet varied with the majority of the studies using 1.5 Tesla, except 3 studies [Erdman (0.35T), Laissy (1.0T) and Ono (0.5T)] which used different ranges of smaller Tesla units for the MRV. Finally, there was variation in the way images were reviewed. Some studies used maximum intensity projection images, while other studies viewed source axial images.

Information Bias

Eighteen of the twenty-three cohort studies did specify the radiological diagnostic criteria of a thrombus in the deep veins, either in lower limbs or pelvis. Five studies (Arnoldussen, Jensen, Pope, Vukov, and Moody) did not mention the radiological criteria used to diagnose DVT. This could have contributed to the heterogeneity, especially given that four (Jensen, Pope, Vukov, Moody) out these five studies were included in the meta-analysis.

Selection Bias

Patient selection was assessed as being high risk for bias in majority of the studies because they either did not recruit their patients consecutively or randomly, or they were

found to have inappropriate exclusions. Only a handful of studies (Cantwell, Evans 1992, Fraser 2002, Jensen, Laissy, Montgomery, and Ono) were noted to have conducted their patient selection in an appropriate fashion.

Recall Bias

Several factors related to interpreting the results of the MRV by the radiologists involved in each study contributed to the wide heterogeneity among the studies. The majority of the studies assigned only one reviewer to interpret the presence of DVT by imagine, only 8 studies (Carpetner, Cantwell, Fraser 2002, Laissy, Vukov,Ono, and Spuentrup) interpreted the results via two independent reviewers. While Catalano et al. used three reviewers to read the results of the index and reference standard, it was not clear from their methods as to whether the index test or reference standard tests were read in a double blinded manner. All studies described the independent interpretation of both the reference standard and the MRV results, except for 2 studies (Ono, and Stover) and these were already excluded from the meta-analysis because of the inability to create 2 x 2 tables.

Experimenter's bias

Seven of the studies (Arnoldussen, Aschauer, Moody, Catalano, Pope, Spritzer, and Spuentrup) were unclear or did not assess the diagnosis of DVT in a double blinded manner, either for MRV or the reference standard. Stover et al. interpreted DVT blinded for MRV only, while it was not clear whether it radiologists were blinded for the reference standard. From the details of the studies above four of our 16 studies included in our meta-analysis (Moody, Catalano, Pope and Spritzer) were found to have experimenter's bias because of questionable blinding practices.

4.8.3 Quantitative Analysis

Overall, MRV- a non-invasive diagnostic tool for DVT appears to perform well when compared to contrast venography - an invasive diagnostic tool for DVT. Moreover, MRV was found to be highly sensitive and specific for the detection of clinically suspected (symptomatic) DVTs. According to the results of our meta-analysis, summary estimates of sensitivity and specificity were 93% and 95%, respectively.

Statistical Heterogeneity

Individually the included studies in our meta-analysis had significant heterogeneity. Four studies (Jensen, Sica, Montgomery, and Vukov) deviated from the other studies with respect to their lower sensitivity estimates. While 3 studies (Sica, Moody, and Montgomery) had lower than average specificity estimates when compared to the other included studies. Factors that may have led to these inconsistencies include: a) the studies lack of description with regards to the criteria used for DVT detection (Vukov and Jensen) b) studies had a small sample size [Vukov (n=10), Sica (n=14), Jensen (n=27)] c) studies lacked a standardized protocol for interpreting the radiographic results (ex. Montgomery had only one reviewer/radiologist only) d) studies had different units of analysis (i.e. some studies analyzed patients while others analyzed at the level of the veins) e) two of the outlier studies recruited asymptomatic patients. Finally, Moody et al. may have had a lower specificity given that they recruited only a small number of symptomatic cases and more importantly radiographic criteria of DVT was not reported and the interpretation of MRV and contrast venography results were not blinded.

Subgroup Analysis

1. Studies including any imaging modality as a reference standard

In comparison to our reference index article (Sampson 2007), we chose to include in our main meta-analysis only studies that considered contrast venography as the reference standard. We then completed a subgroup analysis to see how this would affect our summary estimates by including other diagnostic modalities such as X- ray venography, duplex ultrasound and CT venography. We felt that this was necessary given that contrast venography is the gold standard for diagnosis of DVT in pelvis and lower limbs. Interestingly, we found that the pooled sensitivity and specificity of all studies including any imaging modality as a reference standard to be comparable to the contrast venography only studies, recording a sensitivity and specificity of 94% and 96%, respectively. However, the level of heterogeneity was much higher in meta-analysis that included any imaging modality as a reference standard, in comparison to the contrast venography studies. To complete our main meta-analysis, four studies (Ono, Stover, Aschauer, and Evans 1996) were excluded.. Ono et al. and Stover et al. were noted to have selection bias (only patients who had a positive MRV then underwent the reference standard –contrast venography). As well, it was unclear if Stover et al. insisted on a blinded and independent interpretation of the reference standard. In Aschauer and colleagues study the reviewers were blinded only to the location of thrombus, but were informed about the presence of thrombus in at least one venous segment, increasing bias in their study.

2. Symptomatic versus Asymptomatic DVT

Although the study by Erdman et al. was found to be of overall excellent clinical and methodological quality with low risk of bias and applicability, we chose to exclude it from this symptomatic versus asymptomatic subgroup analysis because they recruited

both symptomatic and asymptomatic patients and did not distinguish between them. In the subgroup analysis, the symptomatic only group recorded a significantly higher sensitivity (97%) in comparison to the asymptomatic patients (61%). Running this subgroup analysis did show a slight improvement in the sensitivity in comparison to the sensitivity of including all patients (both symptomatic and asymptomatic) (93%). In addition we found a lower heterogeneity associated with symptomatic patients in comparison to all patients setting. As for the specificity estimate, both symptomatic and asymptomatic DVT were nearly equal and didn't differ from the all patients setting.

Sensitivity analysis

On visual inspection of the main forest plot for sensitivity there were several outliers, the most obvious being Jensen et al with Sica et al and Montgomery also having lower individual sensitivities. The study by Jensen et al. had several limiting factors that may have contributed to its individual sensitivity estimates being so much lower when compared to the other included studies. These factors included a small number of cases, and no defining radiologic criteria for DVT diagnosis. By dropping Jensen et al. from the meta-analysis, we found a slight improvement on the pooled sensitivity of 95%, while the pooled specificity of 95%, stayed the same. A significant decrease in the heterogeneity for sensitivity was observed (I^2=68.4%) but remained unchanged for specificity (I^2=78.5%).

4.9 Language bias: Exclusion of studies not published in English

Due to time constraints, studies not published in English were excluded. It is possible such studies differ systematically from those published in English. However, given that

only 8 of 166 studies were excluded on this basis, we believe that it is unlikely that inclusion of these studies would materially affect our results.

4.10 Publication Bias

In general, Funnel Plots to assess publication bias for diagnostic test are of little value and so therefore we chose that examine this type of bias. (133)

4.11 Limitations of the study

There were several limitations in our systematic review. First, the nature of data collection used in this systematic review was done in a retrospective manner. Second, the unit of analysis used for each individual study was not standardized. Many studies, reported the unit of analysis as the patient (thrombus detected per patient) while others documented their unit of analysis as the vein (thrombus detected per vein in a lower limb and/or pelvis). This was a clear cause of the methodological heterogeneity and inconsistency seen in this meta-analysis (sensitivity and specificity estimates and I^2 scores). Thirdly, we were unable to use all of the 23 studies included in our qualitative review for the quantitative review as we were unable to abstract the needed data. As well, during our analysis, the statistical values extracted from the 2 x 2 tables in Moody et al. was rejected by the software used for meta-analysis for unknown reasons. We therefore, were unable to use all of the given data and only considered the results obtained for pelvic DVT from this paper. Finally, our motivation to perform this SRMA was to identify MRV as a possible non-invasive diagnostic tool to be used in special populations such as the obese. Unfortunately, none of the studies that we found in our literature search or that were included in our SRMA specifically studied the use of MRV in special

populations. We therefore, cannot make any conclusions as to the whether MRV is a useful diagnostic tool for detection of DVT in the obese patient.

4.12 Strengths of the study

The value of performing a systematic review and meta-analysis (SRMA) on observational studies has been questioned. However, SRMA of observational studies can provide valuable information and summarize diagnostic test accuracy. (Cochrane Handbook page 393-395). By pooling the breadth of information that exists on the topic and using strict criteria as noted in the Cochrane Handbook (pages 391-448), observational studies can make an important contribution to the literature with respect to questions regarding the diagnostic accuracy of specific tests. Despite the listed limitations, we believe that this review embraced the rigorous expectations as set forth by the Cochrane Review.

Strengths of our study include enlisting the help of our institutions expert librarians to perform a rigorous and thorough search of the literature using the index test and target condition as key terms, developing strict inclusion criteria that defined the target condition, reference standard, intended patient group, and the test under evaluation, careful assessment of the risk of bias and study applicability by utilizing the QUADAS-2 quality assessment tool. We completed 2 x 2 tables for each of our 23 studies and corrected for any discrepancies. For example in our reference article we found different sensitivities and specificities reported for Fraser 2002 et al, a different sensitivity for Larcom et al. and different specificities for Catalano and Carpenter. In the individual studies that were added to our review we found a different sensitivity and specificity reported for Evans 1996 & Spritzer and a different specificity for Jensen & Carpenter.

We accounted for the large heterogeneity in our studies by using a random effects model, and by completing subgroup and sensitivity analyses. The populations were very heterogeneous representing adults from around the world with a wide range of ages, of both sexes, and were both from inpatient and outpatient settings and as such made this study fairly generalizable to the general adult population. We also considered confounding within individual studies and assessed various forms of bias. (134) Finally, if a new test is to replace the existing test, it is important to compare the accuracy of both tests on the same population and with the same reference standard. (135) We did just that by performing our meta-analysis only on studies that used contrast venography as the gold standard.

4.13 Differences from the index study

We did a very thorough and extensive search that included the databases that were searched in our index reference article by Sampson et al.: Pubmed, Embase, Scopus, Web of Science and Cochrane. We also completed a hand search. Our final qualitative review included 23 studies, 9 more than our index reference study (Sampson 2007). Of the nine new included studies, 3 studies (Akhtar, Arnoldussen, and Ono) were published after 2007, the year of Sampson et al. publication. Additionally, we found 5 other studies (Aschauer, Montgomery, Stover, Spuentrup, and Moody) that were published before 2007, but that were not included in Sampson's review. Unlike Sampson et al. we only included studies using contrast venography as the reference standard for our main meta-analysis, whereas Sampson's review included studies which used X-ray venography, CT venography and duplex ultrasound as reference standards. As well, to account for the large amount of heterogeneity in the included studies we conducted subgroup analyses

including stratifying symptomatic versus asymptomatic DVTs and performed several sensitivity analyses for outliers. Sampson et al. used Meta-Disc software for running their meta-analysis. We also used this software but had the good fortune to use an updated version, which provided us with the value of inconsistency ($I^{2)}$, an additional value that helps assess heterogeneity within a pooled estimate. Finally, we performed a rigorous assessment of the risk of bias and applicability of each study of the 23 studies included in our review using the most recent and validated tool QUADAS-2 recommended by the Cochrane Review.

4.14 Implications for research and practice

Presently, the gold standard to detect DVT is an invasive study – contrast venography. While there are other diagnostic modalities to detect DVT, to date none have been shown to be comparable to contrast venography. Duplex U/S is a non-invasive and relatively inexpensive tool for the detection of DVT. It is limited by the poor anatomical view especially in the morbidly obese (not useful for pelvic DVT). (99, 105) Contrast enhanced CT venography has a better anatomical view, but has high risk of ionizing radiation and requires contrast material increasing the risk of allergic reactions and nephrotoxicity.(106) Alternatively MRV has been suggested as a non-invasive diagnostic tool. MRV provides better venous anatomy especially in the pelvic region. (98) This is essential in the diagnosis of DVT in special populations such as the obese, where thicker lower limbs and excessive fat tissue, obscuring the view of pelvic veins makes duplex ultrasound non-diagnostic. Since the systematic review and meta-analysis by Sampson and colleagues, additional studies have been published reporting the experience with

MRV as compared to other non-invasive modalities and the gold standard contrast venography.

We completed an exhaustive search of the literature and rigorous methods as set out by the Cochrane review in hopes of shedding more light on this subject. From our results we believe that while MRV may not replace ultrasound as the first-line modality for DVT detection, it should be considered as an alternative especially in special populations such as the obese where other diagnostic tools are not feasible. However, given the vast amount of heterogeneity found amongst the studies, larger patient cohorts are needed to validate the accuracy of this technique in a broader clinical setting (125) and a standardized unit value for analysis may yield a more consistent estimate and therefore provide better evidence. Also, further studies should be conducted to compare the diagnostic accuracy of MRV in patients for whom ultrasound is not feasible as a screening tool for DVT, such as the obese. Finally, a cost analysis study should be considered to compare MRV with other diagnostic modalities.

4.15 Author's conclusion

Our systematic review and meta-analysis did show significant sensitivity and specificity results of MRV comparable to contrast venography for detection of DVT. MRV is an underutilized, non-invasive diagnostic tool for the detection of DVT. It should be further considered for use in special populations such as the obese patient.

However, given the large amount of heterogeneity in the studies, it would be wise to continue investigating this comparison using improved study designs and more appropriate patient populations.

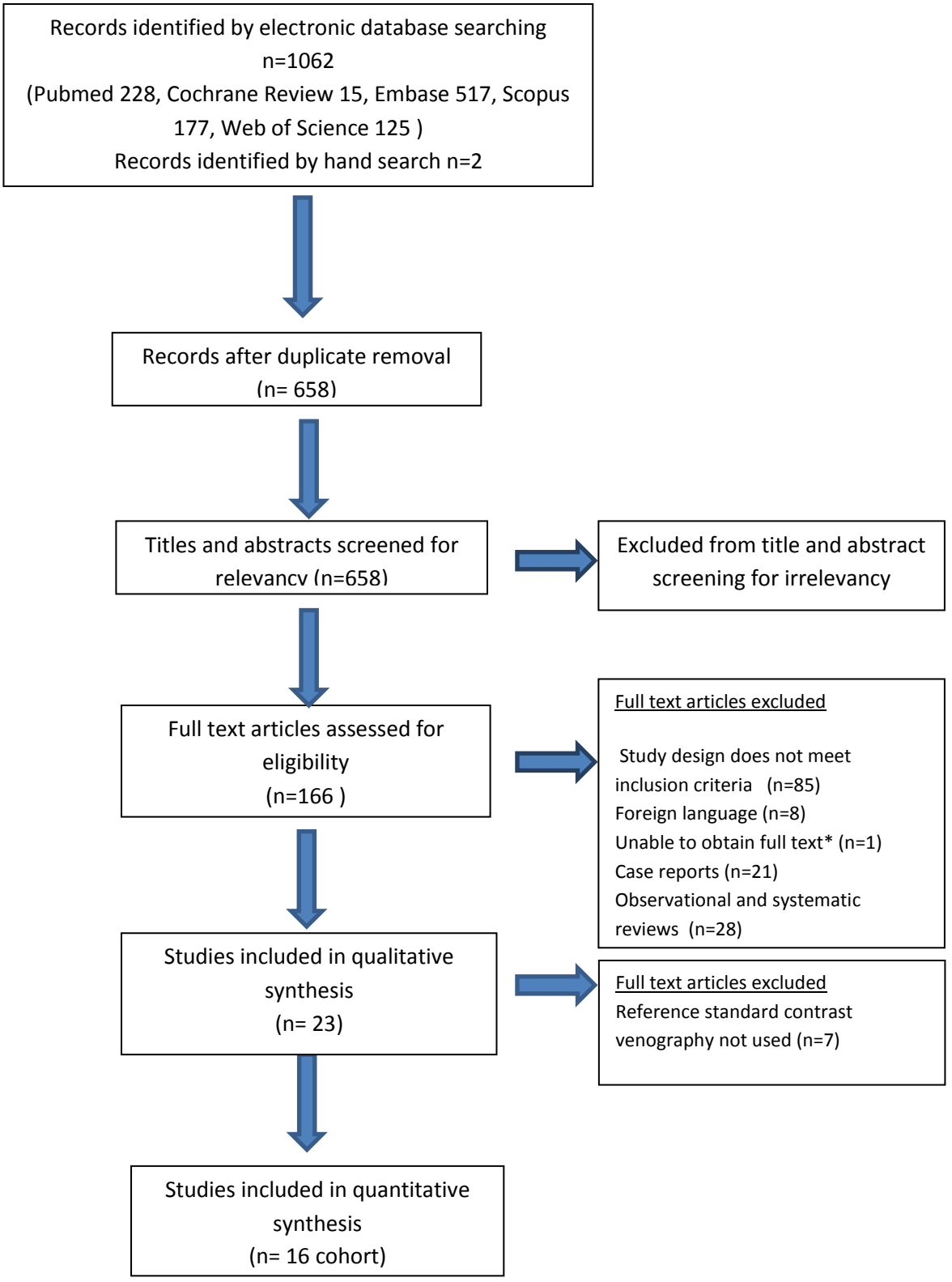
4.16 Potential Conflicts of Interest

There are no known conflicts of interest among members of our review group.

4.17 Acknowledgements

We would like to gratefully thank the librarians at the Welch Center who spent many hours working with us, instructing us, and guiding us through this intricate and detailed study design. Thanks to our team members who worked together diligently to move this protocol forward and get the work done.

Figure 4: MOOSE Diagram



*Cut off for acquiring full text articles from Weldoc (Johns Hopkins University Library Service) was March 10, 2014

Table 8 Characteristics of Included Studies

First author	Year	Study design	Country of origin	Origin of recruitment	n	Setting	Patients	Mean age (range)	Gender (M/F)	DVT (%)	Field strength (Contrast +/-)	Reference standard	Blinded MRV/ Reference standard	Independent reference standard
Arnoldussen	2012	Retrospective cohort	Netherlands	Academic hospital	40	Inpt	Symptomatic	46 (32-73)	19/21	71	1.5 T (-)	Duplex US	No/No	Yes
Akhtar	2010	Prospective cohort	Kingdom of Saudi Arabia	Academic hospital	31	Inpt	Symptomatic	* (18-85)	10/21	71	1.5 T (-)	Duplex US	Yes/Yes	Yes
Ono	2010	Prospective cohort	Japan	Academic hospital	32	Mixed	Mixed	69	8/24	20	0.5 T (-)	X ray venography	Yes/Yes	No
Cantwell	2006	Prospective cohort	Ireland	Academic hospital	24	ED	Symptomatic	(29-87)	11/13	42	1.5 T (-)	Contrast venography	Yes/Yes	Yes
Aschauer	2003	Prospective cohort	Austria	Academic Hospital	12	NR	Symptomatic	55 (21-75)	6/6	30	1.5 T (+)	X ray venography	No/No	Yes
Fraser	2003	Prospective cohort	England	Academic hospital	55	Mixed	Symptomatic	62 (28-86)	23/32	36	1.5 T (+)	Contrast venography	Yes/Yes	Yes
Fraser	2002	Prospective cohort	England	Academic hospital	101	Mixed	Symptomatic	(20-95)	NR	52	1.5 T (-)	Contrast venography	Yes/Yes	Yes
Stover	2002	Prospective cohort	USA	Academic hospital	30	Mixed	Asymptomatic	35 (16-70)	19/11	13	1.5 T (-)	Contrast venography, CT venography	Yes/ Unclear	No
Jensen	2001	Prospective cohort	Denmark	Academic hospital	27	Inpt	Asymptomatic	* (20-73)	15/12	22	1.5 T (-)	Contrast Venography	Yes/Yes	Yes
Sica	2001	Prospective cohort	USA	Academic hospital	14	Mixed	Symptomatic	53 (25-78)	6/8	50	1.5 T (-)	Contrast venography, Duplex US	Yes/Yes	Yes
Spuentrup	2001	Prospective cohort	Germany	Academic hospital	20	NR	NR	(14-88)	NR	58	1.5 T (-)	X ray venography, CT, Duplex US	Unclear/ Unclear	Yes

Moody	1998	Prospective cohort	England	Academic hospital	18	NR	Symptomatic	57 (26-89)	7/11	94	1.5 T (-)	Contrast venography	No/No	Yes
Catalano	1997	Prospective cohort	Italy	Academic hospital	43	NR	Symptomatic	NR	NR	79	1.5 T (-)	Contrast venography	Unclear/ Unclear	Yes
Evans	1996	Prospective cohort	USA	Academic hospital	75	NR	Symptomatic	58 (20-85)	34/41	35	** 1.5 T (-)	Duplex US	Yes/Yes	Yes
Laissy	1996	Prospective cohort	France	Academic hospital	21	NR	Symptomatic DVT/PE	50 (29-67)	16/21	71	1.0 T (-)	Contrast venography, Duplex U/S	Yes/Yes	Yes
Larcom	1996	Prospective cohort	USA	Academic hospital	203	Inpt	Asymptomatic	66 (28-86)	78/113	5	1.5 T (-)	Contrast venography	Yes/Yes	Yes
Montgomery	1995	Prospective cohort	England	Academic hospital	45	Inpt	Asymptomatic	41 (14-87)	30/15	33	1.5 T (-)	Contrast venography	Yes/Yes	Yes
Carpenter	1993	Prospective cohort	USA	Academic hospital	85	NR	Symptomatic	NR	NR	27	1.5 T (-)	Contrast venography, Duplex U/S	Yes/Yes	Yes
Evans	1993	Prospective cohort	USA	Academic hospital	64	NR	Symptomatic	54	34/27	14	1.5 T (-)**	Contrast venography	Yes/Yes	Yes
Spritzer	1993	Retrospective cohort	USA	Academic hospital	54	NR	Symptomatic	NR	NR	48	1.5 T (-)	Contrast venography, Duplex US	Unclear/ Unclear	Yes
Pope	1991	Prospective cohort	USA	Academic Hospital	17	NR	Symptomatic	NR	10/7	53	1.5 T (-)	Contrast venography	Unclear/ Unclear	Yes
Vukov	1991	Prospective cohort	USA	Academic hospital	10	ED	Symptomatic	NR	NR	50	1.5 T (-)	Contrast venography	Yes/Yes	Yes
Erdman	1990	Prospective cohort	USA	Academic hospital	100	Inpt	Mixed	(18-71)	55/45	52	0.35 T (-)	Contrast venography	Yes/Yes	Yes

*Median age was used instead of mean age. ** Contrast enhanced MRV was used only when the non-contrast MRV studies were equivocal.
Inpt=Inpatient ED=Emergency Department US=Ultrasound T-Tesla NR=not reported

Table 9: Bias and applicability

	Study	Risk of Bias				Applicability Concerns		
		Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
1	Akhtar 2009							
2	Arnoldussen 2012							
3	Aschauer 2003							
4	Cantwell 2006							
5	Carpenter 1993							
6	Catalano 1997							
7	Erdman 1990							
8	Evans 1992							
9	Evans 1996							
10	Fraser 2002							
11	Fraser 2003							
12	Jensen 2001							
13	Laissy 1996							
14	Larcom 1996							
15	Montgomery 1994							
16	Pope 1990							
17	Sica 2001							
18	Spritzer 1991							
19	Vukov 1990							
20	Ono 2010							
21	Stover 2001							
22	Spuentrup 2001							
23	Moody 1998							

Figure 5: Graphic representation of bias and applicability

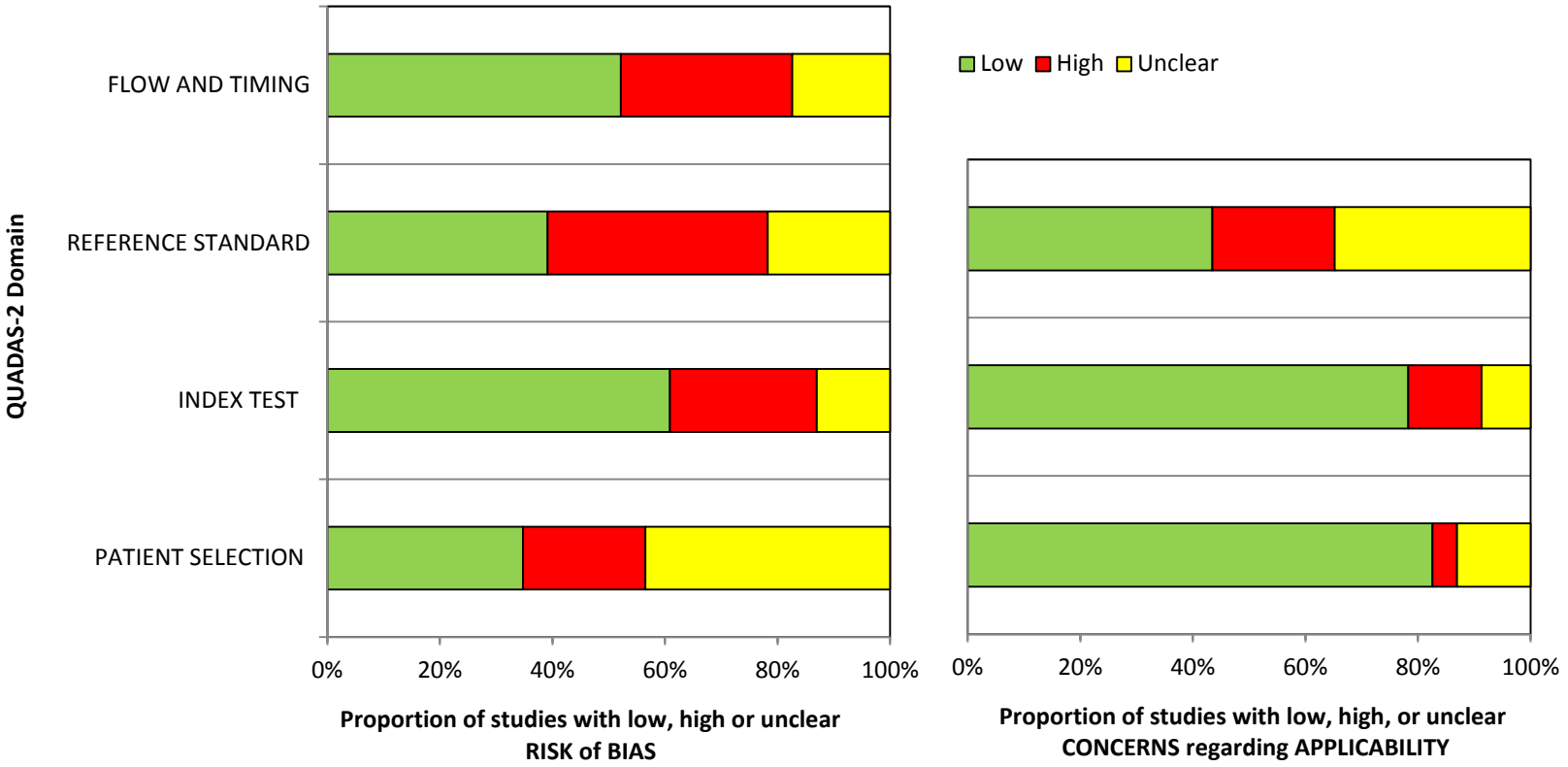


Figure 6: Forest plot for sensitivity of studies using CV as the reference

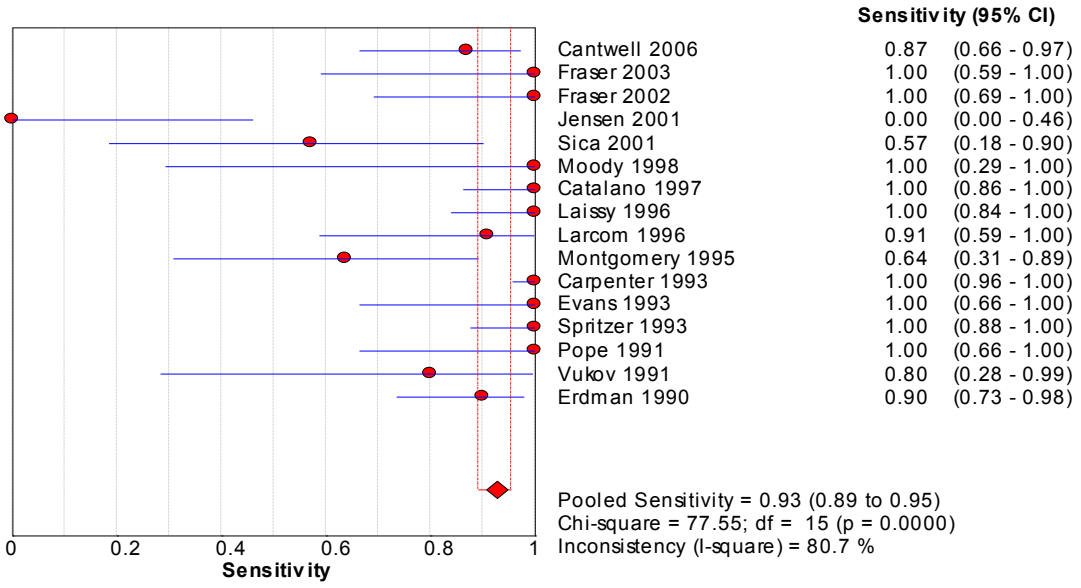


Figure 7: Forest plot for specificity of studies using CV as the reference

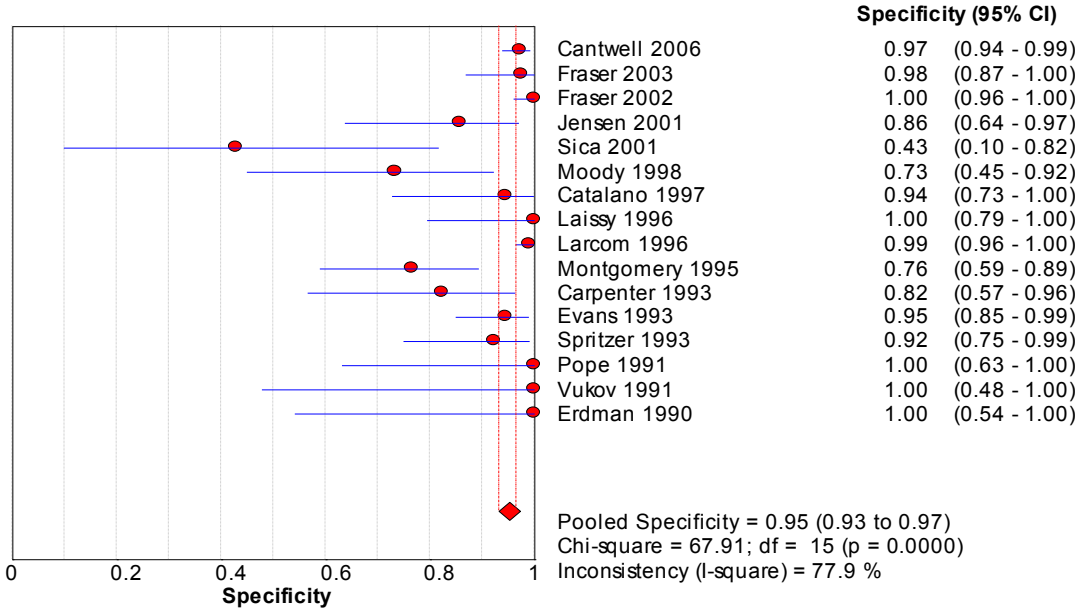


Figure 8 Forest plot for sensitivity of all included studies

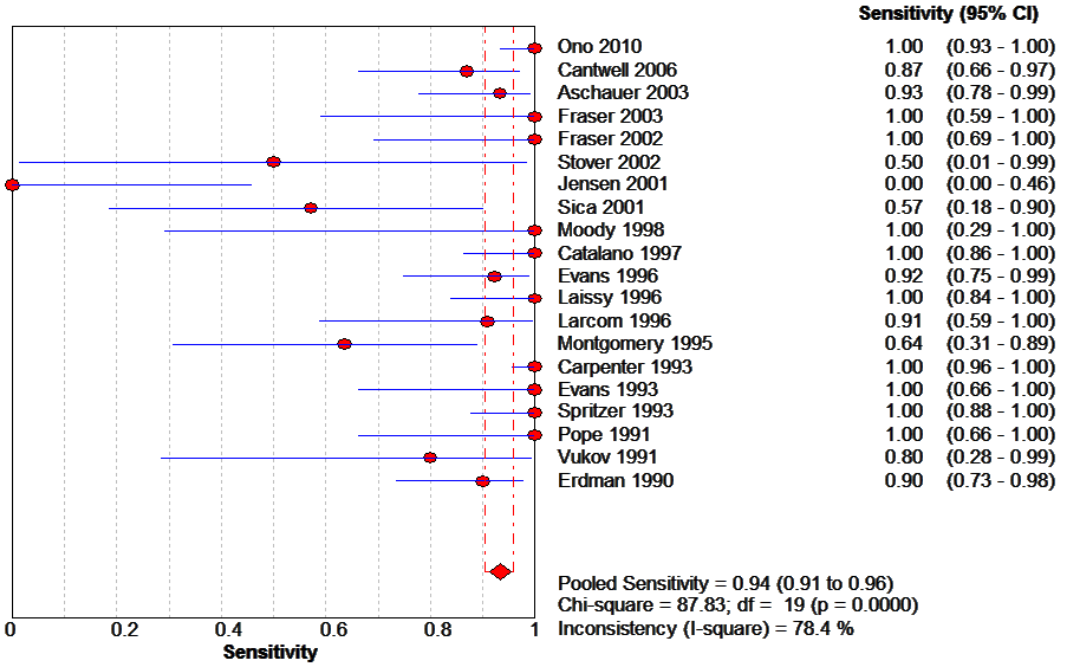


Figure 9 Forest plot for specificity of all included studies

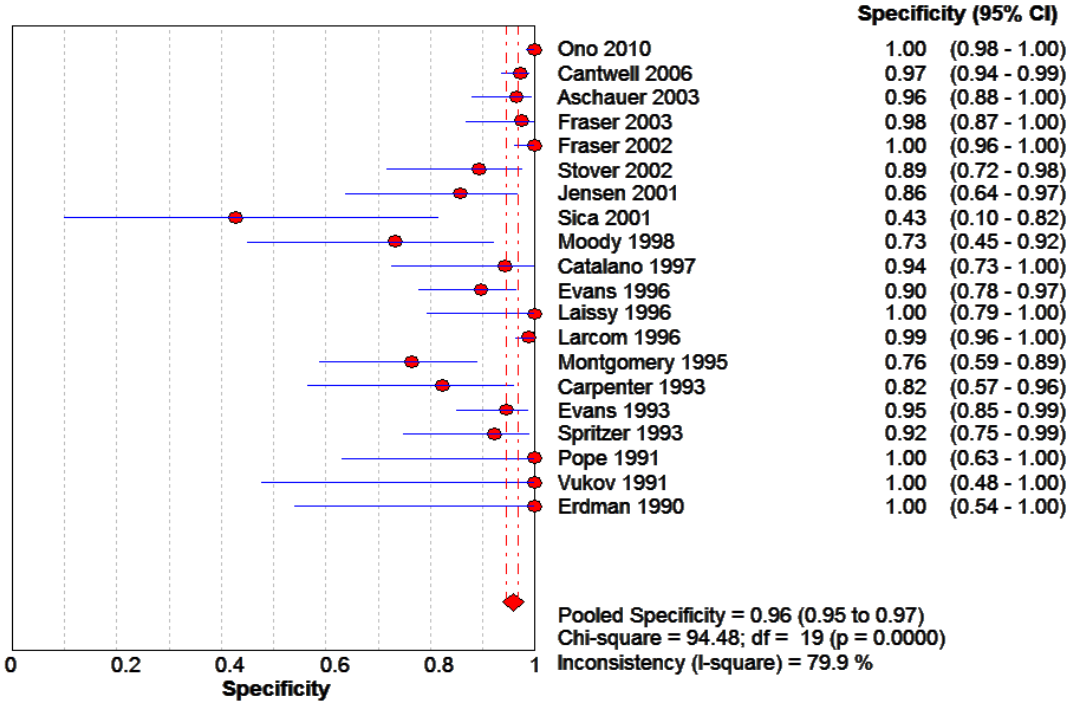


Figure 10 Forest plot for sensitivity of symptomatic DVT

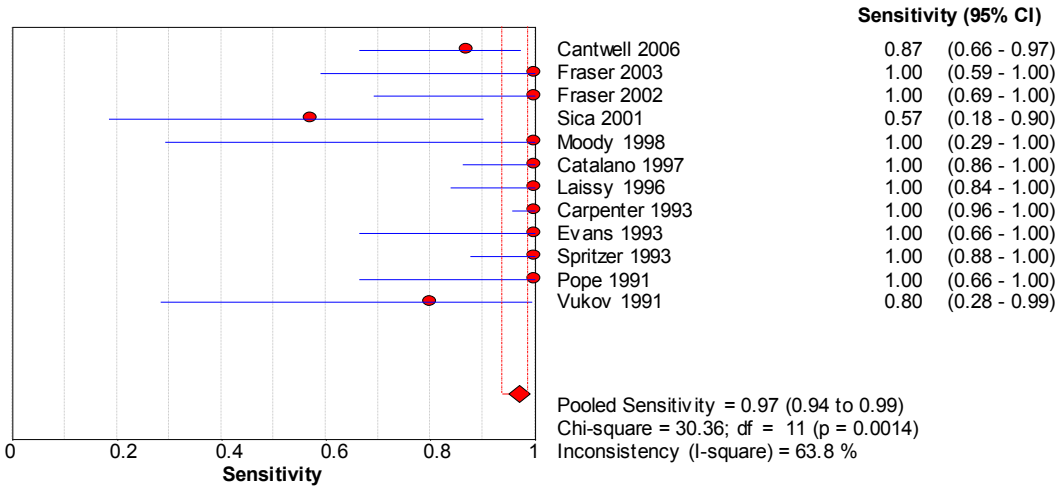


Figure 11 Forest plot for specificity of symptomatic DVT

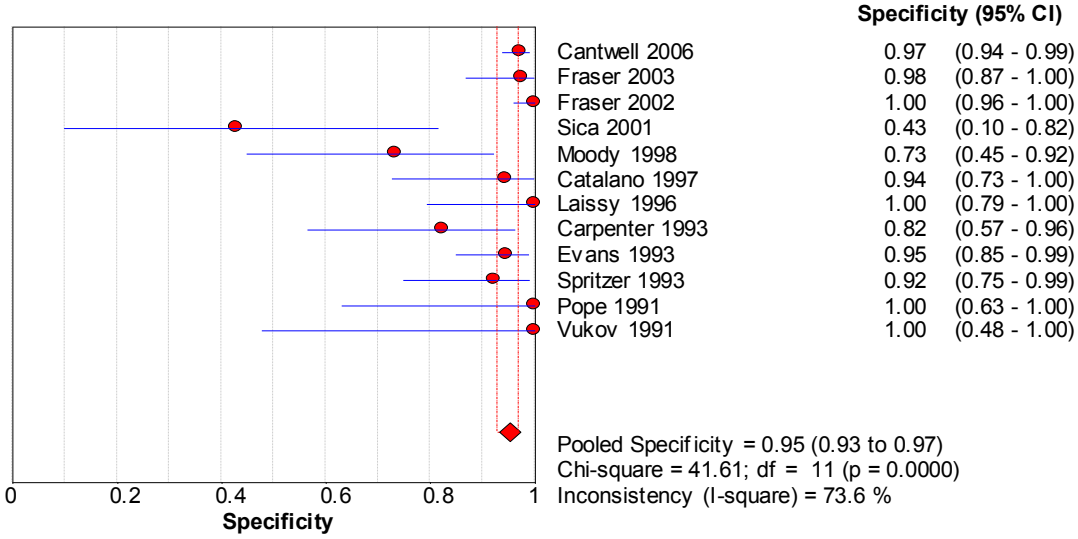


Figure 12 Forest plot for sensitivity of asymptomatic DVT

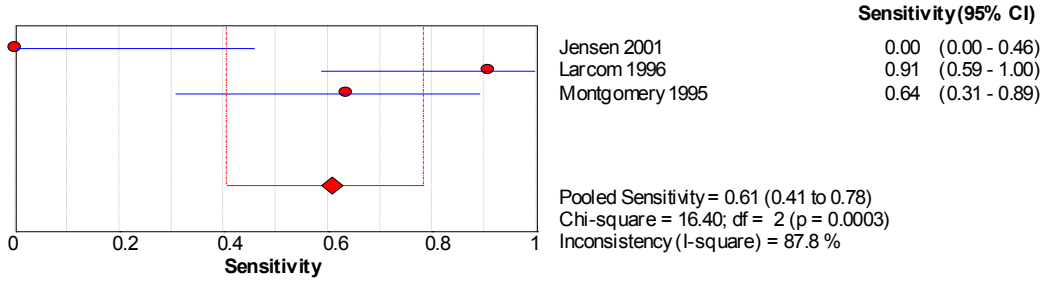


Figure 13 Forest plot for specificity of asymptomatic DVT

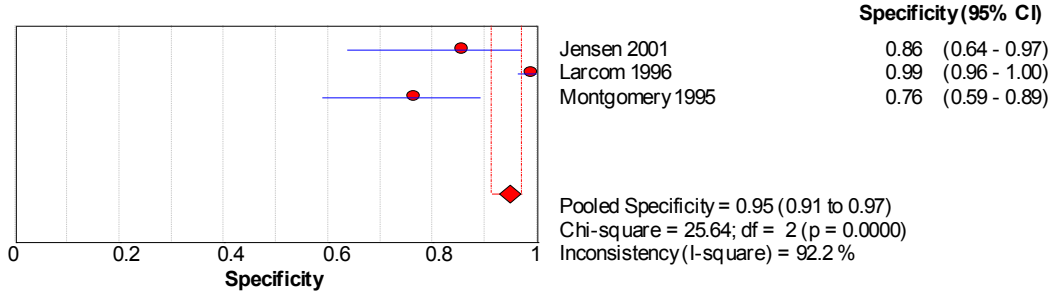


Figure 14 Sensitivity Analysis: Forest plot for sensitivity of asymptomatic DVT without Jensen

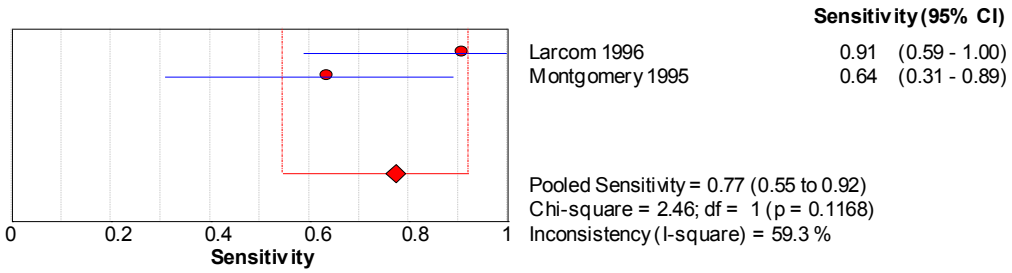


Figure 15 Sensitivity Analysis: Forest plot for specificity of asymptomatic DVT without Jensen

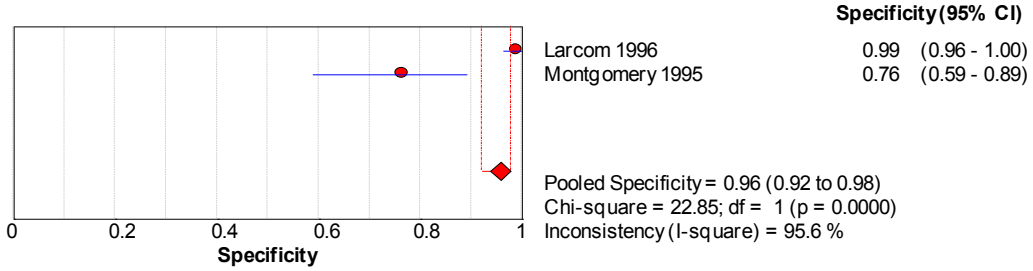


Figure 16 Sensitivity Analysis: Forest plot for sensitivity of main meta-analysis without outliers (Jensen)

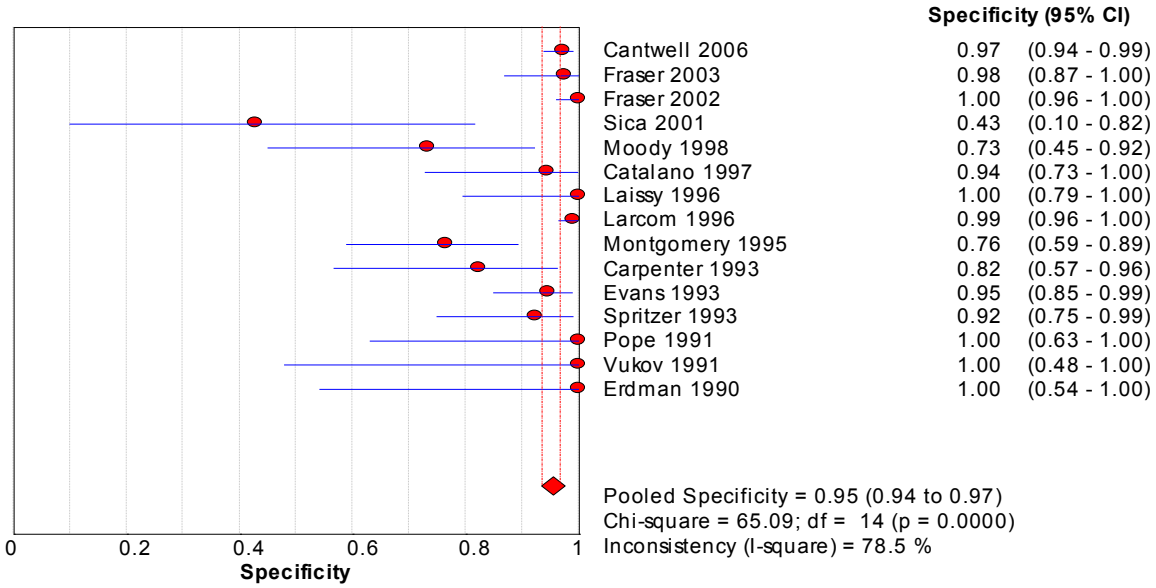


Figure 17 Sensitivity Analysis: Forest plot for specificity of main meta-analysis without the outliers (Jensen)

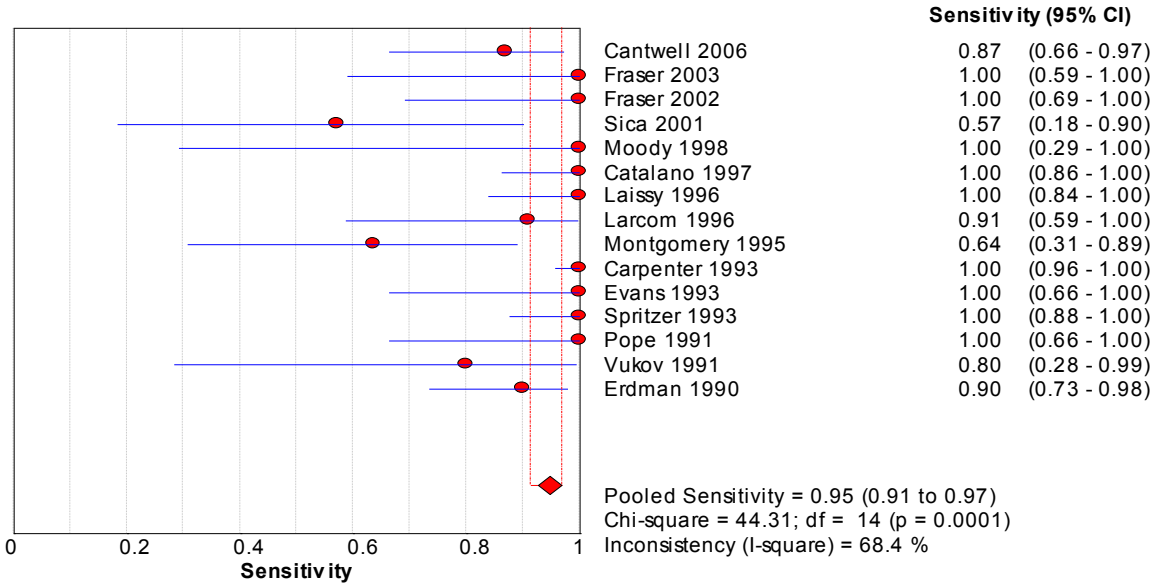


Figure 18 Sensitivity Analysis: Forest plot for sensitivity of main meta-analysis without outliers (Sica)

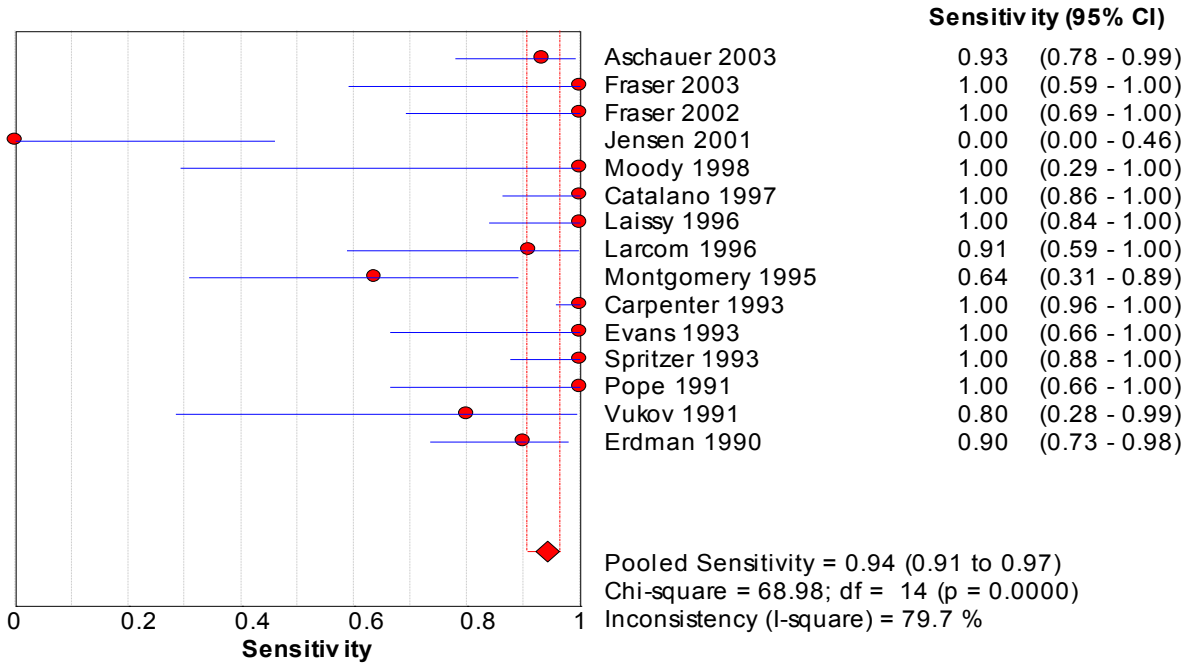


Figure 19 Sensitivity Analysis: Forest plot for specificity of main meta-analysis without outliers (Sica)

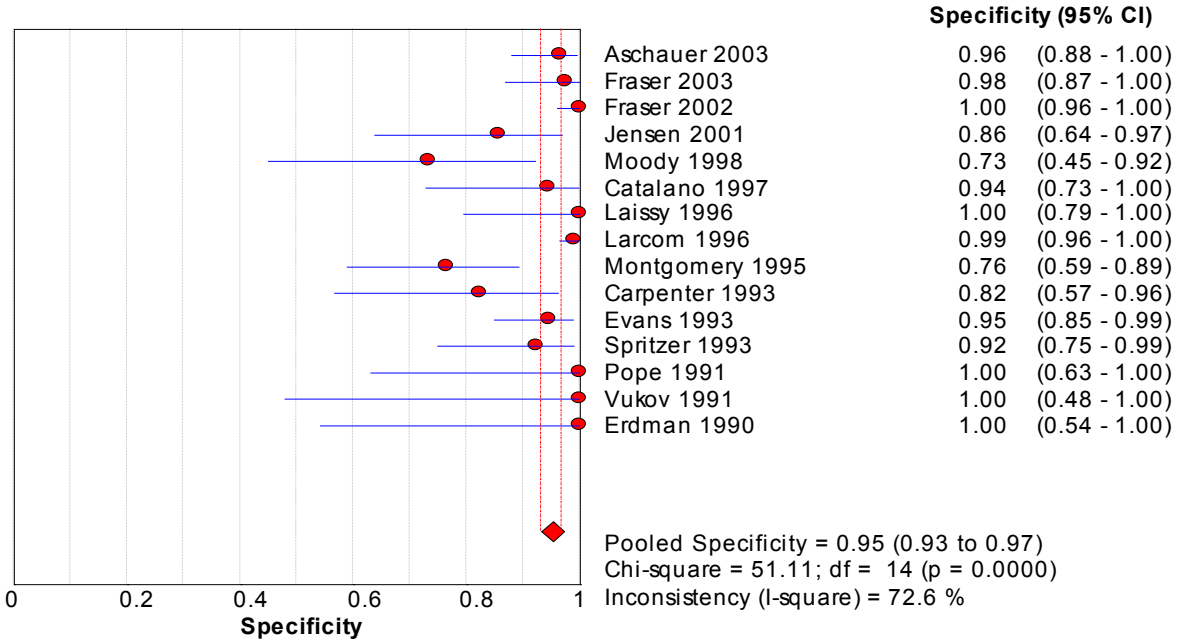


Figure 20 Sensitivity Analysis: Forest plot for sensitivity of main meta-analysis without outliers (Montgomery)

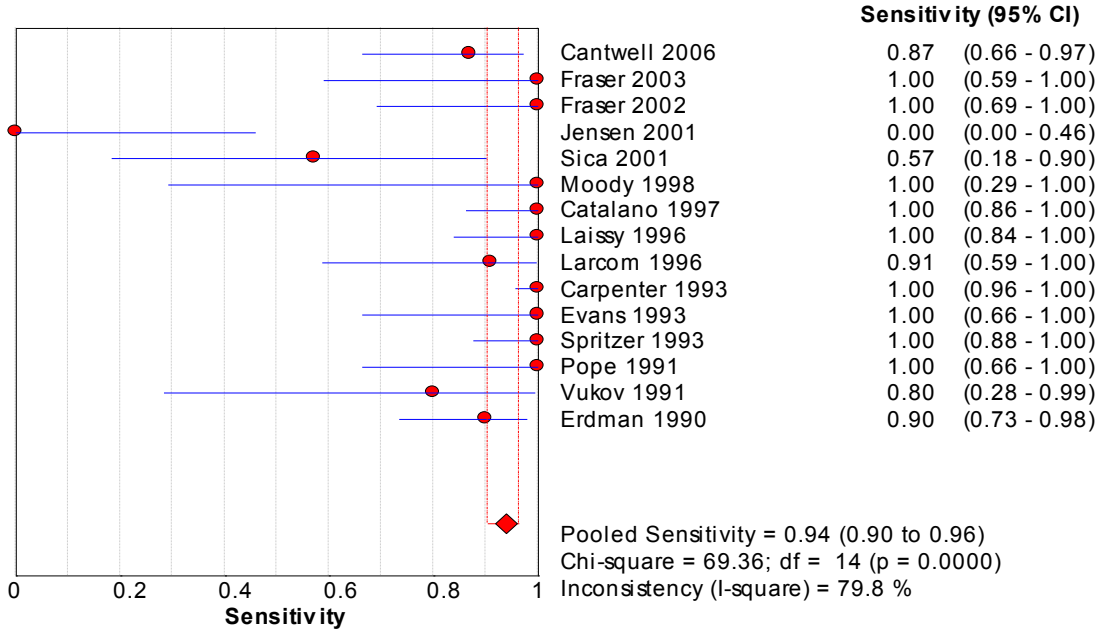


Figure 21 Sensitivity Analysis: Forest plot for specificity of main meta-analysis without outliers (Montgomery)

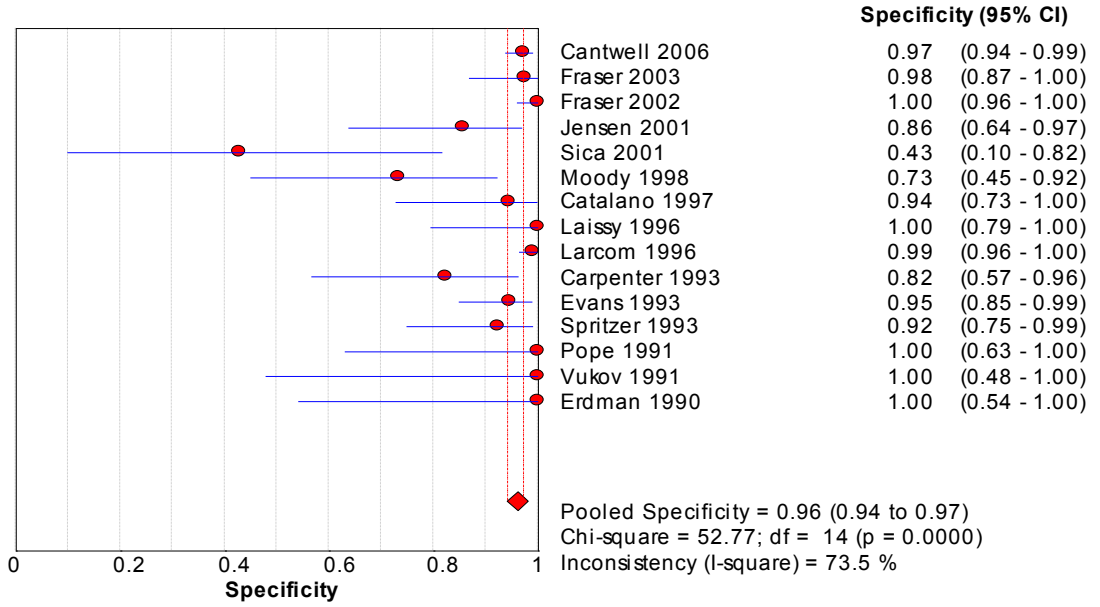


Figure 22 Sensitivity Analysis: Forest plot for sensitivity of main meta-analysis without the outliers (Jensen/Sica/Montgomery)

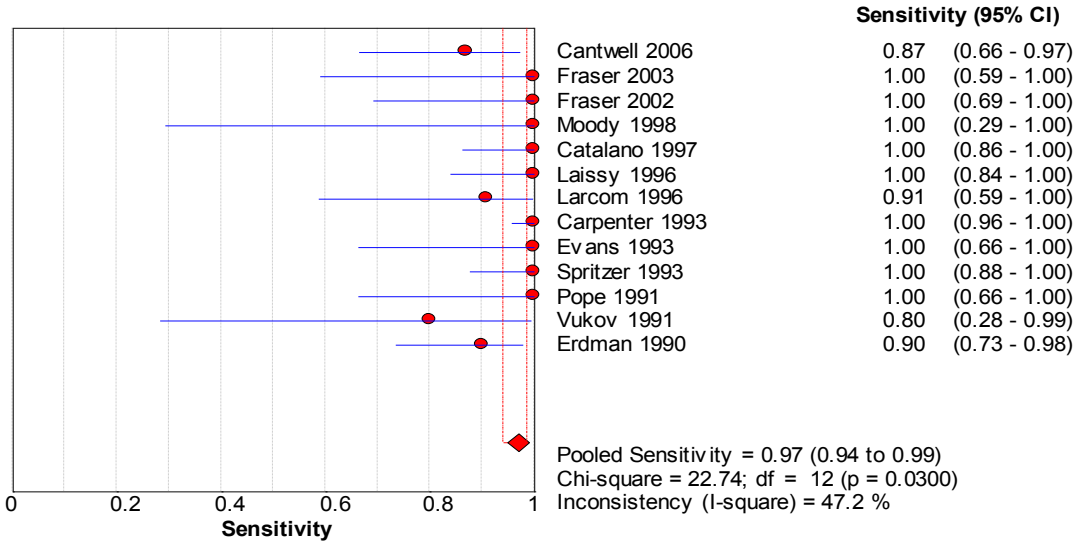
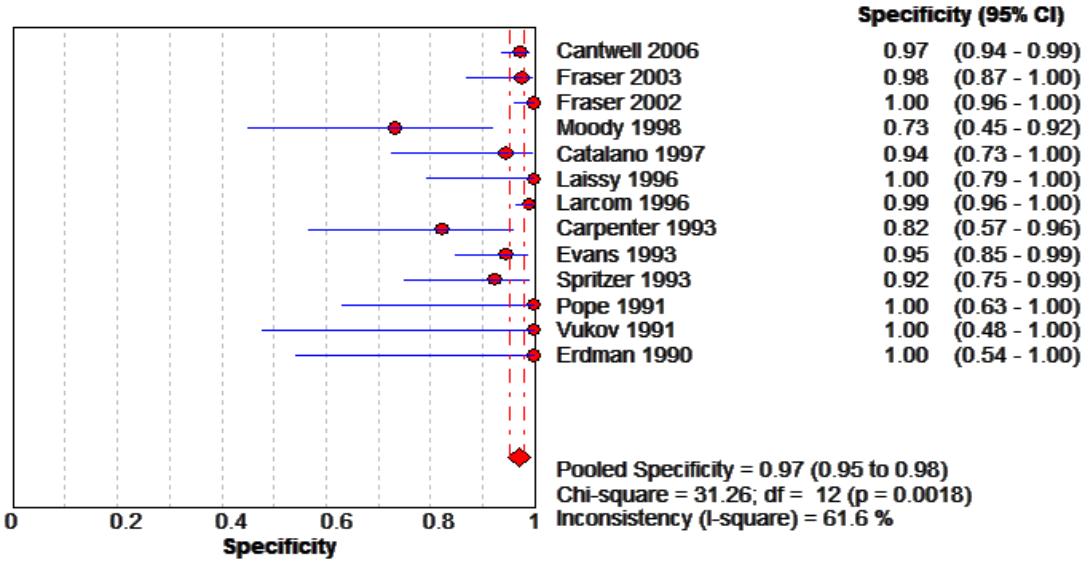


Figure 23 Sensitivity Analysis: Forest plot for specificity of main meta-analysis without the outliers (Jensen/Sica/ Montgomery)



Chapter 5 The EFFORT Trial

Enoxaparin versus **F**ondaparinux **For T**hromboprohylaxis in Bariatric Surgical Patients: A randomized double-blinded pilot trial

5.1 Abstract.

Context: Prophylaxis for venous thromboembolism (VTE) is routinely performed for all patients undergoing bariatric surgery. However, there is disagreement regarding the optimal dosing and duration of anticoagulant therapy. Furthermore, there is little data regarding the incidence of asymptomatic deep venous thrombosis (DVT) in this population.

Objective: To conduct a pilot study using magnetic resonance venography (MRV) to estimate the incidence of asymptomatic deep venous thrombosis (DVT) in bariatric surgical patients receiving enoxaparin or fondaparinux sodium during their perioperative hospitalization.

Design, Setting and Patients: From July 2010 to August 2013, one hundred and ninety-eight consecutive bariatric surgical patients from an academic institution were randomized in a double blinded manner to receive either enoxaparin 40 mg twice daily or fondaparinux sodium 5 mg once daily. Two weeks following surgery the patients returned to clinic to undergo magnetic resonance venography to detect the presence or absence of asymptomatic deep venous thrombosis.

Main Outcome Measures: The primary outcome was asymptomatic DVT. Secondary outcomes were attainment of therapeutic anticoagulation and symptomatic DVT. Safety outcomes were perioperative bleeding, perioperative complications, and death.

Results: Four of 175 patients evaluated developed DVT, two in each arm of the study. Nearly half (47.4%) of patients did not attain target prophylactic anti-factor Xa levels. Adequate anti-factor Xa levels were associated with fondaparinux use and elevated preoperative D-dimer level. No major adverse events occurred in either arm.

Conclusion: Both regimens appear to be equally effective at reducing the risk of DVT. Fondaparinux was much more likely to produce target prophylactic anti-factor Xa levels than enoxaparin. Further prospective studies are needed to determine the optimal DVT prophylaxis regimen in the bariatric surgical population.

5.2 Introduction

Morbid obesity has become epidemic in the United States in the 21st century. It is a major cause of chronic illness and disability, and an important risk factor for diabetes, cardiovascular disease, sleep apnea, and osteoarthritis. Treatment of obesity with lifestyle modification and pharmacologic therapy has yielded disappointing results (136). In contrast, bariatric surgical procedures—Roux-en-Y gastric bypass, laparoscopic sleeve gastrectomy, and laparoscopic adjustable gastric band—have been highly successful in producing sustained weight loss, and in reversing obesity-related co-morbidities (137, 138).

Despite a generally good safety record, bariatric surgery does carry a risk of complications, the two most important of which are anastomotic leak and venous thromboembolism (VTE) (90). Anastomotic leak is usually treated with percutaneous drainage or reoperation, while VTE, which includes deep venous thrombosis (DVT) of the pelvis and lower extremities and pulmonary embolism (PE), is treated with anticoagulation and/or placement of a vena cava filter (84, 139, 140). Anastomotic leak

and VTE prolong hospital stay and are the most common causes of postoperative mortality. In an era of increasing emphasis on patient safety, prevention of these adverse outcomes has taken on great importance. To that end, the American College of Surgeons and the American Society of Metabolic and Bariatric Surgeons have developed a certification program for Centers of Excellence in bariatric surgery, which specifies best practices in patient care. However, a standard dosing regimen for the chemoprevention of VTE in the obese bariatric population has yet to be established.

The usual approach to prevention of perioperative VTE involves early ambulation of the patient, use of pressure stockings, and administration of unfractionated or low molecular weight heparin anticoagulation. While these measures have been widely adopted in the bariatric surgical population, there remains disagreement regarding the optimal administration of pharmacologic VTE prophylaxis. Specifically, the choice of anticoagulant, dose, and duration of therapy remain to be established.

In order to assess the effects of different anticoagulation regimens, it is important to know the baseline frequency of perioperative VTE. Estimates of clinically apparent VTE following bariatric surgery range from 0.2% to 3.8% (3, 7, 71, 90); and symptomatic perioperative pulmonary embolism occurs at a rate of 0.7% to 2.4% (61). The prevalence of asymptomatic VTE in the bariatric surgical population is unknown. However, a post-mortem study by Melinek et al 2002 found that while only 20% of gastric bypass patients had been clinically diagnosed with pulmonary emboli prior to death, 80% had microscopic evidence of pulmonary emboli that likely contributed to their mortality (73).

At present, there are no trials comparing prophylactic anticoagulation regimens in the bariatric surgical population. However, the Enoxican II trial evaluated the use of

enoxaparin in patients with cancer undergoing pelvic or abdominal surgery, and found that 6-10 days of enoxaparin therapy at 40 mg daily resulted in a VTE rate of 12%. An additional 21 days of therapy at 40 mg daily reduced the rate to 4.8% (141). Even though the Enoxican II study was a randomized, blinded trial, the cancer patients were not morbidly obese and the applicability to bariatric patients is questionable. A retrospective study by Hamad, et al, reviewed the outcomes of 668 bariatric patients at five centers who received one of five different enoxaparin dosing regimens, ranging from a single 30 mg preoperative dose to 30 mg/day postoperatively for 10 days (21). The authors concluded that these dosing regimens were safe, yet no definitive conclusions were drawn regarding optimal dosing or duration. Further work by Hamad et al demonstrated that 40 mg twice daily of enoxaparin does not achieve adequate anti-factor Xa levels for prophylaxis of VTE in over half of postoperative gastric bypass patients (142). However; 60 mg twice daily has been shown to increase bleeding risk during the perioperative period (52, 143).

A clinical trial assessing the adequacy of perioperative anticoagulation for DVT prophylaxis requires an accurate means of detecting VTE. Most trials have used conventional invasive venography due to its excellent sensitivity and specificity. Indeed, venography is mandated in all trials submitted to the U.S. Food and Drug Administration for the indication of VTE prophylaxis. However, morbidly obese patients cannot undergo conventional venography due to the difficulty of obtaining venous access of the lower extremities. To avoid this problem, investigators have usually employed duplex ultrasound in place of venography. Unfortunately, the sensitivity of duplex ultrasound in the asymptomatic general population is poor (38 to 62%) (108, 109), and is likely worse

in the morbidly obese due to large lower extremities and the pannus that may overlie the inguinal region and obscure the view of the pelvic veins. Thus an alternative approach is needed. Magnetic resonance venography (MRV) has been performed using an open MRI scanner, and a recent prospective study reported a high sensitivity (92-98%) and specificity (90-100%) compared to standard venography (107, 120).

Our study compares two anticoagulation regimens, enoxaparin 40 mg twice daily and fondaparinux 5 mg once daily, for the prevention of perioperative VTE in the bariatric surgical patient. Enoxaparin and fondaparinux were chosen due to their different pharmacology, which may be expected to produce differences in efficacy and adverse events. In contrast to enoxaparin, fondaparinux is a synthetic molecule that specifically inhibits factor Xa via antithrombin. In addition, fondaparinux is 100% bioavailable, does not undergo metabolism, and may be dosed once daily. Our objectives were to determine (i) the incidence of asymptomatic DVT in each regimen, (ii) the feasibility of using MRV in the bariatric population, and (iii) the adequacy of anticoagulant dosing by measuring anti-factor Xa levels.

5.3 Materials and Methods.

5.3.1 Setting and Subjects

The study was conducted at an academic institution that is accredited by the American College of Surgeons Bariatric Surgery Network. From July 2010 to August 2013, patients were recruited and consented after meeting a standard set of preoperative requirements, including meeting with a bariatric dietitian and assessment by a clinical psychologist. Patients were eligible for the study if they were 18 years or older with a BMI of 35-59 kg/m^2 , and were undergoing laparoscopic vertical sleeve gastrectomy (VSG) or

laparoscopic Roux-en Y gastric bypass (LRYGB). Patients with contraindications to low molecular weight heparin or selective antithrombin III agonists, previous history of DVT or pulmonary emboli (PE), documented clotting/coagulation disorders, history of treatment for cancer within the last year, history of venous stasis or superficial thrombophlebitis, vein stripping or ligation, obesity hypoventilation syndrome, recent history of smoking (within the last year), and BMI>60 (who may have required extended DVT prophylaxis) were excluded. Other exclusion criteria were conditions that would be considered predispositions to increased bleeding including severe hepatic impairment, creatinine clearance of less than 30 ml per minute and a platelet count of less than 100,000 per cubic millimeter. Finally, women of childbearing age were excluded if they were pregnant or were taking estrogen based birth control medication up until less than one month prior to surgery.

The study received investigational review board approval at our institution and written informed consent was obtained from all patients before they underwent randomization. An Investigational New Drug (IND) application was submitted by the principal investigator to study fondaparinux (an approved product) at a once daily dosing of 5mg in the bariatric perioperative surgical patient. This proposal was approved by the United States Food and Drug Administration. A Data Safety and Monitoring Board met quarterly.

5.3.2 Study Design

Patients approved for either VSG or LRYGB underwent a thorough history and physical exam by the patient's primary care physician on a standard intake form. Demographics including age, sex, height, weight and body mass index (BMI), and medical

comorbidities including hypertension, hyperlipidemia, type II diabetes mellitus, sleep apnea, GERD and cancer were documented. All patients were contacted by the pre-operative evaluation clinic nurses, and were required to discontinue any non-steroidal anti-inflammatory drugs and other antiplatelet agents 14 days prior to surgery.

5.3.3 Randomization

After providing informed consent, consecutive patients were randomly assigned on the day of surgery in a 1:1 ratio to either enoxaparin or fondaparinux, using a computer-generated randomization scheme (Microsoft Excel 2007 data analysis tool pack). Uniform distribution was utilized. Variables were drawn with equal probability from all values in the range of 0 to 1. Each block of 4 contained equal number of enoxaparin and fondaparinux treatment assignments. Each successive study participant was randomized by selecting the next available treatment assignment in the random code.

5.3.4 Blinding

Investigational product was obtained as commercial syringes of enoxaparin 40 mg/0.4mL and fondaparinux 5 mg/0.4mL. At the time of dispensing contents of commercial syringes were transferred into a 1 milliliter syringe made by Becton Dickinson for blinding purposes. Due to the different dosing schedules of enoxaparin and fondaparinux, placebo doses were prepared to maintain the blind. Active and placebo syringes were prepared by our inpatient pharmacy and were not identifiable by external appearance. In accordance with current practice, the enoxaparin group received a dose of enoxaparin 40 mg subcutaneously on call to the operating room. To maintain blinding, patients randomized to enoxaparin received placebo (saline) injection six hours following surgery stop time. Beginning on post-operative day one, 40 mg of enoxaparin was administered

subcutaneously twice daily for the duration of the patients hospital stay. The fondaparinux group received a placebo on call to the operating room. Six hours following surgery stop time, the patients were given 5mg of fondaparinux subcutaneously. Beginning on post-operative day one, patients received 5 mg of fondaparinux subcutaneously once daily in the morning and placebo (saline) injection subcutaneously once daily in the evening for the duration of their hospital stay.

All patients had sequential compression devices and anti-embolic stockings placed prior to induction of anesthesia. Four to six hours following the surgery stop time; patients were ambulated in the hallways. Sequential compression devices were removed during ambulation. The use of aspirin, non-steroidal anti-inflammatory drugs, and other antiplatelet agents were prohibited during the patients hospital stay. Study drugs, enoxaparin and fondaparinux were discontinued at the time of patient discharge (average length of hospital stay = 2.5 days). Patients were educated on the importance of ambulation and exercise, and were encouraged to get up and move around at least every 30 minutes while recuperating at home.

5.3.5 Effectiveness of the treatment

Patients underwent outpatient magnetic resonance venography (MRV) of the pelvis and lower extremities between postoperative days 10 and 14. The studies were interpreted by two qualified radiologists independently. Each radiologist was blinded to the type of anticoagulation therapy the participant received, and reviewed the coronal reformatted multiple intensity projections and source axial images. If there was a discrepancy between the interpretations, the radiologists reviewed the studies together and came to a final consensus regarding the presence or absence of clot. If the MRV revealed an

asymptomatic DVT, the patient was immediately evaluated and treated appropriately. Incidental findings aside from asymptomatic or symptomatic DVT were also reported to the patient and their primary care physician.

5.3.6 Efficacy of the drug dose

Anti-factor Xa levels were drawn on all patients in both study arms, three hours after the first dose on post-operative day zero, immediately prior to the second dose on post-operative day one, and three hours after the second dose. All blood draws were performed according to the study schedule (Appendix A.5). The blood was collected in a sodium citrate tube, and analyzed using the standard hematology protocols of the Johns Hopkins clinical laboratory. Laboratory personnel were blinded to the source of the samples. Anti-factor Xa levels were determined using the Siemens Berichrom Heparin Assay to measure both the enoxaparin and the fondaparinux levels. Different calibrators were used for each assay thus allowing the lab to measure both drugs using the same reagent and accounting for the different target prophylactic ranges for the two treatment groups (enoxaparin: 0.2-0.6 IU/ml and fondaparinux: 0.39-0.50 mg/L) (143-145) .

5.3.7 Outcome Measures

The primary outcome was asymptomatic DVT, defined as a positive MRV within two weeks following surgery. The secondary outcomes were attainment of a target prophylactic anti-factor Xa level on the study drug, and symptomatic DVT. Attainment of a target anti-factor Xa level was determined based on blood samples drawn 6 hours after receiving the drug on post-operative day one. This cutoff was the standard for adequate prophylaxis used by the Johns Hopkins Hematology Lab: ≥0.20 IU/mL for enoxaparin

and ≥0.39 mg/L for fondaparinux. Safety outcomes included perioperative bleeding, perioperative complications and death.

5.3.8 Statistical Analysis

Statistical analysis was performed by intention-to-treat. Thus, all patients who were randomized were analyzed. Descriptive analysis included calculations of the means, medians and standard deviations for continuous variables and proportions for categorical variables. Univariable analyses comparing patient characteristics between treatment arms were conducted using Student t- tests for continuous variables and chi-square test or Fisher exact test for categorical variables as appropriate. A similar analysis was performed to evaluate the association of various risk factors with the incidence of DVT and with inadequate anti-factor Xa levels.

For statistical testing, $p<0.05$ (2-tailed) was considered significant. All statistical analyses were performed using Stata statistical software (version 12.1, StataCorp, College Station, Texas).

5.4 Results

5.4.1 Randomization

Three hundred and twenty bariatric surgical patients were screened for eligibility. One hundred and ninety-eight were randomized. Of the 122 patients who were not randomized, 19 refused to participate and 103 were not eligible. Of the 198 patients enrolled in the study, 184 (92.9%) were treated according to the protocol. Of the 14 patients that were not treated according to protocol, three were due to medication errors (one in the enoxaparin treatment arm and two in the fondaparinux treatment arm), and 11 were due to events that necessitated a modification of the treatment protocol (six in the

enoxaparin treatment arm and five in the fondaparinux treatment arm). There were 21 patients (15 in the enoxaparin treatment arm and 6 in the fondaparinux treatment arm) who were not evaluated for asymptomatic DVT because of inability to tolerate the MRV or because they missed the 10-14 day follow-up visit. While these patients did not undergo MRV they were evaluated by a qualified surgeon or nurse practitioner for symptomatic VTE during the standard of care two week post-operative check-up. No symptomatic VTEs were reported amongst any of the patients enrolled in this study. All 198 patients were followed up to two weeks post-operatively (Figure 24).

5.4.2 Baseline Characteristics

The two treatment arms were very homogenous with regard to gender, age, race, weight, height, and co-morbidities (all $p>0.05$). The majority of the patients were female (83.8%), with a mean age of 41.1 (SD ±9.6) and a mean pre-operative BMI of 45.4 (SD± 5.4). Seventy-five patients (37.9%) underwent laparoscopic vertical sleeve gastrectomy and 123 (62.1%) underwent laparoscopic Roux-en Y gastric bypass. The mean operative time for LRYGB and VSG was 202 (SD± 46) minutes and 156 (SD± 41) minutes respectively. The average length of stay (LOS) for the post-operative bariatric surgical patient was 2.4 (SD± 0.6) days. The patient's medical comorbidities associated with obesity included hypertension (52.5%), hyperlipidemia (30.8%), type II diabetes mellitus (27.8%), gastroesophageal reflux (30.8%), cancer (1.5%) and sleep apnea (37.9%). The pre-operative D-dimer (a marker for thrombotic potential) was elevated (≥0.88 mg/L) in 18.1% of patients (Table 10).

5.4.3 Primary Outcome

Of the 175 patients evaluated for asymptomatic DVT by MRV, there were four positive DVTs (2.3%) diagnosed and treated. Two DVTs occurred in the enoxaparin treatment arm and two in the fondaparinux arm (2.4% versus 2.2%, p=1.00). All four DVTs were large, and were located in the left iliac vein. (Figure 25) There were three patients (one in the enoxaparin treatment arm and two in the fondaparinux arm) that were diagnosed with DVT by one reader but not confirmed by the second reader. Even if these are added into the analysis, the resulting DVT incidence is not significantly different between the two treatment arms (3.6% for the enoxaparin treatment arm and 4.3% for the fondaparinux treatment arm; p=1.00).

In general the number of patients with DVT was too low to be able to assess possible risk factors. Patients with a DVT had a higher mean pre-operative BMI than patients without DVT (51.0 kg/m^2 versus 45.3 kg/m^2; p=0.04). Other factors that seemed to be associated with DVT incidence but which did not attain statistical significance included older age (49.5 years versus 40.6 years; p=0.06), Type II diabetes (75.0% versus 25.7%; p=0.06), and hypertension (100.0% versus 52.0%; p=0.12). Univariate analyses of the association between DVT and patient baseline characteristics are summarized in Table 11.

5.4.4 Secondary Outcome

Of the 198 patients in the study, 137 had valid anti-factor Xa data from the post-operative day one blood draw. Almost half of the patients (47.4%) were found to have inadequate anti-factor Xa activity as evaluated on post-operative day 1 at 6 hours after administration of drug. Furthermore, more patients reached target prophylactic anti-factor Xa levels on fondaparinux than on enoxaparin (74.2% versus 32.4%, p<0.001). The only baseline

variables that were found to be associated with attainment of target prophylactic anti-factor Xa level were an elevated pre-operative D-dimer level ($\geq$0.88 mg/L) and bariatric surgery procedure. Among patients who attained target anti-factor Xa levels, 25.0% had an elevated D-dimer versus 9.4% for those who were non-therapeutic (p=0.017). Among patients who were therapeutic, 52.8% underwent Vertical Sleeve Gastrectomy, versus 32.3% for those who were non-therapeutic (p=0.016). No symptomatic DVTs were found in our study. Univariable analyses of key clinical characteristics are summarized in Table 12.

5.4.5 Safety Outcomes

Eight patients experienced minor perioperative bleeding, three patients experienced atrial fibrillation, one patient had elevated creatinine and one patient had thrombocytopenia. Of the eight patients with bleeding none required transfusion, five had increased intraoperative bleeding, one had bright red blood per rectum on postoperative day one, one had melena on postoperative day one and one had an incidental finding of a rectus sheath hematoma that did not lead to dose adjustment.

There were no deaths in either treatment arm. Three patients (two in the enoxaparin and one in the fondaparinux treatment arm) experienced rapid atrial fibrillation post-operatively, which was controlled with medical intervention and eventually resolved. All three patients had a pre-operative history of intermittent atrial fibrillation that was not reported prior to screening and randomization. Minor bleeding, elevated creatinine, and thrombocytopenia were infrequent (Table 13).

Four patients (two in each treatment arm) were re-admitted for nausea, vomiting, and/or dehydration. Two patients (one in each treatment arm) experienced a post-operative rash.

These patients were evaluated by the inpatient dermatology service, who felt the rash was most likely secondary to perioperative antibiotics. One fondaparinux patient had high blood sugar, one fondaparinux patient had a low platelet count, and one enoxaparin patient had post-operative chest pain and shortness of breath. This patient was evaluated for VTE by duplex ultrasound and chest CT, which were both negative. A summary of adverse events can be found in Table 14.

5.4.6 **Discussion and Summary**

This is the first reported randomized double blinded study comparing two different chemoprophylactic agents for the prevention of VTE following bariatric surgery. We compared high dose fondaparInux (5 mg daily) with enoxaparin (40 mg twice daily). While previous studies in non-obese patients have used a 2.5 mg dose of fondaparinux for prophylaxis, we chose a 5 mg dose based on work suggesting that this dose would achieve target anti-factor Xa concentrations in morbidly obese patients more consistently than the 2.5-mg dose (146). Enoxaparin was dosed at 40 mg twice daily based on a previous study by Scholten et al (50).

Our study evaluated all patients for asymptomatic DVT post-operatively. Four patients (2.3%) were identified by MRV to have an asymptomatic DVT two weeks after undergoing uncomplicated bariatric surgery. This is similar to findings in the existing literature for perioperative bariatric patients (0.2 to 3.8%) (52, 90). However, given the potentially serious consequences of asymptomatic DVT, especially iliac vein thrombosis seen in this study, continued investigation of this phenomenon is warranted.

No difference in the rates of DVT was seen between enoxaparin and fondaparinux. However, the small sample size precludes any firm conclusions about the relative

efficacy of these medications. A surprising finding was the high prevalence of inadequate anticoagulation. More patients did not reach target anti-factor Xa levels in the enoxaparin group, a finding that has been suggested by other studies that have examined the dose-response relation of enoxaparin in bariatric surgical patients (147). An elevated preoperative D-dimer level was strongly associated with adequate levels of anti-factor Xa; the meaning of this interesting finding is unclear.

The strength of this study is that it is a double blinded randomized trial using a novel means of detecting DVT. There was homogeneity of both treatment arms allowing for precise comparisons between both study drugs. The population was fairly representative of a typical academic bariatric surgical center in the United States. There are several limitations to this study. First, we treated all cases as incident or new cases. However, we did not obtain baseline ultrasound data on all patients so that we cannot exclude the possibility that some of the clots may have existed prior to the study. Second, this study has a small sample size which made it impossible to draw any causal inferences. Larger trials are needed to confirm whether the two agents are equivalently efficacious at preventing DVT, or whether the striking difference in anti-factor Xa levels seen in our study will result in better clinical efficacy with fondaparinux.

As obesity becomes increasingly prevalent and the numbers of people undergoing bariatric surgery continues to increase, the need for effective and convenient anticoagulation dosing is essential. The American Society for Metabolic and Bariatric Surgery recently issued a position statement on VTE prophylaxis, which states that chemoprophylaxis should be considered in bariatric patients, but which does not specify a preferred regimen.(11) Results of this pilot study suggest that further trials need to be

conducted to determine the optimal agent and dosing for prevention of DVT in the obese population. Additional studies utilizing MRV should be conducted to demonstrate its usefulness in the detection of asymptomatic DVT.

Figure 24 Trial Profile: Enrollment, Randomization and Follow-up of Study Patients

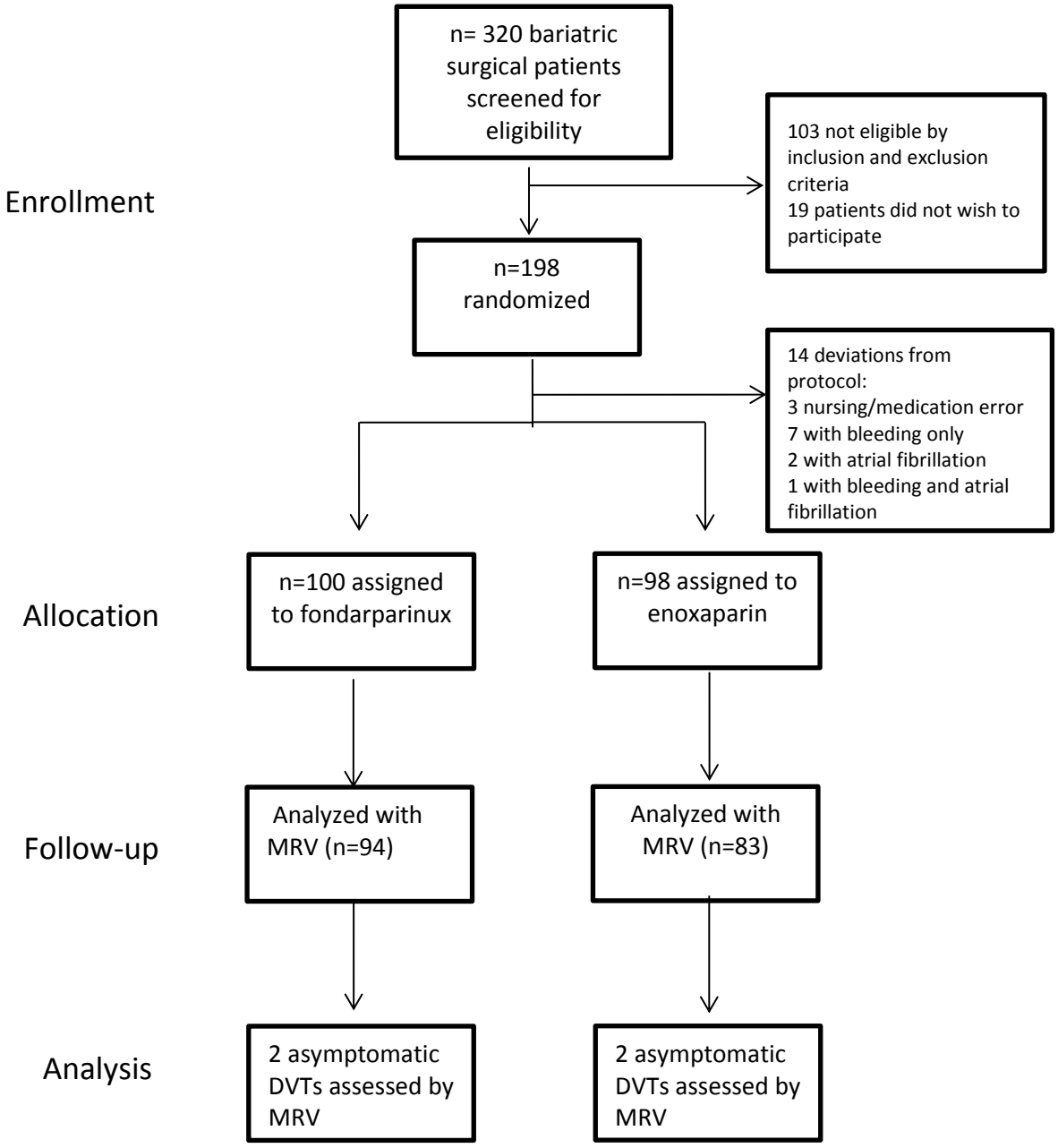


Table 10 Baseline Characteristics of Patients Treated with enoxaparin or fondaparinux

Demographics	**Enoxaparin n=98**	**Fondaparinux n=100**	**Total n=198**	**p-value**
Gender (%)				
Female	82(84.7)	84(84.0)	166(83.8)	0.95
Race (%)				
White, non-Hispanic	63(64.3)	65(65.0)	128(64.6)	
Black, non-Hispanic	31(31.6)	33(33.0)	64(32.3)	
Hispanic	3(3.1)	1(1.0)	4(2.0)	0.78
Age-years (range)	18-65	19-68	18-68	
(Mean ±SD)	41.8±9.0	40.4±10.2	41.1±9.6	0.30
Hospitalization				
Bariatric Procedure (%)				
Vertical Sleeve Gastrectomy	37(37.8)	38(38.0)	75(37.9)	
Roux-en Y Gastric Bypass	61(62.2)	62(62.0)	123(62.1)	0.97
Surgical Time-minutes (Mean ±SD)	183±51	187±49	185±50	0.63
Length of Stay (Mean ±SD)	2.4±0.8	2.5±0.8	2.4±0.8	0.21
Pre-op BMI (Mean ±SD) *	45.7±5.2	45.1±5.5	45.4±5.4	0.44
Pre-op D-dimer	0.9±3.7	1.5±4.4	1.2±4.1	0.30
Medical Comorbidities ∞				

Hypertension	55(56.1)	49(49.0)	104(52.5)	0.32
Hyperlipidemia	29(29.6)	32(32.0)	61(30.8)	0.71
Type II Diabetes Mellitus	27(27.5)	28(28.0)	55(27.8)	0.94
GERD	33.33.7)	28(28.0)	61(30.8)	0.39
Cancer	1(1.0)	2(2.0)	3(1.5)	0.57
Sleep Apnea	33(33.7)	42(42.0)	75(37.9)	0.23
Other Risk Factors				
Smoking status †				
Ever smoked	14(16.9)	17(19.8)	31(18.3)	0.63
Birth Control Pills	7(7.1)	8(8.1)	15(7.6)	0.80
Therapeutic on Study Drug (%) ¥	**2(2.8)**	**49(49)**	**51(37.2)**	**<0.001**

*BMI measured as kg/m^2
∞Medical comorbidities defined by patient's primary care physician
†Patients were all smoke free for at least two months prior to surgery as per standard protocol
□Patients on estrogen based birth control pills one month prior to surgery. All patients were free of birth control pills one month prior to surgery as per protocol.
¥ Therapeutic level for enoxaparin ≥ 0.60 IU/L and for fondaparinux ≥ 0.39 mg/L

Figure 25 MRV image of participant with left iliac vein blood clot

Table 11 Risk Factors for Development of Deep Vein Thrombosis

Demographics	**DVT n=4**	**No DVT n=171**	**Total n=175**	**p-value**
Gender (%)				
Female	3(75.0)	143(83.6)	146(83.4)	0.52
Race (%)				
White, non-Hispanic	3(75.0)	111(64.9)	114(65.1)	
Black, non-Hispanic	1(25.0)	55(32.2)	56(32.0)	
Hispanic	0(0.0)	3(1.7)	3(1.7)	1.00
Age-years (range)	43-56	18-65	18-65	
(Mean ±SD)	49.5±5.4	40.6±9.5	40.8±9.5	0.06
Hospitalization				
Bariatric Procedure (%)				
Vertical Sleeve Gastrectomy	2(50.0)	65(38.0)	67(38.3)	
Roux-en Y Gastric Bypass	2(50.0)	106(62.0)	108(61.7)	0.64
Surgical Time-minutes (Mean±SD)	150±27	187±50	196±50	0.14
Length of Stay (Mean ±SD)	2.5±0.8	2.4±0.8	2.4±0.8	0.85
Pre-op BMI (Mean ±SD) *	51.0±4.8	45.3±5.3	45.4±5.4	0.04
Pre-op D-dimer	0.5±0.4	1.3±4.4	1.2±4.3	0.73
Medical Comorbidities ∞				

Hypertension	4(100.0)	89(52.0)	93(53.1)	0.12
Hyperlipidemia	1(25.0)	53(31.0)	54(30.8)	1.00
Type II Diabetes Mellitus	3(75.0)	44(25.7)	47(26.9)	0.06
GERD	0(0.0)	49(28.6)	49(28.0)	0.58
Cancer	1(25.0)	1(0.6)	2(1.1)	0.045
Sleep Apnea	2(50.0)	68(39.8)	70(40.0)	1.00
Other Risk Factors				
Smoking status †				
Ever smoked	1(25.0)	28(19.0)	29(19.2)	0.58
Birth Control Pills	0(0.0)	13(7.6)	13(7.5)	1.00
Fondaparinux Treatment Arm	2 (50.0)	96 (50.0)	98 (50.0)	1.00
Therapeutic on Study Drug (%) ¥	1(33.3)	42(36.5)	43(36.4)	1.00

*BMI measured as kg/m^2
∞Medical comorbidities defined by patient's primary care physician
†Patients were all smoke free for at least two months prior to surgery as per standard protocol
□Patients on estrogen based birth control pills one month prior to surgery. All patients were free of birth control pills one month prior to surgery as per protocol.
¥ Therapeutic level for enoxaparin ≥ 0.20 IU/L and for fondaparinux ≥ 0.39 mg/L

Table 12 Baseline Characteristics of Patients with and without Therapeutic Dose

Demographics	**Therapeutic n=51**	**Non-Therapeutic n=86**	**Total n=137**	**p-value**
Gender (%)				
Female	44(86.3)	74(86.0)	118(86.1)	0.97
Race (%)				
White, non-Hispanic	36(70.6)	49(57.0)	85(62.0)	
Black, non-Hispanic	13(25.5)	34(39.5)	47(34.3)	
Hispanic	1(2.0)	2(2.3)	3(2.2)	0.40
Age-years (range)	25-68	18-65	18-65	
(Mean ±SD)	42.2±10.5	40.4±9.0	41.0±9.6	0.28
Hospitalization				
Bariatric Procedure (%)				
Vertical Sleeve Gastrectomy	24(47.1)	35(40.7)	59(43.1)	
Roux-en Y Gastric Bypass	27(52.9)	51(59.3)	78(56.9)	0.47
Length of Stay (Mean ±SD)	2.4±0.7	2.4±0.9	2.4±0.8	0.78
Pre-op BMI (Mean ±SD) *	45.4±5.9	46.3±5.4	45.9±5.6	0.36
Pre-op D-dimer	1.4±4.7	0.9±3.9	1.1±4.2	0.52
Medical Comorbidities ∞				

Hypertension	21(41.2)	45(52.3)	66(48.2)	0.21
Hyperlipidemia	14(27.4)	21(24.4)	35(25.6)	0.69
Type II Diabetes Mellitus	13(25.5)	22(25.6)	35(25.6)	0.99
GERD	15(29.4)	29(33.7)	44(32.1)	0.60
Cancer	1(1.5)	1(1.4)	2(1.5)	0.94
Sleep Apnea	23(45.1)	30(34.9)	53(38.7)	0.23
Other Risk Factors				
Smoking status †				
Ever smoked	10(25.6)	13(18.8)	23(21.3)	0.41
Birth Control Pills	4(7.8)	5(5.8)	9(6.6)	0.64
Pre-op D-dimer ≥0.88	25(29.4)	9(10.6)	24(17.6)	0.005
Fondaparinux Treatment Arm	49(96.1)	17(19.8)	66(48.2)	<0.001

*BMI measured as kg/m^2
∞Medical comorbidities defined by patient's primary care physician
†Patients were all smoke free for at least two months prior to surgery as per standard protocol
□Patients on estrogen based birth control pills one month prior to surgery. All patients were free of birth control pills one month prior to surgery as per protocol.
¥ Therapeutic level for Enoxaparin ≥ 0.20 IU/L and for Fondaparinux ≥ 0.39 mg/L

Table 13 Primary, Secondary and Safety Outcomes

Outcome	Enoxaparin	Fondaparinux	Total	Fisher's exact p-value
Primary Outcome	**n=83**	**n=92**	**n=175**	
Asymptomatic DVT (%)	2(2.4)	2(2.2)	4(2.3)	1.00
Secondary Outcome	**n=71**	**n=66**	**n=137**	
Therapeutic on Drug	23(32.4)	49(74.2)	72(52.5)	<0.001
	n=98	**n=100**	**n=198**	
Symptomatic DVT	0(0.0)	0(0.0)	0(0.0)	1.00
Safety Outcomes	**n=98**	**n=100**	**n=198**	
Minor Bleeding (%)	5(5.1)	3(3.0)	8(4.0)	0.49
Increased Creatinine (%)	0(0.0)	1(1.0)	1(0.5)	1.00
Rapid atrial fibrillation (%)	1(1.0)	1(1.0)	2(1.0)	1.00
Thrombocytopenia (%)	0(0.0)	1(1.0)	1(1.0)	1.00

Table 14 Incidence of Adverse Events

Adverse Event	Enoxaparin (n=98)	Fondaparinux (n=100)	Total n=(198)
Intra-operative bleeding	4 (4.1%)	2 (2.0%)	6 (6.1%)
Rectus sheath hematoma	0 (0.0%)	1 (1.0%)	1 (0.05%)
Melena	1 (1.0%)	0 (0.0%)	1 (0.05%)
Bright red blood per rectum	1 (1.0%)	0 (0.0%)	1 (0.05%)
Rapid atrial fibrillation	2 (1.0%)	1 (1.0%)	3 (1.5%)
Elevated creatinine	0 (0.0%)	1 (1.0%)	1 (0.05%)
Thrombocytopenia	0 (0.0%)	1 (1.0%)	1 (0.05%)
Rash	1 (1.0%)	1 (1.0%)	2 (1.0%)
Nausea and vomiting	2 (1.0%)	2 (2.0%)	4 (2.0%)

Chapter 6 Public health-based approaches and future work in the prevention of VTE in this special population.

6.1 Public Health Relevance

In recent years there has been a marked increase in the awareness of patient safety with special attention focused on VTE prevention at both the federal and national level. Programs have been implemented to raise public and healthcare awareness, increase surveillance and research efforts with specific goals to reduce VTE events and improve outcomes in the hospitalized patient. Moreover, it is well recognized that in certain special populations such as the obese surgical patient, the risk of VTE may be three times as high as the general population. (148)

In 2011, a new program was developed by the U.S. Department of Health and Human Services (Partnership for Patient Better Care, Lower Costs) aimed at reducing the number of preventable VTE cases in the hospitalized patient. (15) Using the National Hospital Discharge Survey (NHDS) the CDC estimated that between 2007 to 2009 there were over 500,000 VTE events in hospitalized adult patients (>18yrs old) within the United States. (149) They recognized that the majority of DVT and PE events could be prevented and that there was opportunity to reduce disease burden via implementation of evidence-based prevention strategies within the hospital setting. Simply, this could be achieved by using appropriate administration of prophylaxis which may include pharmacologic agents or mechanical devices.

Johns Hopkins Bayview Medical Center recognized that their VTE event rates were higher than the national average and therefore created a VTE task force committee with the main goal of reducing the VTE events in their hospital population.

6.2 Previous work

6.2.1 Invited Presentations

On March 10, 2010 I was invited to be a guest speaker at the Johns Hopkins Hospital 2nd Annual Symposium In Recognition Of DVT Awareness Month. My topic of discussion was the Prevention of VTE in the Bariatric Surgical Patient: Barriers specific to VTE prevention in bariatric surgical patients and, how to overcome these barriers. This presentation is now archived on the Johns Hopkins website under Educational Videos.

http://webcast.jhu.edu/Mediasite/Play/12c7e4266bcb4a98b76b9b60605895c7

Figure 26 The Johns Hopkins Symposium in Recognition of DVT Awareness Month 2010

Home > News and Publications > For the Media > Current News Releases

Johns Hopkins Hospital Symposium In Recognition Of DVT Awareness Month

Release Date: March 10, 2010

WHAT:

Johns Hopkins Hospital symposium in recognition of DVT Awareness Month

WHEN:

Friday, March 5

8 a.m. – 12 p.m.

WHERE:

Johns Hopkins Hospital's Hurd Hall

600 North Wolfe Street

Baltimore, Md.

DETAILS:

It has rightly been called a silent epidemic. Deep vein thrombosis (DVT), which affects up to

FOR THE MEDIA

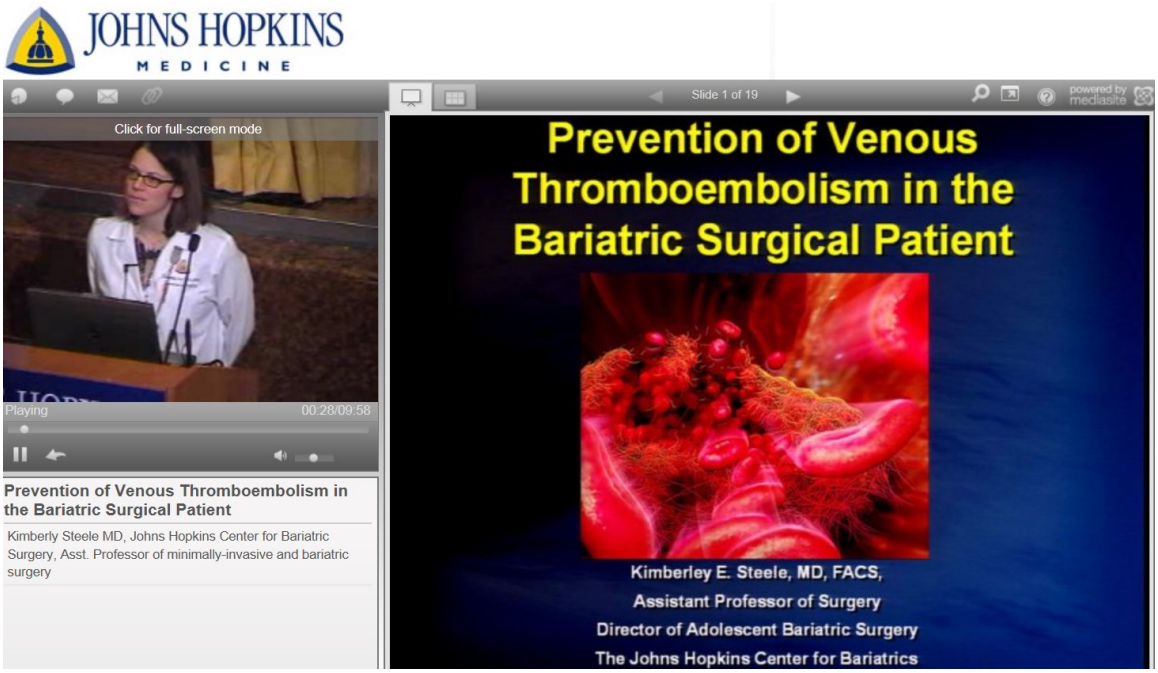
PRESS CONTACT:

To cover the event, set up interviews or for further details, call John M. Lazarou at 410-502-8902 or e-mail **Jlazaro1@jhmi.edu** . Hopkins faculty members are available for press interviews.

Useful Links

- Contact JHM Media Team
- Find a Doctor
- Search Contacts by Beat

Figure 27 Educational Video: Prevention of Venous Thromboembolism in the Bariatric Surgical Patient by Kimberley E. Steele, M.D.



6.2.2 Invited Committees

In 2011, I was honored to be asked to represent surgery, more specifically bariatric surgery to become a member of a task force/committee to work on improved ways to prevent VTE during a hospital admission. The Johns Hopkins Bayviwe Medical Center had a higher than national average of in hospital VTE rates and needed to address this problem. The committee included an orthopedic surgeon, an obstetric and gynecologic surgeon, a bariatric surgeon (this author), a hospitalist, a physical therapist and a pharmacist. We met once a week for 10 months reviewing hospital data, previous preventative measures, completing staff surveys and then finally making recommendations for improvement.

Our recommendations included:

1. We created education pamphlets for distribution to our patients during their hospital admission. (Figure 28)

2. Standard protocols that were part of order sets. (Figure 29)

3. Mandatory questionnaires that a physician had to fill in while completing hospital admission orders. This questionnaire ascertained the VTE risk profile for the patient and then provided VTE recommendations. (Figure 30)

4. Alerts while completing orders. Physicians are unable to finish hospital admission orders until the proper VTE prophylaxis was ordered.

5. Creation of educational material for our patients including extended prophylaxis and Coumadin teaching.

Figure 28: Screenshot of VTE Educational Pamphlet

Ankle exercises should be done as often as possible. They can be done while lying on your back with your legs spread slightly apart or while sitting at the edge of your bed.

Rotations: Slowly move one foot clockwise in a circle. Repeat this movement five times on each foot. Then slowly move one foot in a counter-clockwise circle. Repeat this movement five times on each foot.

Stretches: Keeping your knee straight, flex one foot toward your body, hold for five seconds, then stretch it away from your body and hold for five seconds. Repeat this exercise five times on each foot.

To get out of bed safely:

- Tighten your stomach muscles.
- Roll onto your side, moving your body as one unit. Don't twist.
- Scoot on your side to the edge of the bed.
- Push your body up with one elbow and the opposite hand. As you push up, gently swing both legs to the floor. Keep your stomach tight as you push up.

We are here to help with every step of your recovery. Please don't hesitate to ask if you ever have questions or need assistance.

JOHNS HOPKINS MEDICINE

Preventing Deep Venous Thrombosis and Pulmonary Embolism

JOHNS HOPKINS MEDICINE

At Johns Hopkins Bayview Medical Center, we want you to recover well. One key to a successful recovery is the prevention of deep venous thrombosis (DVT) and pulmonary embolism (PE). A DVT is a blood clot that can form in the large vessels of the arms, legs and pelvis. If the clot becomes dislodged, it can travel to the lungs. This is called a PE, which can be life-threatening.

Patients play an important role in preventing DVT and PE. By reading this booklet and completing the exercises as described, you are working toward a successful recovery.

Risk Factors for DVT and PE:

- Immobility/bed rest
- Surgery
- Previous DVT or PE
- Pregnancy
- Smoking
- Previous use of birth control pills
- Obesity
- Cancer
- Clotting problems (certain genetic disorders)

Your Doctor May Recommend:

- Early and frequent walking
- Leg/ankle exercises
- SCDs (sequential compression devices)
- TED compression hose
- Blood thinners (oral or injected)

Prevent DVT and PE by:

- Doing leg and ankle exercises if recommended by your doctor, nurse or physical therapist.
- Walking early and often, as soon as your doctor gives you permission. Please ask for your nurse's help the first time you get out of bed.
- Wearing your SCDs while you are in bed and making sure that the devices are working. They can be uncomfortable, but they save lives.
- Wearing your TED compression hose at all times.

General Expectations:

Level 1

- Ankle exercises every hour when awake.

Level 2

- Ankle exercises every hour when awake.
- Move out of bed and into the chair; walk to the bathroom. **(Please ask your nurse for assistance the first time you get out of bed.)**

Level 3

- Ankle exercises every hour when awake.
- Walk 10 feet in hall (two markers) twice in the morning.
- Walk 20 feet in hall (four markers) twice in the afternoon.

Level 4

- Ankle exercises every hour when awake.
- Walk 30 feet in hall (six markers) four times.
- Get of bed for all meals.
- Continue frequent walking and leg and ankle exercises at home.

If you are unsure of which level you are to complete, please ask your nurse.

6.3 **VTE Inside Hopkins Bayview Website:** VTE Risk Stratification Policy and Algorithm

http://www.insidehopkinsbayview.org/pharmacy/anticoagulation/VTEstratification.html

Figure 29 VTE Prophylaxis Risk Stratification Policy and Algorithm: Johns Hopkins Bayview Intranet

INSIDE HOPKINS BAYVIEW

Departments/Services | Dining | Human Resources | Banner | Epic | Meditech | Shuttle

- Anticoagulation Therapy Management Resource
- Antigoagulation Service Policy and Procedure
- Anticoagulation Clinic Intake and Referral Form
- Conversion Guide for Interchange of Injectable Anticoagulants
- Enoxaparin (Lovenox) Guidelines
- Heparin-Induced Thrombocytopenia (HIT) Guidelines
- Emergent Reversal of Excess Anticoagulation In Hemorrhagic Stroke
- Direct Thrombin Inhibitors for the Treatment of Heparin Induced Thromocytopenia
- VTE Stratification Policy and Algorithm
- Warfarin Patient Guide
- Warfarin Guidelines
- Required Elements of National Patient Safety Goal
- Summary of Work on the National Consensus Standards for the Prevention and Care of Venous Thromoembolism (VTE)

Home > Pharmacy > Anticoagulation Therapy Management

Venous Thromboembolism (VTE) Prophylaxis Risk Stratfication Policy and Algorithm

- Stratification Scheme for Medicine, Trauma, Intensive Care and Surgery
- Stratification Scheme for Orthopaedic Surgery
- Special Considerations
- Meditech Functionality to Assist Prescribers (examples)

Medicine, Trauma, Intensive Care and Surgery

Risk Category	Risk Factors	VTE Prophylaxis Regimen
Low Risk	- Age ≤ 60 years of age - Fully mobile - No other risk factors	- Early and aggressive ambulation
Moderate Risk	Two or more of the following: - Minor surgery [1] - Age > 60 years of age - Obesity as defined by BMI > 30kg/m^2	- Heparin 5000 units subcutaneously every 12 hours **OR** - TEDS® Compression Stockings or Sequential Compression Devices (SCD) if heparin in contraindicated
High Risk	- Previous VTE - Malignancy - Thrombophilic State or Disorder - Major Surgery[2] - Immobility or Prolonged Stay (ICU admission of estimated length of stay of > four days)	- Heparin 5000 units subcutaneously every 8 hours **OR** - Enoxaparin 40mg subcutaneously every 24 hours - Option to add Graded Compression Stockings (GCS) and/or SCD
Very High Risk	- Major trauma (e.g. burn, spinal chord injury) - > 1 "High Risk" Factor	- Enoxaparin 40mg subcutaneously every 24 hours **OR** - Heparin 5000 units subcutaneously every 8 hours **AND** - GCS and/or SCD

[1] Procedure lasting ≤ 2 hours or at the discretion of the provider
[2] Procedure last > 2 hours
[3] For estimated creatinine clearance (CrCl) < 30 ml/min, subcutaneous heparin use is strongly recommended. If enoxaparin is used the manufacturer recommends 30mg subcutaneously every 24 hours.

▲ Back to Top

Orthopaedic Surgery

Risk Category	Risk Factors	VTE Prophylaxis Regimen
Low Risk	- Upper extremity fractures	- Early mobilization
Moderate Risk	- Lower extremity soft tissue surgery **OR** arthroscopy	- Early mobilization **OR** - Enoxaparin 40mg subcutaneously every 24 hours for 2 to 6 weeks, if no other risk factors exist.[1] - May consider fondaparinux
High Risk	- Total hip or knee arthroplasty with no additional risk factors - Lower extremity pelvis fractures - Total hip or knee arthroplasty **WITH** additional risk factors (e.g. previous VTE, prolonged immobilization, hypercoaguable state)	- Enoxaparin 40mg subcutaneously every 24 hours for a period of up to six weeks after surgery **OR** - Enoxaparin 40mg subcutaneously in conjunction with adjusted dose warfarin (until INR is therapeutic) for up to six weeks post surgery.[2] - May consider fondaparinux These must be given in conjunction with: - Early mobilization and GCS and/or SCD

[1] For patients with an estimated CrCl of < 30ml/mon, manufacturer recommends enoxaparin 30mg subcutaneously every 24 hours

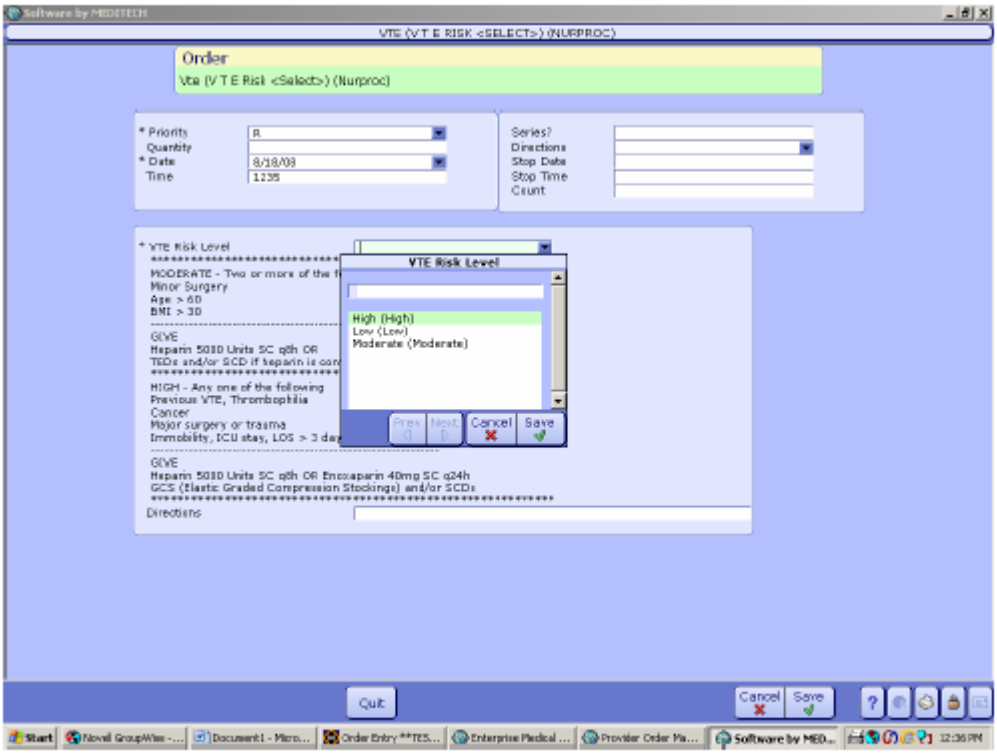
[2] Per guidelines for the American Academy of Orthopaedic Surgeons, aspirin at a dose of 325mg orally twice daily can be considered when patients are at a standard risk for VTE (i.e. no history of VTE or hypercoaguable state) or when the bleeding risk is considered above standard (i.e. history of a bleeding disorder, recent gastrointestinal bleed or recent hemorrhagic stroke)

▲ Back to Top

Special Considerations

1. Moderate Risk Stratification also can be considered for:
   a) Active Heart Failure (New York Heart Association Class III or IV)
   b) Ventilator Dependent Respiratory Failure
   c) Cerebrovascular Accident within 3 months
   d) Acute infection or sepsis
   e) Pregnancy/post-partum patient
2. Gastric Bypass Patient
   a) For open procedure, give heparin 5,000 units subcutaneously every 8 hours
   b) For laparoscopic procedure, give enoxaparin 40mg subcutaneously every 12 hours for patients < 400 pounds OR enoxaparin 60mg subcutaneously every 12 hours for patients ≥ 400 pounds (or at the discretion of the attending surgeon)

Figure 30 Physician Order Entry VTE Prophylaxis Risk Guide and Standardization



6.4 Future Projects

Project Name*: **APB study*** – Apixaban Pharmacokinetics in Bariatric Patients: A study to determine the pharmokinetics and pharmodynamics of apixaban in obese patients who undergo bariatric surgery.

Type of support: Drug plus funding – submitted to Pfizer/Bristol Meyers December 2013

Study Rationale: Obesity is now the leading health problem of the 21st century. Weight reduction by conservative methods including diet and exercise has had poor success rates. There has been a substantial increase in the use of bariatric surgery to provide sustained weight loss and thus a reduction in the medical comorbidities that are associated with obesity. However, because these procedures may alter the anatomical and physiological aspects of the gastrointestinal system, there is a possibility of altered pharmacokinetics to medications particularly when taken orally. Furthermore, patients typically lose anywhere from 50 to 75% of their estimated excess body mass approximately one to two years following surgery. This successful therapeutic outcome of the surgery may be causing long term changes in the pharmacokinetics that are independent of any direct anatomical or physiologic changes induced by the procedure.

Physicians and surgeons are very interested in the oral anticoagulants for this special patient population. To date, there is no approved dosing for the obese patient (especially when considering surgical intervention such as bariatric surgery).

Our Center for Bariatric Surgery is interested in conducting a pharmacokinetic study of apixaban in the obese adult population. More interesting would be to see how the dose

may change pre- vs. post-bariatric surgery (this will be important for physicians as more and more patients undergo this procedure worldwide and many may require anticoagulation in their future healthcare).

Specific Aims and Hypotheses:

Specific Aim 1: To determine the pharmacokinetics of apixaban in patients with a body mass index (BMI) of 35 kg/m2 or greater.

Hypothesis 1a: Obese patients prior to bariatric surgical intervention, compared to normal weight historical controls, will have a decrease in both Cmax and AUC when given the standard dose of 5 mg of apixaban.

Specific Aim 2: To determine the pharmacokinetics of apixaban in the bariatric surgical patient who has undergone Roux-en Y gastric bypass (RYGB) or Vertical Sleeve Gastrectomy (VSG) at 1, 6, 12 and 18 months post-op.

Hypothesis 2a: Patients who have recently undergone RYGB surgery (1 month post-op) will have a decrease in both the C_{max} and AUC when given the standard dose of 5 mg of apixaban.

Hypothesis 2b: Patients who have recently undergone VSG surgery (1 month post-op) will have a decrease in both the C_{max} and AUC when given the standard dose of 5 mg of

apixaban. The magnitude of the decrease in C_{max} and AUC will be less than that seen in RYGB patients.

Rationale: Anatomic alteration of the GI tract will immediately reduce absorption in all post-operative bariatric patients. In RYGB patients, the attenuated small bowel and altered bile acid composition will lead to decreased absorption of the drug, whereas in sleeve gastrectomy patients prolonged gastric emptying will affect pharmacokinetics.

These findings will be important when considering the use of apixaban as an oral anticoagulation option for perioperative VTE prophylaxis in the bariatric population, both in the acute hospital setting and after discharge in patients requiring extended VTE prophylaxis or treatment.

Hypothesis 2c: Patients who have undergone bariatric surgery (6, 12, and 18 months post-op) will have an increase in Cmax and AUC when given the standard dose of 5 mg of apixaban.

Hypothesis 2d: Patients who have undergone RYGB (6, 12, and 18 months post-op) will have a greater increase in both C_{max} and AUC than VSG patients when given the standard dose of 5 mg of apixaban.

Rationale: Patients who are 6 to 18 months post-bariatric surgery generally have a 30-40% decrease in excess body weight. This decrease in body weight reduces volume of distribution of drug, resulting in higher plasma levels.

The effect of RYGB vs sleeve gastrectomy on long-term pharmacokinetics is difficult to predict because of the opposing effects of greater weight loss with reduced absorption in the RYGB patient.

These findings will be important when considering apixaban as an oral medication for long-term post-op bariatric patients that may require anticoagulation for stroke, myocardial infarction, atrial fibrillation or orthopedic procedures such as hip or knee replacements.

Specific Aim 3: To measure the effect of apixaban on Factor Xa activity in bariatric surgical patients pre-operatively then at 1, 6, 12 and 18 months post-operatively.

Hypothesis 3a: In spite of the changes in pharmacokinetics, the pharmacodynamics response (measured with Factor Xa activity) will not differ by more than 10% in comparing pre-surgical response to that at 1, 6, 12 and 18 months after surgery.

Rationale: The changes in pharmacokinetics should not lead to a different dose-response relationship in the Factor Xa activity of individual patients following dosing with apixaban 5 mg. Were there to be a significant change in pharmacodynamics, other factors due to the altered anatomy or substantial weight loss would need to be invoked to explain that altered relationship.

Study Endpoints:

a. **Primary objective:** To determine the durability or change in pharmacokinetics and pharmacodynamics of apixaban in patients with a body mass index (BMI) of 35 kg/m2 or greater who undergo one of two bariatric surgical procedures.

b. Secondary objectives:

1. To compare/contrast the pharmacokinetics and pharmacodynamics of apixaban in bariatric surgical patients who have undergone RYGB vs. VSG.

2. To determine how the pharmacokinetics of the drug may differ when there is significant post-operative surgical weight loss (>40% estimated excess body weight) 12 to 18 months following surgery.

Treatment: Dose schedule, duration, and concurrent medications: 5 mg of apixaban given within one month before bariatric surgery, then 1, 6 and 12 months after bariatric surgery if patient loses at least 30% of body weight, and then again within 18 months of surgery if patient achieves 40% loss of body weight. There will be no required concurrent medications. Excluded medications are mentioned below.

Study population: Obese patients with a body mass index (BMI) of 35 kg/m2 or greater that have been approved for bariatric surgery at the Johns Hopkins Center for Bariatric Surgery from Jan. 2014 until all patients recruited.

Sample size/sample size justification: We propose to study 25 subjects in each arm (RYGB vs. VSG). We have accounted for loss to follow-up (even with a 36% (9 in each group) drop-out rate, we would have enough subjects (16 per group) to demonstrate a 25 % change in AUC with an alpha error of 0.05 and a beta error of 0.2 (Power of 80%). If there is no loss to follow-up and all patients remain in the study, this will allow us to demonstrate a 20% change in AUC with an alpha error of 0.05 and a beta error of 0.2. These calculations were calculated based on the following data: Ratio of geometric mean point estimated for high body weight (>120 kg) vs. normal body weight for C_{max} = 0.692 (0.586, 0.818) and AUC (INF) = 0.77 (0.652, 0.912). (1)

Inclusion/Exclusion Criteria

Inclusion Criteria:

Men or women, 18 to 65 years old with a BMI of 35 kg/m2 or greater who are undergoing laparoscopic bariatric surgery, i.e., laparoscopic VSG and laparoscopic RYGB.

Exclusion Criteria:

1. History of documented clotting/coagulation disorder.
2. History of cancer (within the last year)
3. Any diagnosis requiring anti-coagulation
4. History of hypersensitivity reaction to apixaban
5. Active clinically significant bleeding

Study Assessments (and methodology): Consenting subjects will be hospitalized overnight in the JHH Clinical Research Center. A dose of 5 mg apixaban will be administered, and blood samples for apixaban concentration and Factor Xa activity will be collected before and at 1, 2, 3, 4, 6, 8 and 24 hours after dosing. The apixaban concentrations will be measured at Pfizer, and the Xa activity measured at JHH.

Data and statistical Plan: Routine pharmacokinetic data will be determined, including Cmax, Tmax and AUC for each subject at each dosing time, and compared within subjects and between subjects and between groups. Factor Xa activity will be compared to apixaban concentration at each time point.

References

A. Appendices

A.2 CPT Codes

Appendix A: Definitions of Bariatric Surgery

CPT-4 Codes	Description
43770	Laparoscopy, surgical, gastric restrictive procedure: placement of adjustable gastric band
43644	Laparoscopy, surgical, gastric restrictive procedure with gastric bypass and Roux-en-Y gastroenterostomy (roux limb 150 cm or less)
43645	Laparoscopy, surgical, gastric restrictive with gastric bypass and small intestine reconstruction to limit absorption
43842	Gastric restrictive procedure, without gastric bypass, for morbid obesity, vertical banded gastroplasty
43843	Other gastric restrictive procedures, without gastric bypass, and other than Vertical Banded Gastroplasty
43844	Laparoscopic gastric restrictive procedure with gastric bypass and Roux en Y gastroenterostomy
43845	Gastric restrictive procedure with partial gastrectomy, pylorus-preserving duodenoileostomy and ileolieostomy to limit absorption (BPD)
43846	Gastric restrictive procedure, with gastric bypass, for morbid obesity; with short limb (less than 100 cm) Roux-en-Y gastroenterostomy
43847	Gastric restrictive procedure, with small intestine reconstruction to limit absorption; with long limb (>150 cm) Roux-en-Y
43659	Gastrectomy, total; with Roux-en-Y reconstruction; Mini -gastric bypass
S2082	Laparoscopy, surgical; gastric restrictive procedure, adjustable gastric band includes placement of subcutaneous port
S2085	Laparoscopic gastric bypass
ICD-9 Codes	**Description**
44.68	Laparoscopic gastroplasty Banding Silastic vertical banding Vertical banded gastroplasty (VBG) Code also any synchronous laparoscopic gastroenterostomy (44.38)
44.95	Laparoscopic gastric restrictive procedure Adjustable gastric band and port insertion

The following ICD-9 codes are considered to indicate bariatric surgery when used in conjunction with ICD-9 278.01 (Morbid Obesity) as any diagnosis.

CPT-4 Codes	Description	Additional Requirements
43.89	Partial gastrectomy with bypass gastrogastrostomy Sleeve resection of stomach	with 278.01
44.31	High gastric bypass Printen and Mason gastric bypass	with 278.01
44.38	Laparoscopic gastroenterostomy Bypass: gastroduodenostomy gastroenterostomy gastrogastrostomy Laparoscopic gastrojejunostomy without gastrectomy NEC	with 278.01
44.39	Other gastroenterostomy Bypass gastroduodenostomy gastroenterostomy gastrogastrostomy Gastrojejunostomy without gastrectomy NOS	with 278.01

We excluded patients who have the following ICD-9 diagnosis codes during the same hospitalization as their bariatric procedure

ICD-9	Description
150.x	Malignant neoplasm of esophagus
151.x	Malignant neoplasm of stomach
152.x	Malignant neoplasm of small intestine, including duodenum
157.x	Malignant neoplasm of pancreas
199.x	Malignant neoplasm without specification of site

*** The following three codes must have been listed as the primary diagnosis code for that hospitalization (we will not exclude patients who have these as secondary diagnoses)

531.x	Gastric ulcer
532.x	Duodenal ulcer
533.x	Peptic ulcer, site unspecified

We excluded individuals with the follow revision codes prior to the procedure of interest.

CPT-4 Codes	Description
43771	Laparoscopy, surgical, gastric restrictive procedure; revision of adjustable gastric restrictive device component only
43772	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device component only
43773	Laparoscopy, surgical, gastric restrictive procedure; removal and replacement of adjustable gastric restrictive device component only
43774	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device and subcutaneous port components
43848	Revision, open, of gastric restrictive procedure for morbid obesity other than adjustable gastric restrictive device (separate procedure)
43850	Revision of gastroduodenal anastomosis (gastroduodenostomy) with reconstruction; without vagotomy
43855	Revision of gastroduodenal anastomosis (gastroduodenostomy) with reconstruction; with vagotomy
43860	Revision of gastrojejunal anastomosis (gastrojejunostomy) with reconstruction with or without partial gastrectomy or intestine resection; without vagotomy
43865	Revision of gastrojejunal anastomosis (gastrojejunostomy) with reconstruction with or without partial gastrectomy or intestine resection; with vagotomy
43886	Gastric restrictive procedure open; revision of subcutaneous port component only
43887	Gastric restrictive procedure open; removal of subcutaneous port component only
43888	Gastric restrictive procedure open; removal and replacement of subcutaneous port component only
4469	Other repair of stomach
4496	Laparoscopic revision of gastric restrictive procedure
4497	Laparoscopic removal of gastric restrictive device(s)

A.4.1 Search Strategy

PUBMED

((((("Phlebography"[Mesh]) AND "Magnetic Resonance Imaging"[Mesh] OR "magnetic resonance venography" OR mrv OR ("magnetic resonance" AND venography [tw]) OR "mr venography" OR ("mr" AND venography))) AND (("Venous Thrombosis"[Mesh] AND deep [tiab]) OR DVT [tw] OR "deep vein thrombosis" [tw] OR "deep vein thromboses" [tw]))
Searched 2/17/2014

228 citations retrieved

EMBASE

#3	**#1** AND **#2**	517
#2	**'deep vein thrombosis'**/exp OR (**'venous thromboembolism'**/exp AND **deep**:ab,ti) OR **dvt**:ab,ti OR (**'deep vein'** NEAR/3 **thrombos***):ab,ti	44,243
#1	**'phlebography'**/exp AND **'nuclear magnetic resonance imaging'**/exp OR (**'magnetic resonance'** NEAR/3 **venography**):ab,ti OR **mrv**:ab,ti OR (**mr** NEAR/3 **venography**):ab,ti OR **'magnetic resonance venography'**:ab,ti	3,772

Searched 2/17/2014

COCHRANE

Search Name: Magnetic resonance venography for deep vein thrombosis
Last Saved: 17/02/2014 18:33:53.042
Description:

ID	Search
#1	MeSH descriptor: [Phlebography] explode all trees
#2	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#3	"magnetic resonance" near/3 venography or mrv or mr near/3 venography
#4	(#1 and #2) or #3
#5	MeSH descriptor: [Venous Thrombosis] explode all trees
#6	#5 and deep
#7	dvt or "deep vein" near/3 thrombos*
#8	#6 or #7
#9	#4 and #8

15 total citations retrieved
3 Cochrane reviews
3 Other Reviews
9 Trials

SCOPUS

((TITLE-ABS-KEY(**"magnetic resonance"** W/3 **venography**) OR TITLE-ABS-KEY(**mrv**) OR TITLE-ABS-KEY(**mr** W/3 **venography**) OR TITLE-ABS-KEY(**"magnetic resonance venography"**))) AND ((TITLE-ABS-KEY(**"deep vein thrombosis"**) OR TITLE-ABS-KEY(**"deep vein"** W/3 **thrombos***) OR TITLE-ABS-KEY(**dvt** OR **dvts**)))
Searched 2/17/2014

177 citations retrieved

WEB OF SCIENCE

TOPIC: *((((("magnetic resonance" NEAR/3 venography) OR (mrv) OR (mr NEAR/3 venography) OR ("magnetic resonance venography")))) AND* **TOPIC:** *((((("deep vein thrombosis") OR ("deep vein" NEAR/3 thrombos*) OR (dvt OR dvts))))*
Timespan=All years. Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC.
Searched 2/17/2014

125 citations retrieved

Hand Search was performed on 4 of the top 40 impact journals: Radiology, Investigative Radiology, Journal of Magnetic Resonance Imaging, JAMA surgery and Clinical Orthopaedics and Related Research. No further articles were obtained by the teams overall search.

Summary

Total citations retrieved:	1062
Duplicates removed:	406
Remaining citations:	**656**

A.4.2 Cohort Data Extraction Form

Characteristics of Cohort studies (can do the same for case-control studies if there are any)

A. Review author
B. Study ID
C. Date completed
D. Methods
1. Total number of subjects recruited in the study (exclude studies with <10 patients), number of cases
2. Exclusion criteria
3. Diagnosis of DVT present prior to MV

E. Participants
6. Country of origin
7. Setting (where cases recruited from)-specify Yes or no for options below
(a) Healthcare setting (hospitals/clinics)
(b) Academic (university hospitals)
(c) Registry
(d) Community
(e) Other, please specify
8. (a)Age (mean) (b) age (SD)
9. Gender Female (N,%)
10. Race N(%)
(a) American Indian or Alaskan Native
(b) Asian
(c) Black/African American
(d) Native Hawaiian/Pacific Islander
(e) Spanish/Hispanic/Latino
(f) White
(g) Other, please specify

F. Exposure
11. Procedure type
(a) MRV
(d) Other-specify
12. What type of MRV was used for the procedure?
13. Was MRV done with or without contrast?
14. Reference standard used?
(a) ultrasound/duplex
(b) CT

G. Outcome
19. No. of true positives
20. No of. true negatives

21. No. of false positives
22. No. of false negatives

H. Other variables of interest

I. Measures of association

25. Which measure of association was reported?
(a) Odds ratio (b) ln(Odds ratio)
(c) Other measure of association, specify
(d) ln(measure of association)
27. SE of measure
(a) ln(SE of measure)
28. 95% CI of measure
29. List variables adjusted for:
30. Other notes:

A.4.3 Risk of Bias Assessment

QUADAS-2 Quality of Study and Risk of Bias Data Collection Form

Study Title and Date of Publication:_____

Author:_____

Phase 1: State the review question:

Patients (setting, intended use of index test, presentation, prior testing): Index test(s): Reference standard and target condition:

Phase 2: Draw a flow diagram for the primary study

Phase 3: Risk of bias and applicability judgments

QUADAS-2 is structured so that 4 key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:

1. Was a consecutive or random sample of patients enrolled?

Yes/No/Unclear

2. Was a case-control design avoided?

Yes/No/Unclear

3. Did the study avoid inappropriate exclusions?

Yes/No/Unclear

Could the selection of patients have introduced bias?

RISK: LOW/HIGH/UNCLEAR

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):

Is there concern that the included patients do not match the review question?

CONCERN: LOW/HIGH/UNCLEAR

DOMAIN 2: INDEX TEST(S)

If more than one index test was used, please complete for each test.

A. Risk of Bias

Describe the index test and how it was conducted and interpreted:

1. Were the index test results interpreted without knowledge of the results of the reference standard?

Yes/No/Unclear

2. If a threshold was used, was it pre-specified?

Yes/No/Unclear

Could the conduct or interpretation of the index test have introduced bias?

RISK: LOW /HIGH/UNCLEAR

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?

CONCERN: LOW /HIGH/UNCLEAR

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted:

1. Is the reference standard likely to correctly classify the target condition?

Yes/No/Unclear

2. Were the reference standard results interpreted without knowledge of the results of the index test?

Yes/No/Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

RISK: LOW /HIGH/UNCLEAR

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

CONCERN: LOW /HIGH/UNCLEAR

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):

Describe the time interval and any interventions between index test(s) and reference standard:

1. Was there an appropriate interval between index test(s) and reference standard?

Yes/No/Unclear

2. Did all patients receive a reference standard?

Yes/No/Unclear

3. Did patients receive the same reference standard?

Yes/No/Unclear

4. Were all patients included in the analysis?

Yes/No/Unclear

Could the patient flow have introduced bias?

RISK: LOW /HIGH/UNCLEAR

***accessed from**: http://www.bris.ac.uk/quadas/quadas-2/

A.5 Study Timeline of Drug Administration

Appendix B: Study Timeline of Drug Administration

Day	Time	Fondaparinux	Enoxaparin
POD 0	1 to 2 hours before start of operation	Placebo subcutaneous	40 mg subcutaneous
	3 hours after first dose	Blood draw for Anti-factor Xa	Blood draw for Anti-factor Xa
	6 hours after OR stop	5 mg subcutaneous	Placebo subcutaneous
POD 1	9:45 a.m.	Blood draw for Anti-factor Xa	Blood draw for Anti-factor Xa
	10:00 a.m.	5 mg subcutaneous	40 mg subcutaneous
	1:00 p.m.	Blood draw for Anti-factor Xa	Blood draw for Anti-factor Xa
	10:00 p.m.	Placebo subcutaneous	40 mg subcutaneous
POD 2	10:00 a.m.	5 mg subcutaneous	40 mg subcutaneous
	10:00 p.m.	Placebo subcutaneous	40 mg subcutaneous

B. Bibliography

1. Mukherjee D, Lidor AO, Chu KM, Gearhart SL, Haut ER, Chang DC. Postoperative venous thromboembolism rates vary significantly after different types of major abdominal operations. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2008 Nov;12(11):2015-22. PubMed PMID: 18668299. Epub 2008/08/01. eng.

2. Nguyen NT, Hinojosa MW, Fayad C, Varela E, Konyalian V, Stamos MJ, et al. Laparoscopic surgery is associated with a lower incidence of venous thromboembolism compared with open surgery. Annals of surgery. 2007 Dec;246(6):1021-7. PubMed PMID: 18043105. Epub 2007/11/29. eng.

3. Prystowsky JB, Morasch MD, Eskandari MK, Hungness ES, Nagle AP. Prospective analysis of the incidence of deep venous thrombosis in bariatric surgery patients. Surgery. 2005 Oct;138(4):759-63; discussion 63-5. PubMed PMID: 16269306. Epub 2005/11/05. eng.

4. Encinosa WE, Bernard DM, Du D, Steiner CA. Recent improvements in bariatric surgery outcomes. Medical care. 2009 May;47(5):531-5. PubMed PMID: 19318997. Epub 2009/03/26. eng.

5. Carmody BJ, Sugerman HJ, Kellum JM, Jamal MK, Johnson JM, Carbonell AM, et al. Pulmonary embolism complicating bariatric surgery: detailed analysis of a single institution's 24-year experience. Journal of the American College of Surgeons. 2006 Dec;203(6):831-7. PubMed PMID: 17116551. Epub 2006/11/23. eng.

6. Abou-Nukta F, Alkhoury F, Arroyo K, Bakhos C, Gutweiler J, Reinhold R, et al. Clinical pulmonary embolus after gastric bypass surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2006 Jan-Feb;2(1):24-8; discussion 9. PubMed PMID: 16925309. Epub 2006/08/24. eng.

7. Gonzalez QH, Tishler DS, Plata-Munoz JJ, Bondora A, Vickers SM, Leath T, et al. Incidence of clinically evident deep venous thrombosis after laparoscopic Roux-en-Y gastric

bypass. Surgical endoscopy. 2004 Jul;18(7):1082-4. PubMed PMID: 15156394. Epub 2004/05/25. eng.

8. Gonzalez R, Haines K, Nelson LG, Gallagher SF, Murr MM. Predictive factors of thromboembolic events in patients undergoing Roux-en-Y gastric bypass. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2006 Jan-Feb;2(1):30-5; discussion 5-6. PubMed PMID: 16925311. Epub 2006/08/24. eng.

9. Brasileiro AL, Miranda F, Jr., Ettinger JE, Castro AA, Pitta GB, de Moura LK, et al. Incidence of lower limbs deep vein thrombosis after open and laparoscopic gastric bypass: a prospective study. Obesity surgery. 2008 Jan;18(1):52-7. PubMed PMID: 18080727. Epub 2007/12/18. eng.

10. Westling A, Bergqvist D, Bostrom A, Karacagil S, Gustavsson S. Incidence of deep venous thrombosis in patients undergoing obesity surgery. World journal of surgery. 2002 Apr;26(4):470-3. PubMed PMID: 11910482. Epub 2002/03/23. eng.

11. American Society for M, Bariatric Surgery Clinical Issues C. ASMBS updated position statement on prophylactic measures to reduce the risk of venous thromboembolism in bariatric surgery patients. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2013 Jul-Aug;9(4):493-7. PubMed PMID: 23769113. Epub 2013/06/19. eng.

12. Stein PD, Matta F. Pulmonary embolism and deep venous thrombosis following bariatric surgery. Obesity surgery. 2013 May;23(5):663-8. PubMed PMID: 23404239. Epub 2013/02/14. eng.

13. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. American journal of preventive medicine. 2010 Apr;38(4 Suppl):S495-501. PubMed PMID: 20331949. Epub 2010/04/02. eng.

14. Bikdeli B, Sharif-Kashani B. Prophylaxis for venous thromboembolism: a great global divide between expert guidelines and clinical practice? Seminars in thrombosis and hemostasis. 2012 Mar;38(2):144-55. PubMed PMID: 22422329. Epub 2012/03/17. eng.

15. Centers for Disease C, Prevention. Venous thromboembolism in adult hospitalizations - United States, 2007-2009. MMWR Morbidity and mortality weekly report. 2012 Jun 8;61(22):401-4. PubMed PMID: 22672974. Epub 2012/06/08. eng.

16. Shah SK, Clair DG. Which lower-extremity DVTs should be removed early? Cleveland Clinic journal of medicine. 2013 Sep;80(9):546-7. PubMed PMID: 24001962. Epub 2013/09/05. eng.

17. Spyropoulos AC, Hussein M, Lin J, Battleman D. Rates of venous thromboembolism occurrence in medical patients among the insured population. Thrombosis and haemostasis. 2009 Nov;102(5):951-7. PubMed PMID: 19888534. Epub 2009/11/06. eng.

18. Guyatt GH, Akl EA, Crowther M, Schunemann HJ, Gutterman DD, Zelman Lewis S, et al. Introduction to the ninth edition: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):48S-52S. PubMed PMID: 22315255. Pubmed Central PMCID: 3278068. Epub 2012/02/15. eng.

19. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ, American College of Chest Physicians Antithrombotic T, et al. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):7S-47S. PubMed PMID: 22315257. Pubmed Central PMCID: 3278060. Epub 2012/03/15. eng.

20. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):381S-453S. PubMed PMID: 18574271. Epub 2008/07/24. eng.

21. Hamad GG, Choban PS. Enoxaparin for thromboprophylaxis in morbidly obese patients undergoing bariatric surgery: findings of the prophylaxis against VTE outcomes in bariatric surgery patients receiving enoxaparin (PROBE) study. Obesity surgery. 2005 Nov-Dec;15(10):1368-74. PubMed PMID: 16354513. Epub 2005/12/16. eng.

22. Rocha AT, de Vasconcellos AG, da Luz Neto ER, Araujo DM, Alves ES, Lopes AA. Risk of venous thromboembolism and efficacy of thromboprophylaxis in hospitalized obese medical patients and in obese patients undergoing bariatric surgery. Obesity surgery. 2006 Dec;16(12):1645-55. PubMed PMID: 17217642. Epub 2007/01/16. eng.

23. Nguyen NT, Owings JT, Gosselin R, Pevec WC, Lee SJ, Goldman C, et al. Systemic coagulation and fibrinolysis after laparoscopic and open gastric bypass. Archives of surgery (Chicago, Ill : 1960). 2001 Aug;136(8):909-16. PubMed PMID: 11485526. Epub 2001/08/17. eng.

24. Rose SC, Zwiebel WJ, Murdock LE, Hofmann AA, Priest DL, Knighton RA, et al. Insensitivity of color Doppler flow imaging for detection of acute calf deep venous thrombosis in asymptomatic postoperative patients. Journal of vascular and interventional radiology : JVIR. 1993 Jan-Feb;4(1):111-7. PubMed PMID: 8425087. Epub 1993/01/01. eng.

25. Associates PM. Decreasing the incidence of venous thromboembolism in high-risk abdominal surgery. Journal of Clinical Prevention. 2004;2(1):13-8.

26. Pruthi RK. Review of the American College of Chest Physicians 2012 Guidelines for Anticoagulation Therapy and Prevention of Thrombosis. Seminars in hematology. 2013 Jul;50(3):251-8. PubMed PMID: 23953342. Epub 2013/08/21. eng.

27. Lachiewicz PF, Kelley SS, Haden LR. Two mechanical devices for prophylaxis of thromboembolism after total knee arthroplasty. A prospective, randomised study. The Journal of bone and joint surgery British volume. 2004 Nov;86(8):1137-41. PubMed PMID: 15568526. Epub 2004/12/01. eng.

28. Gagner M, Selzer F, Belle SH, Bessler M, Courcoulas AP, Dakin GF, et al. Adding chemoprophylaxis to sequential compression might not reduce risk of venous thromboembolism in bariatric surgery patients. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2012 Nov-Dec;8(6):663-70. PubMed PMID: 22963819. Pubmed Central PMCID: 3498574. Epub 2012/09/12. eng.

29. Kebede S, Prakasa KR, Shermock K, Shihab HM, Brotman DJ, Sharma R, et al. A systematic review of venous thromboembolism prophylaxis strategies in patients with renal insufficiency, obesity, or on antiplatelet agents. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2013 Jul;8(7):394-401. PubMed PMID: 23761111. Epub 2013/06/14. eng.

30. Cuker A. Unfractionated heparin for the treatment of venous thromboembolism: best practices and areas of uncertainty. Seminars in thrombosis and hemostasis. 2012 Sep;38(6):593-9. PubMed PMID: 22718256. Epub 2012/06/22. eng.

31. Jackson CM. Mechanism of heparin action. Bailliere's clinical haematology. 1990 Jul;3(3):483-504. PubMed PMID: 2176902. Epub 1990/07/01. eng.

32. Hemker HC, Beguin S. Mode of action of unfractionated and low molecular weight heparins on the generation of thrombin in plasma. Haemostasis. 1990;20 Suppl 1:81-92. PubMed PMID: 1964667. Epub 1990/01/01. eng.

33. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin : The seventh accp conference on antithrombotic and thrombolytic therapy. CHEST Journal. 2004;126(3_suppl):188S-203S.

34. Beguin S, Hemker HC. Mode of action of enoxaparin in plasma. Acta chirurgica Scandinavica Supplementum. 1990;556:51-6. PubMed PMID: 1963017. Epub 1990/01/01. eng.

35. Rojas L, Aizman A, Ernst D, Acuna MP, Moya P, Mellado R, et al. Anti-xa activity after enoxaparin prophylaxis in hospitalized patients weighing less than fifty-five kilograms. Thrombosis research. 2013 Dec;132(6):761-4. PubMed PMID: 24521789. Epub 2014/02/14. eng.

36. Paolucci F, Clavies MC, Donat F, Necciari J. Fondaparinux sodium mechanism of action: identification of specific binding to purified and human plasma-derived proteins. Clinical pharmacokinetics. 2002;41 Suppl 2:11-8. PubMed PMID: 12383040. Epub 2002/10/18. eng.

37. Nagler M, Haslauer M, Wuillemin WA. Fondaparinux - data on efficacy and safety in special situations. Thrombosis research. 2012 Apr;129(4):407-17. PubMed PMID: 22133273. Epub 2011/12/03. eng.

38. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. The New England journal of medicine. 2006 Apr 6;354(14):1464-76. PubMed PMID: 16537663. Epub 2006/03/16. eng.

39. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet. 2007 Sep 15;370(9591):949-56. PubMed PMID: 17869635. Epub 2007/09/18. eng.

40. Burness CB, Perry CM. Rivaroxaban: a review of its use in the treatment of deep vein thrombosis or pulmonary embolism and the prevention of recurrent venous thromboembolism. Drugs. 2014 Feb;74(2):243-62. PubMed PMID: 24430916. Epub 2014/01/17. eng.

41. Bhanwra S, Ahluwalia K. The new factor Xa inhibitor: Apixaban. Journal of pharmacology & pharmacotherapeutics. 2014 Jan;5(1):12-4. PubMed PMID: 24554904. Epub 2014/02/21. Eng.

42. Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. BMJ (Clinical research ed). 2012;344:e3675. PubMed PMID: 22700784. Pubmed Central PMCID: 3375207. Epub 2012/06/16. eng.

43. Dweck MR, Shah AS, Fox KA. Anticoagulation in atrial fibrillation: the present and the future. JRSM cardiovascular disease. 2012;1(5). PubMed PMID: 24175070. Pubmed Central PMCID: PMC3738362. Epub 2012/01/01. Eng.

44. Miller MT, Rovito PF. An approach to venous thromboembolism prophylaxis in laparoscopic Roux-en-Y gastric bypass surgery. Obesity surgery. 2004 Jun-Jul;14(6):731-7. PubMed PMID: 15318974. Epub 2004/08/21. eng.

45. Cotter SA, Cantrell W, Fisher B, Shopnick R. Efficacy of venous thromboembolism prophylaxis in morbidly obese patients undergoing gastric bypass surgery. Obesity surgery. 2005 Oct;15(9):1316-20. PubMed PMID: 16259895. Epub 2005/11/02. eng.

46. Imberti D, Baldini E, Pierfranceschi MG, Nicolini A, Cartelli C, De Paoli M, et al. Prophylaxis of Venous Thromboembolism with Low Molecular Weight Heparin in Bariatric Surgery: a Prospective, Randomised Pilot Study Evaluating Two Doses of Parnaparin (BAFLUX Study). Obesity surgery. 2013 Oct 27. PubMed PMID: 24163189. Epub 2013/10/29. Eng.

47. Kothari SN, Lambert PJ, Mathiason MA. Best Poster Award. A comparison of thromboembolic and bleeding events following laparoscopic gastric bypass in patients treated with prophylactic regimens of unfractionated heparin or enoxaparin. American journal of surgery. 2007 Dec;194(6):709-11. PubMed PMID: 18005758. Epub 2007/11/17. eng.

48. Birkmeyer NJ, Finks JF, Carlin AM, Chengelis DL, Krause KR, Hawasli AA, et al. Comparative effectiveness of unfractionated and low-molecular-weight heparin for prevention of venous thromboembolism following bariatric surgery. Archives of surgery (Chicago, Ill : 1960). 2012 Nov 1;147(11):994-8. PubMed PMID: 23165612. Epub 2012/11/21. eng.

49. Agarwal R, Hecht TE, Lazo MC, Umscheid CA. Venous thromboembolism prophylaxis for patients undergoing bariatric surgery: a systematic review. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2010 Mar 4;6(2):213-20. PubMed PMID: 20176509. Epub 2010/02/24. eng.

50. Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. Obesity surgery. 2002 Feb;12(1):19-24. PubMed PMID: 11868291. Epub 2002/03/01. eng.

51. Becattini C, Agnelli G, Manina G, Noya G, Rondelli F. Venous thromboembolism after laparoscopic bariatric surgery for morbid obesity: clinical burden and prevention. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2012 Jan-Feb;8(1):108-15. PubMed PMID: 22014482. Epub 2011/10/22. eng.

52. Brotman DJ, Shihab HM, Prakasa KR, Kebede S, Haut ER, Sharma R, et al. Pharmacologic and mechanical strategies for preventing venous thromboembolism after bariatric surgery: a systematic review and meta-analysis. JAMA surgery. 2013 Jul;148(7):675-86. PubMed PMID: 23754086. Epub 2013/06/12. eng.

53. Raftopoulos I, Martindale C, Cronin A, Steinberg J. The effect of extended post-discharge chemical thromboprophylaxis on venous thromboembolism rates after bariatric surgery: a prospective comparison trial. Surgical endoscopy. 2008 Nov;22(11):2384-91. PubMed PMID: 18622558. Epub 2008/07/16. eng.

54. Magee CJ, Barry J, Javed S, Macadam R, Kerrigan D. Extended thromboprophylaxis reduces incidence of postoperative venous thromboembolism in laparoscopic bariatric surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2010 May-Jun;6(3):322-5. PubMed PMID: 20510295. Epub 2010/06/01. eng.

55. Dupont PA. The Mobin-Uddin umbrella filter in the management of proven and threatened pulmonary embolism. Annals of the Royal College of Surgeons of England. 1976 Jul;58(4):318-21. PubMed PMID: 942169. Pubmed Central PMCID: 2493728. Epub 1976/07/01. eng.

56. Weinberg I, Kaufman J, Jaff MR. Inferior Vena Cava Filters. JACC: Cardiovascular Interventions. 2013;6(6):539-47.

57. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. The New England journal of medicine. 2002 Mar 28;346(13):975-80. PubMed PMID: 11919306. Epub 2002/03/29. eng.

58. Heit JA. The epidemiology of venous thromboembolism in the community. Arteriosclerosis, thrombosis, and vascular biology. 2008 Mar;28(3):370-2. PubMed PMID: 18296591. Pubmed Central PMCID: 2873781. Epub 2008/02/26. eng.

59. Office of the Surgeon General USDoHaHS. Acting Surgeon General Issues 'Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism. Available from: http:www.surgeongeneral.gov/news/pressreleases/pr20080915.html.

60. Qadan M, Tyson M, McCafferty MH, Hohmann SF, Polk HC, Jr. Venous thromboembolism in elective operations: balancing the choices. Surgery. 2008 Oct;144(4):654-60, discussion 60-1. PubMed PMID: 18847651. Epub 2008/10/14. eng.

61. Sapala JA, Wood MH, Schuhknecht MP, Sapala MA. Fatal pulmonary embolism after bariatric operations for morbid obesity: a 24-year retrospective analysis. Obesity surgery. 2003 Dec;13(6):819-25. PubMed PMID: 14738663. Epub 2004/01/24. eng.

62. Morino M, Toppino M, Forestieri P, Angrisani L, Allaix ME, Scopinaro N. Mortality after bariatric surgery: analysis of 13,871 morbidly obese patients from a national registry. Annals of surgery. 2007 Dec;246(6):1002-7; discussion 7-9. PubMed PMID: 18043102. Epub 2007/11/29. eng.

63. Livingston EH, Huerta S, Arthur D, Lee S, De Shields S, Heber D. Male gender is a predictor of morbidity and age a predictor of mortality for patients undergoing gastric bypass surgery. Annals of surgery. 2002 Nov;236(5):576-82. PubMed PMID: 12409663. Pubmed Central PMCID: 1422615. Epub 2002/11/01. eng.

64. Hutter MM, Randall S, Khuri SF, Henderson WG, Abbott WM, Warshaw AL. Laparoscopic versus open gastric bypass for morbid obesity: a multicenter, prospective, risk-

adjusted analysis from the National Surgical Quality Improvement Program. Annals of surgery. 2006 May;243(5):657-62; discussion 62-6. PubMed PMID: 16633001. Pubmed Central PMCID: 1570562. Epub 2006/04/25. eng.

65. Clinical Issues Committee of the American Society for M, Bariatric S. Prophylactic measures to reduce the risk of venous thromboembolism in bariatric surgery patients. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2007 Sep-Oct;3(5):494-5. PubMed PMID: 17903767. Epub 2007/10/02. eng.

66. Barba CA, Harrington C, Loewen M. Status of venous thromboembolism prophylaxis among bariatric surgeons: have we changed our practice during the past decade? Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2009 May-Jun;5(3):352-6. PubMed PMID: 19342305. Epub 2009/04/04. eng.

67. Gargiulo NJ, 3rd, Veith FJ, Lipsitz EC, Suggs WD, Ohki T, Goodman E, et al. The incidence of pulmonary embolism in open versus laparoscopic gastric bypass. Annals of vascular surgery. 2007 Sep;21(5):556-9. PubMed PMID: 17823038. Epub 2007/09/08. eng.

68. Vaziri K, Bhanot P, Hungness ES, Morasch MD, Prystowsky JB, Nagle AP. Retrievable inferior vena cava filters in high-risk patients undergoing bariatric surgery. Surgical endoscopy. 2009 Oct;23(10):2203-7. PubMed PMID: 19184212. Epub 2009/02/03. eng.

69. Smith MD, Patterson E, Wahed AS, Belle SH, Berk PD, Courcoulas AP, et al. Thirty-day mortality after bariatric surgery: independently adjudicated causes of death in the longitudinal assessment of bariatric surgery. Obesity surgery. 2011 Nov;21(11):1687-92. PubMed PMID: 21866378. Pubmed Central PMCID: PMC3249614. Epub 2011/08/26. eng.

70. Bellen B, Godoy Ide B, Reis AA, Bertevello P. Venous insufficiency and thromboembolic disease in bariatric surgery patients. Arquivos de gastroenterologia. 2013 Jul-Sep;50(3):191-5. PubMed PMID: 24322190. Epub 2013/12/11. eng.

71. Escalante-Tattersfield T, Tucker O, Fajnwaks P, Szomstein S, Rosenthal RJ. Incidence of deep vein thrombosis in morbidly obese patients undergoing laparoscopic Roux-en-Y gastric

bypass. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2008 Mar-Apr;4(2):126-30. PubMed PMID: 18359453. Epub 2008/03/25. eng.

72. Kardys CM, Stoner MC, Manwaring ML, Barker M, Macdonald KG, Pender JR, et al. Safety and efficacy of intravascular ultrasound-guided inferior vena cava filter in super obese bariatric patients. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2008 Jan-Feb;4(1):50-4. PubMed PMID: 18065293. Epub 2007/12/11. eng.

73. Melinek J, Livingston E, Cortina G, Fishbein MC. Autopsy findings following gastric bypass surgery for morbid obesity. Archives of pathology & laboratory medicine. 2002 Sep;126(9):1091-5. PubMed PMID: 12204059. Epub 2002/09/03. eng.

74. Rodriguez JL, Lopez JM, Proctor MC, Conley JL, Gerndt SJ, Marx MV, et al. Early placement of prophylactic vena caval filters in injured patients at high risk for pulmonary embolism. The Journal of trauma. 1996 May;40(5):797-802; discussion -4. PubMed PMID: 8614083. Epub 1996/05/01. eng.

75. Haut ER, Garcia LJ, Shihab HM, Brotman DJ, Stevens KA, Sharma R, et al. The Effectiveness of Prophylactic Inferior Vena Cava Filters in Trauma Patients: A Systematic Review and Meta-analysis. JAMA surgery. 2013 Nov 6. PubMed PMID: 24195920. Epub 2013/11/08. Eng.

76. Keeling WB, Haines K, Stone PA, Armstrong PA, Murr MM, Shames ML. Current indications for preoperative inferior vena cava filter insertion in patients undergoing surgery for morbid obesity. Obesity surgery. 2005 Aug;15(7):1009-12. PubMed PMID: 16105398. Epub 2005/08/18. eng.

77. Li W, Gorecki P, Semaan E, Briggs W, Tortolani AJ, D'Ayala M. Concurrent prophylactic placement of inferior vena cava filter in gastric bypass and adjustable banding operations in the Bariatric Outcomes Longitudinal Database. Journal of vascular surgery. 2012 Jun;55(6):1690-5. PubMed PMID: 22360915. Epub 2012/03/01. eng.

78. Steele KE, Prokopowicz GP, Chang HY, Richards T, Clark JM, Weiner JP, et al. Risk of complications after bariatric surgery among individuals with and without type 2 diabetes mellitus. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2012 May-Jun;8(3):305-30. PubMed PMID: 21880549. Epub 2011/09/02. eng.

79. Obeid FN, Bowling WM, Fike JS, Durant JA. Efficacy of prophylactic inferior vena cavea filter placement in bariatric surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2007;3:606-8.

80. Trigilio-Black CM, Ringley CD, McBride CL, Sorensen VJ, Thompson JS, Longo GM, et al. Inferior vena cava filter placement for pulmonary embolism risk reduction in super morbidly obese undergoing bariatric surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2007 Jul-Aug;3(4):461-4. PubMed PMID: 17544921. Epub 2007/06/05. eng.

81. Sing RF, Fischer PE. Inferior vena cava filters: indications and management. Current opinion in cardiology. 2013 Nov;28(6):625-31. PubMed PMID: 24100649. Epub 2013/10/09. eng.

82. Schuster R, Hagedorn JC, Curet MJ, Morton JM. Retrievable inferior vena cava filters may be safely applied in gastric bypass surgery. Surgical endoscopy. 2007 Dec;21(12):2277-9. PubMed PMID: 17440780. Epub 2007/04/19. eng.

83. Wehrenberg-Klee E, Stavropoulos SW. Inferior vena cava filters for primary prophylaxis: when are they indicated? Seminars in interventional radiology. 2012 Mar;29(1):29-35. PubMed PMID: 23450194. Pubmed Central PMCID: PMC3348757. Epub 2013/03/02. eng.

84. Schweitzer M, Steele KE, Lidor A, Magnuson T. Acute vena cava thrombosis after placement of retrievable inferior vena cava filter before laparoscopic gastric bypass. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2006 Nov-Dec;2(6):661-3. PubMed PMID: 16979958. Epub 2006/09/19. eng.

85. Birkmeyer NJ, Finks JF, English WJ, Carlin AM, Hawasli AA, Genaw JA, et al. Risks and benefits of prophylactic inferior vena cava filters in patients undergoing bariatric surgery. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2013 Apr;8(4):173-7. PubMed PMID: 23401464. Epub 2013/02/13. eng.

86. Rajasekhar A, Crowther M. Inferior vena caval filter insertion prior to bariatric surgery: a systematic review of the literature. Journal of thrombosis and haemostasis : JTH. 2010 Jun;8(6):1266-70. PubMed PMID: 20345723. Epub 2010/03/30. eng.

87. Nguyen NT, Masoomi H, Magno CP, Nguyen XM, Laugenour K, Lane J. Trends in use of bariatric surgery, 2003-2008. Journal of the American College of Surgeons. 2011 Aug;213(2):261-6. PubMed PMID: 21624841. Epub 2011/06/01. eng.

88. Kohn GP, Galanko JA, Overby DW, Farrell TM. Recent trends in bariatric surgery case volume in the United States. Surgery. 2009 Aug;146(2):375-80. PubMed PMID: 19628098. Epub 2009/07/25. eng.

89. Administration. USFAD. Removing retrievable inferior vena cava filters: initial communication. http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm221676.htm. 2August 9, 2010 [updated 2/14/2014; cited 2011 9/20/2011].

90. Steele KE, Schweitzer MA, Prokopowicz G, Shore AD, Eaton LC, Lidor AO, et al. The long-term risk of venous thromboembolism following bariatric surgery. Obesity surgery. 2011 Sep;21(9):1371-6. PubMed PMID: 21625911. Epub 2011/06/01. eng.

91. Birkmeyer NJ, Dimick JB, Share D, Hawasli A, English WJ, Genaw J, et al. Hospital complication rates with bariatric surgery in Michigan. JAMA : the journal of the American Medical Association. 2010 Jul 28;304(4):435-42. PubMed PMID: 20664044. Epub 2010/07/29. eng.

92. Birkmeyer NJ, Share D, Baser O, Carlin AM, Finks JF, Pesta CM, et al. Preoperative placement of inferior vena cava filters and outcomes after gastric bypass surgery. Annals of surgery. 2010 Aug;252(2):313-8. PubMed PMID: 20622663. Epub 2010/07/14. eng.

93. 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. PubMed PMID: 17371890. Epub 2007/03/21. eng.

94. Segal JB, Streiff MB, Hofmann LV, Thornton K, Bass EB. Management of venous thromboembolism: a systematic review for a practice guideline. Annals of internal medicine. 2007 Feb 6;146(3):211-22. PubMed PMID: 17261856. Epub 2007/01/31. eng.

95. 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. Annals of internal medicine. 2007 Feb 6;146(3):204-10. PubMed PMID: 17261857. Epub 2007/01/31. eng.

96. Hyers TM. Venous thromboembolism. American journal of respiratory and critical care medicine. 1999 Jan;159(1):1-14. PubMed PMID: 9872811. Epub 1999/01/05. eng.

97. Blann AD, Lip GY. Venous thromboembolism. BMJ (Clinical research ed). 2006 Jan 28;332(7535):215-9. PubMed PMID: 16439400. Pubmed Central PMCID: PMC1352055. Epub 2006/01/28. eng.

98. Carpenter JP, Holland GA, Baum RA, Owen RS, Carpenter JT, Cope C. Magnetic resonance venography for the detection of deep venous thrombosis: comparison with contrast venography and duplex Doppler ultrasonography. Journal of vascular surgery. 1993 Nov;18(5):734-41. PubMed PMID: 8230557. Epub 1993/11/01. eng.

99. Lim KE, Hsu YY, Hsu WC, Huang CC. Combined computed tomography venography and pulmonary angiography for the diagnosis PE and DVT in the ED. The American journal of emergency medicine. 2004 Jul;22(4):301-6. PubMed PMID: 15258873. Epub 2004/07/20. eng.

100. Darvall KA, Sam RC, Silverman SH, Bradbury AW, Adam DJ. Obesity and thrombosis. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2007 Feb;33(2):223-33. PubMed PMID: 17185009. Epub 2006/12/23. eng.

101. Van Guilder GP, Hoetzer GL, Greiner JJ, Stauffer BL, DeSouza CA. Metabolic syndrome and endothelial fibrinolytic capacity in obese adults. American journal of physiology Regulatory, integrative and comparative physiology. 2008 Jan;294(1):R39-44. PubMed PMID: 17959703. Epub 2007/10/26. eng.

102. Martinelli I. Risk factors in venous thromboembolism. Thrombosis and haemostasis. 2001 Jul;86(1):395-403. PubMed PMID: 11487029. Epub 2001/08/07. eng.

103. Cham MD, Yankelevitz DF, Shaham D, Shah AA, Sherman L, Lewis A, et al. Deep venous thrombosis: detection by using indirect CT venography. The Pulmonary Angiography-Indirect CT Venography Cooperative Group. Radiology. 2000 Sep;216(3):744-51. PubMed PMID: 10966705. Epub 2000/08/31. eng.

104. Montgomery KD, Potter HG, Helfet DL. Magnetic resonance venography to evaluate the deep venous system of the pelvis in patients who have an acetabular fracture. The Journal of bone and joint surgery American volume. 1995 Nov;77(11):1639-49. PubMed PMID: 7593073. Epub 1995/11/01. eng.

105. Cantwell CP, Cradock A, Bruzzi J, Fitzpatrick P, Eustace S, Murray JG. MR venography with true fast imaging with steady-state precession for suspected lower-limb deep vein thrombosis. Journal of vascular and interventional radiology : JVIR. 2006 Nov;17(11 Pt 1):1763-9. PubMed PMID: 17142706. Epub 2006/12/05. eng.

106. Cantrell SW, Ward KS, Van Wickllin SA. Translating research on venous thromboembolism into practice. AORN journal. 2007 Oct;86(4):590-606. PubMed PMID: 18236606. Epub 2008/02/02. eng.

107. Laissy JP, Cinqualbre A, Loshkajian A, Henry-Feugeas MC, Crestani B, Riquelme C, et al. Assessment of deep venous thrombosis in the lower limbs and pelvis: MR venography versus duplex Doppler sonography. AJR American journal of roentgenology. 1996 Oct;167(4):971-5. PubMed PMID: 8819396. Epub 1996/10/01. eng.

108. Davidson BL, Elliott CG, Lensing AW. Low accuracy of color Doppler ultrasound in the detection of proximal leg vein thrombosis in asymptomatic high-risk patients. The RD Heparin Arthroplasty Group. Annals of internal medicine. 1992 Nov 1;117(9):735-8. PubMed PMID: 1416575. Epub 1992/11/01. eng.

109. Wells PS, Lensing AW, Davidson BL, Prins MH, Hirsh J. Accuracy of ultrasound for the diagnosis of deep venous thrombosis in asymptomatic patients after orthopedic surgery. A meta-analysis. Annals of internal medicine. 1995 Jan 1;122(1):47-53. PubMed PMID: 7985896. Epub 1995/01/01. eng.

110. Sampson FC, Goodacre SW, Thomas SM, van Beek EJ. The accuracy of MRI in diagnosis of suspected deep vein thrombosis: systematic review and meta-analysis. European radiology. 2007 Jan;17(1):175-81. PubMed PMID: 16628439. Epub 2006/04/22. eng.

111. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA : the journal of the American Medical Association. 2000 Apr 19;283(15):2008-12. PubMed PMID: 10789670. Epub 2000/05/02. eng.

112. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011 Oct 18;155(8):529-36. PubMed PMID: 22007046. Epub 2011/10/19. eng.

113. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC medical research methodology. 2006;6:31. PubMed PMID: 16836745. Pubmed Central PMCID: 1552081. Epub 2006/07/14. eng.

114. Higgins JPT GS. Cochrane Handbook for Systematic Reviews of Interventions. The Atrium Southern Gate, Chichester, West Sussex, PO19 8SQ: John Wiley & Sons Ltd.; 2009 and 2010 [cited 2014 March 30, 2014].

115. Akhtar SS, Nabi Z, Salim KP, Balah AS, Adli K. Magnetic resonance venography and venous ultrasonography for diagnosing deep venous thrombosis. Saudi medical journal. 2010 Jan;31(1):88-90. PubMed PMID: 20062908. Epub 2010/01/12. eng.

116. Arnoldussen CW, de Graaf R, Wittens CH, de Haan MW. Value of magnetic resonance venography and computed tomographic venography in lower extremity chronic venous disease. Phlebology / Venous Forum of the Royal Society of Medicine. 2013 Mar;28 Suppl 1:169-75. PubMed PMID: 23482555. Epub 2013/03/27. eng.

117. Aschauer M, Deutschmann HA, Stollberger R, Hausegger KA, Obernosterer A, Schollnast H, et al. Value of a blood pool contrast agent in MR venography of the lower extremities and pelvis: preliminary results in 12 patients. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine. 2003 Nov;50(5):993-1002. PubMed PMID: 14587010. Epub 2003/10/31. eng.

118. Catalano C, Pavone P, Laghi A, Scipioni A, Fanelli F, Assael FG, et al. Role of MR venography in the evaluation of deep venous thrombosis. Acta radiologica (Stockholm, Sweden : 1987). 1997 Sep;38(5):907-12. PubMed PMID: 9332254. Epub 1997/10/23. eng.

119. Evans AJ, Sostman HD, Knelson MH, Spritzer CE, Newman GE, Paine SS, et al. 1992 ARRS Executive Council Award. Detection of deep venous thrombosis: prospective comparison of MR imaging with contrast venography. AJR American journal of roentgenology. 1993 Jul;161(1):131-9. PubMed PMID: 8517292. Epub 1993/07/01. eng.

120. Evans AJ, Sostman HD, Witty LA, Paulson EK, Spritzer CE, Hertzberg BS, et al. Detection of deep venous thrombosis: prospective comparison of MR imaging and sonography.

Journal of magnetic resonance imaging : JMRI. 1996 Jan-Feb;6(1):44-51. PubMed PMID: 8851402. Epub 1996/01/01. eng.

121. Fraser DG, Moody AR, Morgan PS, Martel AL, Davidson I. Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. Annals of internal medicine. 2002 Jan 15;136(2):89-98. PubMed PMID: 11790060. Epub 2002/01/16. eng.

122. Pope CF, Dietz MJ, Ezekowitz MD, Gore JC. Technical variables influencing the detection of acute deep vein thrombosis by magnetic resonance imaging. Magnetic resonance imaging. 1991;9(3):379-88. PubMed PMID: 1881257. Epub 1991/01/01. eng.

123. Sica GT, Pugach ME, Koniaris LS, Goldhaber SZ, Polak JF, Mukerjee A, et al. Isolated calf vein thrombosis: comparison of MR venography and conventional venography after initial sonography in symptomatic patients. Academic radiology. 2001 Sep;8(9):856-63. PubMed PMID: 11724040. Epub 2001/11/29. eng.

124. Spritzer CE, Norconk JJ, Jr., Sostman HD, Coleman RE. Detection of deep venous thrombosis by magnetic resonance imaging. Chest. 1993 Jul;104(1):54-60. PubMed PMID: 8325117. Epub 1993/07/01. eng.

125. Vukov LF, Berquist TH, King BF. Magnetic resonance imaging for calf deep venous thrombophlebitis. Annals of emergency medicine. 1991 May;20(5):497-9. PubMed PMID: 2024787. Epub 1991/05/01. eng.

126. Moody AR, Pollock JG, O'Connor AR, Bagnall M. Lower-limb deep venous thrombosis: direct MR imaging of the thrombus. Radiology. 1998 Nov;209(2):349-55. PubMed PMID: 9807558. Epub 1998/11/10. eng.

127. Jensen AD, Borris LC, Christiansen TM, Lundorf E. Accuracy of magnetic resonance imaging in the diagnosis of deep vein thrombosis in asymptomatic patients with injuries of the lower extremity. A pilot study. Thrombosis research. 2001 Mar 15;101(6):423-6. PubMed PMID: 11322998. Epub 2001/04/27. eng.

128. Larcom PG, Lotke PA, Steinberg ME, Holland G, Foster S. Magnetic resonance venography versus contrast venography to diagnose thrombosis after joint surgery. Clinical orthopaedics and related research. 1996 Oct(331):209-15. PubMed PMID: 8895640. Epub 1996/10/01. eng.

129. Stover MD, Morgan SJ, Bosse MJ, Sims SH, Howard BJ, Stackhouse D, et al. Prospective comparison of contrast-enhanced computed tomography versus magnetic resonance venography in the detection of occult deep pelvic vein thrombosis in patients with pelvic and acetabular fractures. Journal of orthopaedic trauma. 2002 Oct;16(9):613-21. PubMed PMID: 12368640. Epub 2002/10/09. eng.

130. Erdman WA, Jayson HT, Redman HC, Miller GL, Parkey RW, Peshock RW. Deep venous thrombosis of extremities: role of MR imaging in the diagnosis. Radiology. 1990 Feb;174(2):425-31. PubMed PMID: 2404315. Epub 1990/02/01. eng.

131. Ono A, Murase K, Taniguchi T, Shibutani O, Takata S, Kobashi Y, et al. Deep venous thrombosis: diagnostic value of non-contrast-enhanced MR venography using electrocardiography-triggered three-dimensional half-Fourier FSE. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine. 2010 Jul;64(1):88-97. PubMed PMID: 20572137. Epub 2010/06/24. eng.

132. Spuentrup E, Buecker A, Stuber M, Gunther RW. MR-venography using high resolution True-FISP. RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin. 2001 Aug;173(8):686-90. PubMed PMID: 11570236. Epub 2001/09/26. eng.

133. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. Journal of clinical epidemiology. 2005 Sep;58(9):882-93. PubMed PMID: 16085191. Epub 2005/08/09. eng.

134. Bartolucci A. The significance of clinical trials and the role of meta-analyses. Journal of surgical oncology. 1999 Nov;72(3):121-3. PubMed PMID: 10562356. Epub 1999/11/24. eng.

135. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of diagnostic test accuracy. Annals of internal medicine. 2008 Dec 16;149(12):889-97. PubMed PMID: 19075208. Pubmed Central PMCID: PMC2956514. Epub 2008/12/17. eng.

136. Wadden TA. Treatment of obesity by moderate and severe caloric restriction. Results of clinical research trials. Annals of internal medicine. 1993 Oct 1;119(7 Pt 2):688-93. PubMed PMID: 8363198. Epub 1993/10/01. eng.

137. Kissane NA, Pratt JS. Medical and surgical treatment of obesity. Best practice & research Clinical anaesthesiology. 2011 Mar;25(1):11-25. PubMed PMID: 21516910. Epub 2011/04/27. eng.

138. O'Brien PE, McPhail T, Chaston TB, Dixon JB. Systematic review of medium-term weight loss after bariatric operations. Obesity surgery. 2006 Aug;16(8):1032-40. PubMed PMID: 16901357. Epub 2006/08/12. eng.

139. Halmi D, Kolesnikov E. Preoperative placement of retreivable inferior vena cava filters in bariatric surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2007 Nov-Dec;3(6):602-5. PubMed PMID: 17544920. Epub 2007/06/05. eng.

140. Singh S, Haut ER, Brotman DJ, Sharma R, Chelladurai Y, Shermock KM, et al. Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations. Rockville MD2013 May.

141. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. The New England journal of medicine. 2002 Mar 28;346(13):975-80. PubMed PMID: 11919306. Epub 2002/03/29. eng.

142. Hamad GG, Bergqvist D. Venous thromboembolism in bariatric surgery patients: an update of risk and prevention. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2007 Jan-Feb;3(1):97-102. PubMed PMID: 17196437. Epub 2007/01/02. eng.

143. Rowan BO, Kuhl DA, Lee MD, Tichansky DS, Madan AK. Anti-Xa levels in bariatric surgery patients receiving prophylactic enoxaparin. Obesity surgery. 2008 Feb;18(2):162-6. PubMed PMID: 18165884. Epub 2008/01/01. eng.

144. Ludwig KP, Simons HJ, Mone M, Barton RG, Kimball EJ. Implementation of an enoxaparin protocol for venous thromboembolism prophylaxis in obese surgical intensive care unit patients. The Annals of pharmacotherapy. 2011 Nov;45(11):1356-62. PubMed PMID: 22009998. Epub 2011/10/20. eng.

145. Martinez L, Burnett A, Borrego M, Streeter JC, Townsend K, Garcia D. Effect of fondaparinux prophylaxis on anti-factor Xa concentrations in patients with morbid obesity. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2011 Sep 15;68(18):1716-22. PubMed PMID: 21880887. Epub 2011/09/02. eng.

146. Raftopoulus I C-HA, Gourash W, et al. Pharmacokinetic properties of fondaparinux sodium in morbidly obese volunteers indicate that a single, weight-independent daily dose for thromboprophylaxis is feasible. Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Philadelphia, PA2008.

147. Borkgren-Okonek MJ, Hart RW, Pantano JE, Rantis PC, Jr., Guske PJ, Kane JM, Jr., et al. Enoxaparin thromboprophylaxis in gastric bypass patients: extended duration, dose stratification, and antifactor Xa activity. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2008 Sep-Oct;4(5):625-31. PubMed PMID: 18261965. Epub 2008/02/12. eng.

148. Beckman MG HC, Critchley SE, Ortel TL Venous thromboembolism: a public health concern. American journal of preventive medicine. 2010;38(4 Suppl):S495–501.

:S495–501.

149. Hall MJ DC, Williams SN, Golosinskiy A, Schwartzman A. . National Hospital Discharge Survey: 2007 summary. Natl Health Stat Rep. 2010;26:1–20,24.

.

C. Curriculum Vitae

CURRICULUM VITAE

The Johns Hopkins University School of Medicine

Kimberley Eden Steele, M.D., Ph.D. Candidate, F.A.C.S.

Demographic and Personal Information

Current Appointment

2006-present	Assistant Professor, Department of Surgery, Johns Hopkins
2009-present	Director of Adolescent Bariatric Surgery, The Johns Hopkins Center for Bariatric Surgery
2009-present	Director of Surgical Simulation and Education, Johns Hopkins Bayview Medical Center
2012-present	Associate Director of the Center for Surgical Trials and Outcomes Research (CSTOR)

Personal Data

The Johns Hopkins Center for Bariatric Surgery
4940 Eastern Avenue, A399
Baltimore, MD 21224
410-550-8553
410-550-1822
ksteele3@jhmi.edu

Education and Training

Education

1986–1990	University of Toronto, Toronto, Ontario BSc in Biology (Major); Anthropology (Minor)
1994-1995	University of Toronto, Toronto, Ontario Honors BSc in Human Biology (Major); German (Minor) Graduated with High Honors
1996-2000	Ross University School of Medicine, Distinguished Scholar/Valedictorian, Doctorate of Medicine

2011-2012	The Johns Hopkins Bloomberg School of Public Health, Graduate Training in Clinical Investigation (GTPCI), Completed MHS qualifications
2012 to present	The Johns Hopkins Bloomberg School of Public Health, Graduate Training in Clinical Investigation (GTPCI), Ph.D. Candidate

Training

2000-2001	Internship in Department of Surgery, Penn State College of Medicine
2001-2004	Residency in Department of Surgery, Penn State College of Medicine
2004-2005	Administrative Chief Resident for Trauma in Department of Surgery, Penn State College of Medicine
2004-2005	Chief Resident in Department of Surgery, Penn State College of Medicine
2005-2006	MIS Fellow in Department of Surgery, Johns Hopkins University, School of Medicine

Professional Experience

2006 to 2007	Instructor of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD
2007 to present	Assistant Professor of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD
2008 to 2011	Associate Director, The Johns Hopkins University School of Medicine Surgical Clerkship, Baltimore, MD
2009 to present	Director of Adolescent Bariatric Surgery, The Johns Hopkins Center for Bariatric Surgery, Baltimore, MD
2009 to present	Director of Surgical Simulation and Education, The Johns Hopkins Bayview Medical Center, Baltimore, MD
2012 to present	Associate Director of the Center for Surgical Trials and Outcomes (CSTOR), The Johns Hopkins University School of Medicine, Department of Surgery, Baltimore, MD
2012 to present	Director of Surgical Research, Department of Surgery, Johns Hopkins Bayview Medical Center, Baltimore, MD

Research Interests

Obesity causes and consequences, metabolic and bariatric surgery, surgical education and simulation, surgical outcomes, minimally invasive surgical techniques and foregut surgery.

Research Activities

Peer Reviewed Original Science Publications

1. Schweitzer MA, **Steele KE**, Lidor AO. *Failure of the Adjustable Gastric Band System Due To a Leak of Saline.* Surgery for Obesity and Related Disease, 2006; 2:413.

2. Schweitzer MA, **Steele KE**, Gandsas A, Lidor A, Magnuson T*, Vessel Sealing Energy Devices Used In Laparoscopic Bariatric Surgery.* Bariatric Times, April 2006;3:14-15.

3. Schweitzer MA**, Steele KE**, Lidor AO. *Acute Vena Cava Thrombosis after Placement of Retrievable IVC Filter Prior to Laparoscopic Gastric Bypass.* Surgical Obesity and Related Diseases, 2006; 2:661-663.

4. Syin D, Magnuson T, Flum D, **Steele KE**, Griffith J, Nicholson W, Uddin S, Millman A, Schweitzer M, Pawlik T,Chang D, Pronovost P, Makary M. *Pregnancy Outcomes after Bariatric Surgery.* Bariatric Nursing and Surgical Patient Care. June 1, 2007, 2(2): 113-118.

5. **Steele KE**, Prokopowicz GP, Lidor AO, Magnuson TH, Schweitzer MA. *Laparoscopic antecolic Roux-en-Y gastric bypass with closure of internal defects leads to fewer internal hernias than retrocolic approach.* Surgical Endoscopy, 2008 Sep; 22. (9):2056-61

6. **Steele KE**, Schweitzer MA, Lyn-Sue J, Kantsevoy SV. *Flexible Transgastric Peritoneoscopy And Liver Biopsy: A Feasibility Study In Humans.* Gastrointestial Endoscopy, 2008 Jul; 68. (1):61-6.

7. Melton-Meaux GB, **Steele KE**, Schweitzer MA, Prokopowicz GP, Lidor AO, Magnuson TH*. Suboptimal weight loss after gastric bypass surgery: correlation of demographics, co-morbidities, and insurance status with outcomes.* Journal of Gastrointestinal Surgery, 2008, 12 (2): 250-255.

8. Burke A, Jamshidi R, Eaton L, **Steele KE**. *Contraceptive use and unplanned pregnancy after bariatric surgery: results from the Reproductive Outcomes after Bariatric Surgery Survey*. Contraception. 2008 Aug; 78(2), 172.

9. Schweitzer MA, Mitchell M, **Steele KE**, Lyn-Sue J, Okolo P. *Transoral Endoscopic Closure of a Gastric Fistula*. Surgery for Obesity and Related Diseases: Official journal of the American Metabolic and Bariatric Surgery 2009; 5(2):283-4.

10. Sarvansky V, Jun J, Li J, Nanayakkara A, Fonti S, Moser A, **Steele KE**, Schweitzer MA, Patil SP, Bhanot S, Schwartz AR, Polotsky VY. *Dyslipidemia and Atherosclerosis Induced by Chronic Intermittent Hypoxia Are Attenuated by Deficiency of Stearoyl Coenzyme A Desaturase.* Circulation Research, 2008; 103: 1173-1180.

11. Polotsky V, Clark J, Fonti S, Schwartz A, Schweitzer M, **Steele KE**, Torbenson M. *Obstructive Sleep Apnea, Insulin Resistance and Steatohepatitis in Severe Obesity.* American Journal of Respiratory and Critical Care Medicine 2009, 179:228-234.

12. Gupta A, Chang D, **Steele KE**, Schweitzer MA, Lyn- Sue J, Lidor A*. Looking Beyond Age and Comorbidities as Predictors of Outcomes in Paraesophageal Hernia Repair.* Journal of Gastrointestinal Surgery: Official journal of the Society for Surgery of the Alimentary Tract 2008; 12(12):2119-24.

13**. Steele KE**, Mitchell M, Okolo P, Schweitzer M. *Transoral Endoscopic Closure of a Gastric Fistula.* Surgery for Obesity and Related Diseases: Official journal of the American Metabolic and Bariatric Surgery 2009; 5(2):283-4.

14. Nguyen H, **Steele KE,** Magnuson T, Lidor A, Schweitzer M. *What Bariatric Operation Would ASMBS Members Choose for Themselves?* Bariatric Times, March 2009.

15. Bennett W, Gilson M, Jamshidi R, Burke A, Segal J**, Steele KE**, Makary M, Clark J. *Impact of Bariatric Surgery on Hypertensive Disorders in Pregnancy*. British Medicine Journal, 2010; 340:c1662.

16. Spencer A, Magnuson T, Nguyen H, **Steele KE**, Lidor A, Schweitzer M. *The Evidence for Staple Line Buttress Material*. Bariatric Times, September 2009.

17. Semins MJ, Matlaga BR, Shore AD, **Steele KE**, Magnuson TH, Johns R, Makary M. *The Effect of Gastric Banding on Kidney Stone Disease.* J Urology, 2009; June 181(6):2573-7.

18. Semins M, Asplin J, **Steele KE**, Assimos D, Lingeman J, Donahue S, Magnuson T, Schweitzer M, Matlaga B. *The Effect of Restrictive Bariatric Surgery on Urinary Stone Risk Factors.* J Urology, 2010 Oct; 76(4):826-9.

19. **Steele KE**, Prokopowicz GP, Schweitzer MA, Magnuson TH, Lidor AO, Kuwabawa H, Kumar A, Brasic J, Wong DF. *Alterations of Central Dopamine Receptors Before and After Gastric Bypass Surgery*. Obesity Surgery, 2010; 20:369-374.

20. Datta TJ, **Steele KE**, Scwheitzer Ma. *Laparoscopic Left Adrenalectomy after Laparoscopic Gastric Bypass*. Surgical Obesity and Relaedt Diseases. 2010 May-June; 6(3): 306-7.

21. Datta TJ, **Steele KE**, Schweitzer M, *Laparoscopic Revision of Gastrojejunostomy Revision with Truncal Vagotomy for Persistent Marginal Ulcer after Roux-en-Y Gastric Bypass.* Surg Obes Relat Dis.
2010 Sep-Oct;6(5):561-2.

22. Pallayova M, **Steele KE**, Magnuson TH, Schweitzer MA, Hill NR, Bevans-Fonti S, Schwartz AR. *Sleep apnea predicts alterations in glucose homeostasis and biomarkers in obese adults with normal and impaired glucose metabolism.* Cardiovascular Diabetology. 2010 Dec 1;9:83.

23. Pallayova M, **Steele KE**, Magnuson TH, Schweitzer MA, Smith PL, Patil SP, Bevans-Fonti S, Polotsky VY, Schwartz AR. *Sleep Apnea Determines Soluble TNF-alpha Response to Massive Weight Loss.* Obesity Surgery. 2011 Sep;21(9):1413-23.

24. Lin B, Hyndman ME, **Steele KE**, Feng Z, Trock BJ, Schweitzer MA, Pavlovich CP. *Incidence and risk factors for inguinal and incisional hernia after laparoscopic radical prostatectomy.* Urology. 2011 Apr;77(4):957-62. [Epub 2011 Feb 18.]

25. Lidor AO, Chang DC, Feinberg RL, **Steele KE**, Schweitzer MA, Franco MM. *Morbidity and mortality associated with antireflux surgery with or without paraesophageal hernia: a large ACS NSQIP analysis.* Surgical Endoscopy. 2011 Sep;25(9):3101-8. Epub 2011 Apr 22.

26. **Steele KE**, Schweitzer M, Shore A, Makary M, Nguyen H, Lidor A, Prokopowicz G, Magnuson T. *Long-term Risk of Venous Thromboembolism Following Bariatric Surgery.* Obesity Surgery. 2011 Sep; 21(9):1371-6.

27. **Steele KE**, Prokopowicz GP, Chang H, Richards T, Clark J, Weiner J, Bleich S, Wu A, Segal J. *Risk of Complications after Bariatric Surgery Among Individuals With and Without Type 2 Diabetes Mellitus.* Surgical Obesity and Related Diseases. 2012 May-Jun;8(3):305-30. Epub 2011 Jun 15.

28. Bleich S, Chang H, **Steele KE,** Segal J. *Impact of Bariatric Surgery on Healthcare Utilization and Costs among Patients with Diabetes.* Medical Care. 2012 Jan;50(1):58-65.

29. **Steele KE**, Lidor A, Magnuson T, Wong D, Schweitzer MA. *Obesity and the Brain: Implications for the Surgeon.* Bariatric Times. 2011;8(7):12–13.

30. Eaton, LCB, Walsh CM, Magnuson TH, Schweitzer MA, Lidor AO, Nguyen HT, **Steele, KE**. *An online bariatric surgery information session is as effective as an in-person information session.* Surgical Obesity and Related Diseases. 2012 Mar-Apr;8(2):225-9; discussion 229. Epub 2011 Nov 7.

31. Tymitz K, **Steele KE**, Schweitzer M. *Laparoscopic single-incision repair of internal hernia defects using an intracorporeal suturing techniques.* Surgical Obesity and Related Diseases, 20011; 7(6):778-80.

32. Coughlin J, Guarda A, Clark J, Furtado M, **Steele KE**, Heinberg L. "*A Screening Tool to Assess and Manage Behavioral Risk in the Postoperative Bariatric Surgery Patient: The WATCH".* The Journal of Clinical Psychology in Medical Settings (J Clin Psychol Med Settings). 2013 Dec; 20(4):456-63.

33. Chen, C, Colbert-Getz J, Green I, **Steele KE**, Lawson S, Chou B, Andersen D, Satin A. *Warm-Up on a Simulator Improves Resident's Performance in Laparoscopic Surgery: A Randomized Trial.* Int Urogynecol J. 2013 Oct; 24(10):1615-22.

34. Kawaji Q, Marohn M.,Stem M, Fleming R. M., Schweitzer M.A., **Steele KE**, Lidor A.O. *Defining Recurrence After Paraesophageal Hernia Repair: Correlating Symptoms And Radiographic Findings.* Surgery. 2013 Aug; 154(2):171-8.

35. Knoepp L., Semins MJ, Shore A, Wright J, **Steele KE**, Chen G, Matlaga B, Clark J, Makary M. *Does Bariatric Surgery Affect Urinary Incontinence?* Urology. 2013 Sep; 82(3):547-51.

Review Articles

1. **Steele KE**, Makary MA, Eckhauser FE*. Review of Postoperative Surveillance in Patients with Colorectal Cancer Who Have Undergone Curative Resection*. American Journal of Oncology Review, 2006; 24(3): 386-394.

2. Gupta A, **Steele KE**, Schweitzer M, Lidor A, Lyn-Sue J. *Surgical Site Infection in the Morbidly Obese Patient:* A Review. Bariatric Times 2008; 5: 30-33.

3. Hyams E, **Steele KE**, Matlaga B. *Bariatric Surgery and Risk of Stone Disease*. American Urology Society. 2012 Update Series Volume 31 [CME]

State of The Art Articles

1. **Steele KE**, Schweitzer MA, Lidor AO. *Prophylaxis of Venous Thromboembolism in Gastric Bypass Patients: The State of The Art.* Bariatric Times Sept, 2006; 3:8-9.

Educational Publications

Case Reports

1. **Steele KE**, Schweitzer MA, Lidor AO, Magnuson TH. *An Unusual Case of a Gastric Bezoar Causing Obstruction after Roux-en Y Gastric Bypass*. Surgery for Obesity and Related Diseases, 2006;2:536-537.

Invited Critique & Editorials

1. **Steele KE.** Hospital Complication Rates with Bariatric Surgery in Michigan Centers of Excellence: The Emperor's New Clothes? Archives of Surgery, *Arch Surg.* 2011;146(3):254-255.

2. **Steele KE.** Recent National Trends in the Use of Adolescent Inpatient Bariatric Surgery, 2000 through 2009. Why Isn't Bariatric Surgery for Adolescents Catching On? *JAMA Surg.* 2013; 148(4): 314-315.

Book Chapters

1**. Steele KE**, Lidor AO, Laparoscopic Cholecystectomy. In Cameron JL, editor. Current Surgical Therapy 9th edition. Mosby; 2008: chapter-Minimally Invasive Surgery.

2. Marohn MR, **Steele KE**, Lawler LP. Minimally Invasive Surgical and Image Guided Interventional Approaches to the Spleen. In Yeo CJ, editor. Shackleford's Surgery of the Alimentary Tract. 5th edition. Chpt 127, pp 1780-1797. Saunders/Elsevier; 2007.

3**. Steele KE**, Wolfgang C. Nutrition. General Surgery Review, 2nd edition Makary MA, editor. Chpt 38, pp 461-471. Ladner-Drysdale: Washington D.C., 2006.

4. **Steele KE**, Dackiw A. Adrenal Gland. General Surgery Review, 2nd edition, Makary MA, editor. Ladner-Drysdale: Chpt 19, pp 269-284. Washington D.C., 2006.

5. **Steele KE**, Magnuson T, Schweitzer MA. Obesity and Bariatrics. General Surgery Review, 2nd edition Makary MA, editor. Chpt 14, pp 199-206. Ladner-Drysdale: Washington D.C., 2006.

6. **Steele KE**, Lidor AO. Hasson Canula. The Sages Manual of Strategic Decision Making: Case Studies in Minimal Access Surgery. Ch1, pp5-7 Springer 2008.

7**. Steele, KE**, Zeiger, MA Testosteronoma - Contemporary Endocrinology, A Cased-Based Guide to Clinical Endocrinology**.** Part XVI, 489-497. Humana Press/Elsevier, 2008.

8. Vaidya V, **Steele KE**, Schweitzer M, Shermak M. Surgical Weight Loss for Obesity. Kaplan and Sadock's Synopsis of Psychiatry 9th Edition: Behavioral Sciences/Clinical Psychiatry. Sadock B, Sadock VA and Ruiz P, editor. Chpt 24.4, pp 2273-2289. Lippincott, Williams and Wilkins, 2009.

9. **Steele KE**, The Stomach and Duodenum. Chapter 13. Lawrence Textbooks, Essentials of General Surgery 5th edition. Chpt 13. pp 244-273. Lippincott, Williams and Wilkins, 2013.

10. **Steele KE**, Wolfgang C., De la paz E. Nutrition. General Surgery Review, 3rd edition Makary MA, editor. Ladner-Drysdale: Washington D.C., 2013. (in press)

11. **Steele KE**, Magnuson T, Zuberi K. Obesity and Bariatrics. General Surgery Review, 3rd edition Makary MA, editor. Ladner-Drysdale: Washington D.C., 2013. (in press)

Monographs

1. **Steele KE**, Burke A. American College of Obstetricians and Gynecologists (ACOG) - Clinical Updates in Women's Health Care. *Weight Loss Surgery and Obesity*. Vol XII, No. 1. Jan. 2013.

Video Presentations

1. **Steele KE**, Schweitzer MA, Laparoscopic Revision of a Staple Line Dehiscence after Open Roux-en-Y Gastric Bypass. 2007 Video- Based Education Session accepted for presentation at American College of Surgeons on New Orleans 2007.

2. Schweitzer MA, Mitchell M, **Steele KE**, Lynn-Sue J, Okolo P. Transoral endoscopic closure of a gastric fistula. American Society of Metabolic and Bariatric Surgeons, Video Session, Washington, DC, June 2008.

3. Nguyen H, Schweitzer MA, **Steele KE**, Lidor AO. Laparoscopic Truncal Vagotomy and Gastrojejunostomy for Chronic Marginal Ulcer after Gastric Bypass. SAGES Video Sessions, 2009.

Extramural Sponsorship

Current Grants

1. 11/30/2008 to present, Mechanisms of sleep apnea in severe obesity.
   Identification number - RO1HL050381
   Sponsor- NIH
   Total direct costs=$1,030,196. Current year direct costs=$247,613.
   Principal Investigator- Alan R Schwartz, M.D.,
   Co-investigator – Kimberley E. Steele, M.D., percent effort - as needed. Active recruitment

2. 8/2009 to present, A pilot study to determine the feasibility of conducting a randomized clinical trial comparing fondaparinux sodium (Arixtra) once daily with enoxaparin (Lovenox) twice daily with respect to preventing venothromboembolism after bariatric surgery in obese patients.
   Sponsor - Glaxo SmithKline Investigational Initiated Grant
   Grant award=$348,936.00
   Principal Investigator - Kimberley E. Steele, M.D.,percent effort - 4%. Active recruitment.

3. 05/2010 to present, Improving Diabetes through Lifestyle of Surgery (IDeaLs) Clinical Trial. Laparoscopic Roux-en Y Gastric Bypass, Laparoscopic Adjustable Gastric Banding or Diet Alone in the lower BMI of 30 to 35.
   Identification number - 5KL2RR025006
   Sponsor – NIH
   Total direct costs= $250,000.
   Principal Investigator - Jeanne Clark, M.D.
   Co-investigator - Kimberley E. Steele, M.D., percent effort - as needed. Active recruitment.

4. 07/01/2011 to 05/30/2014, **NIH Clinical Scholar Award (KL2): Institute for Clinical and Translational Research, The Johns Hopkins University.**
   Identification number - 5KL2RR025006.
   Total award amount: $301,080.
   Principal Investigator – Kimberley E. Steele, M.D., percent effort – 80%, Presently, at the Johns Hopkins Bloomberg School of Public Health completing my Ph.D. in Graduate Training and Clinical Investigations. Scheduled to graduate June 2014.

5. 07/2013 to 06/2015, Serum Contraceptive Hormone Levels before and after gastric bypass surgery
   Sponsor – Family Planning Association
   Total award – $250,000
   Principal Investigator – Ann Burke, M.D., M.P.H.
   Co-PI – Kimberley E. Steele, M.D., percent effort – 1%, have not started recruitment

6. 07/2013 to 6/30/2014, Neurochemical Changes Induced by Bariatric Surgery: The Gut-Brain Axis and its Relationship to Weight Loss
   Sponsor – American Metabolic and Bariatric Society (ASMBS)
   Total grant award - $ 49, 632.
   Principal Investigator – Kimberley E. Steele, M.D., percent effort – 5%

Pending Grants

1. 10/2014 to 01/31/2018, Neurobiolgic Biologic Alterations in Bariatric Surgery: Taste response and weight loss (K23 application)
   Sponsor – NIH, NIDDK
   Total grant award – $742, 298.
   Principal Investigator – Kimberley E. Steele, M.D., percent effort – 75%, to be reviewed in June 2013.
   Primary Mentor – Dr. Timothy Moran

2. 07/2014 to 06/30/2015, Supplementary Funding for the K23 grant: Neurobiologic Alterations in Bariatric Surgery: Taste response and weight loss
   Sponsor – The Johns Hopkins Bloomberg School of Public Health 2013: The Bacon Field Chow Memorial Fellowship Award
   Total grant award - $23, 500
   Principal Investigator – Kimberley E. Steele, M.D., percent effort – 1%

3. 07/2014 to 06/2016, The Effect of Pre-operative Warm-up on Operative Performance
   Sponsor – Society of American Gastrointestinal and Endoscopic Surgeons
   Total grant award – $29, 666
   Principal Investigator – Kimberley E. Steele, M.D., percent effort – 5%

4. 10/2014, Feasibility and Safety of the OverStitch Endoluminal Vertical Sleeve Gastroplasty
   Sponsor – NIH (R21)
   Total award - $429, 752
   Principal Investigator – Nisa Maruthur, M.D., M.P.H.
   Co-Investigator – Kimberley E. Steele, M.D., percent effort – 1%

5. 07/2014 to 07/2015, Metagenomic Analysis of the Human Gut Microbiome before and after Bariatric Surgery: Comparison of Roux-en Y Gastric Bypass and Sleeve Gastrectomy
   Sponsor – Hopkins Digestive Diseases Basic Research Core Center Pilot Project
   Total award – $25, 000
   Principal Investigator – Jeanne Clark, M.D.
   Co-Investigator – Kimberley E. Steele, M.D., percent effort 1%

6. 12/01/2014 to 11/18/2019, Implementing behavioral treatment to reverse weight gain after bariatric surgery
   Sponsor – NIH subcontract with University of Pennsylvania
   Total award - $1,678,270.00
   Prinicipal Investigator – Janelle Coughlin, Ph.D.

Co-Investigator – Kimberley E. Steele M.D., percent effort 5%

7. 07/01/2014 to 06/30/2016, *APB study* – Apixaban Pharmacokinetics in Bariatric Patients: A study to determine the pharmokinetics and pharmodynamics of apixaban in obese patients who undergo bariatric surgery.
   Sponsor- Pfizer
   Total award - $100,000.00.
   Prinicpal Investigator-Kimberley E. Steele M.D.
   Co-investiagors-Brent Petty M.D., Michael Streiff M.D., Thomas Kickler M.D., Charlie Flexner M.D., Michael Schweitzer M.D., Thomas Magnuson M.D.

8. 07/01/2014 to 06/30/2016, The SAVIOR trial: **S**urgical **A**pplication of **V**ac dressings **I**n **O**bese patients to **R**educe wound complications.
   Sponsor-KCI
   Total award-$100,000.00.
   Principal Investigator-Kimberley E. Steele M.D., Mahmood Malas M.D., M.P.H.

9. 07/01/2014 to 06/30/2015, Educating the Bariatric Surgical Patient: *A comprehensive educational video to enhance patient learning and improve patient safety and outcomes in the peri-operative period*.
   Sponsor- Hospital Relations Committee of The Women's Board of Johns Hopkins
   Total award-$15,455.00
   Principal Investigator-Kimberley E. Steele M.D., Taylor Beauregard Kelamis, RN and Nicole Shacochis-Edwards, RN.

Previous Grants

1. 8/2006 to 8/2007, Brain dopamine receptor activity in obese subjects before and after gastric bypass surgery.
   Sponsor - The Association of Women Surgeons,
   Grant award=$25,000
   Principal Investigator - Kimberley E. Steele, M.D., percent effort - as needed.
   Project completed and paper published.

2. 07/2009 to 04/2010. An Agency for Healthcare Research and Quality (AHRQ)/Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network Grant Project. Bariatrics and diabetes.
   Sponsor – AHRQ (DEcIDE)
   Principal Investigator - Jody Segal, M.D.
   Co-Investigator - Kimberley E. Steele M.D., percent effort=17%. Project completed. Three papers published.

Intramural Sponsorship

1. 04/2/2007 to present, Association of Taq A1 allele with suboptimal weight loss in obese patients undergoing Roux-en Y gastric bypass.
   Sponsor - The Johns Hopkins University School of Medicine Department of Surgery
   Total grant award=$20,000.

Principal Investigator - Kimberley E. Steele, M.D., percent effort=as needed.
Active recruitment.

2. 07/01/2013 to 06/30/2015, **Clinician Scientist Award**.
   Sponsor – The Johns Hopkins University School of Medicine, Dean Rothman
   Total grant award=$160,000.
   Principal Investigator – Kimberley E. Steele, M.D., percent effort=75% protected time.

Research Program Building / Leadership

07/2012 to present	Associate Director of The Center for Surgical Trials and Outcomes Research (CSTOR), Department of Surgery, JHSOM. In my capacity, I am responsible for supervising (2 research coordinators and a research nurse) the day to day operations, education and leadership of our faculty's clinical trials.
07/2012 to present	Director of Surgical Research, Department of Surgery, Johns Hopkins Bayview Medical Center. I supervise two research coordinators and mentor medical students, pre-med students, housestaff, MPH/graduate students/Ph.D. students, PA's, NPs and fellows in surgical research and clinical trials.

Educational Activities

Classroom Instruction

1997-1999	Tutorial Leader for Anatomy and Physical Diagnosis and Clinical Medicine Ross University Year 2 Medical Students, Ross University School of Medicine, Portsmouth, Dominica.
04/2003	Third Year Medical Students Surgical Clerkship Penn State College of Medicine, Instructor, Hershey, PA
08/2003	Chest Tubes and Their Management In-service for Critical Care Nursing/SICU, Instructor, Penn State College of Medicine Hershey, PA
05/25-26/2004	ATLS Course General Surgery Incoming Residents, Instructor, Penn State College of Medicine Hershey, PA
07/21-29/2004	The First Three Days in Surgery General Surgery Incoming Residents, Instructor, Penn State College of Medicine, Hershey, PA
09/2006 to 2011	Basic Surgical Clerkship for Medical Students, Preceptor (meet once weekly for 1 to 2 hours), Johns Hopkins University Medical School, Baltimore, MD

09/2006 to 2011	Student Surgical Clerkship Weekly Lecture Series, Associate Director of the Surgical Clerkship, Johns Hopkins Bayview Medical Center, Baltimore, MD
07/2007, 2008, 2009	OSATS for the General Surgery Incoming Interns, Faculty, Blalock 12th floor, MISTC Johns Hopkins Hospital, Baltimore, MD
09/2007 to 2011	Laparoscopic Simulation Curriculum for the Surgical Clerkship, 4 hour lab/course given quarterly to all medical students years 2 to 4 in the surgery clerkship, Faculty, Blalock 12th floor, MISTC Johns Hopkins Hospital, Baltimore, MD
01/31/08 to 2012	Basic and Complex Laparoscopic Skills Curriculum, responsible for developing and teaching these modules to surgical interns and residents, 3 hour labs every Thursday, Author and Faculty, The Johns Hopkins Surgical Residency Program, Baltimore, MD
08/2009 to 2012	General Surgery Skills (Chest Tubes, PETs, PEGs, bronchoscopy, bowel anastomoses, hernias, trauma, vascular anastomoses), responsible for developing and teaching these modules to surgical interns and residents, 3 hour labs every Thursday, Author and Faculty, The Johns Hopkins Surgical Residency Program, Baltimore, MD
11/2008 to present	Mock Orals, Faculty for surgical residents PGY 3-5, quarterly to semi-annually, Johns Hopkins Department of Surgery, Baltimore, MD.
03/28/2010	PRECEDE Surgical Clerkship Lecture Series: Basic Radiology, 1 hour lecture, Substitute Faculty, Blalock 12th floor MISTC, Johns Hopkins Hospital, Baltimore, MD
05/13/2010	Surgical Resident Lecture Series, Complications and Management of Bariatric Patients, 1 hour lecture, Faculty, Blalock 12th floor MISTC, Baltimore, MD
05/18/2010	Surgical Boot Camp for Medical Students, Assistant Director and Faculty, The Johns Hopkins University School of Medicine Surgical Clerkship, Blalock 12th floor MISTC, Baltimore, MD.
10/25/2010	PRECEDE Surgical Clerkship Lecture Series: Basic Radiology, 1 hour lecture, Substitute Faculty, Blalock 12th floor MISTC, Johns Hopkins Hospital, Baltimore, MD
10/19/2010 to 10/22/2010	Intersession: Metabolism and Obesity, Small Work Group Leader (Management of Obesity via Surgery) and Debate (Adolescent Bariatric Surgery), The Armstrong Building, Baltimore, MD

2/17, 2/24 and 3/3/2011	Transition to the Wards (TTW): Clinical History and Physical Exams, Faculty (2nd year medical students 3hrs per session), Johns Hopkins Hospital, Baltimore, MD
3/3/2011	Surgical Management of Obesity, Faculty (1 hour lecture to the surgical intern class), Turner Auditorium, Baltimore, MD
3/3/2011	Transition to the Wards (TTW): Examiner of medical students on placement of intravenous catheter (two hour session), JHOC Simulation Center, Baltimore, MD
4/6/2011 and 5/18/2011	PRECEDE: Central Line Sterile Technique and Safe Placement, didactic and technical skills lab, Faculty (15 medical students per three hour session), JHOC Simulation Center, Baltimore, MD
4/6/2011	PRECEDE: One hour lecture on GI Bleeding, Faculty, Blalock 12th floor MISTC, Baltimore, MD
5/20/2011	The Halsted: "New Hands" Surgical Send Off Camp for Medical Students, Faculty, (2 hour session), The Johns Hopkins University School of Medicine Surgical Clerkship, Blalock 12th floor MISTC, Baltimore, MD.
10/19/2011 to 10/20/2011	Intersession: Metabolism and Obesity. Small Work Group Leader (Management of Obesity via Surgery) and Debate (Adolescent Bariatric Surgery: Should It Be Done?), Faculty, the Armstrong Building, Baltimore, MD
12/14/2011	Health Promotion and Disease Prevention Course: Obesity and Surgical Options (lecture for the first year medical students), Faculty, The Armstrong Building, Baltimore, MD
02/25/2013	Transition to the Wards(TTW 2013), Surgical Scrub and Gown Practical Session, 9 to noon and Knot Tying and Suturing session, 1 to 5pm, Faculty, the Armstrong Building, Baltimore, MD
02/26/2013	Transition to the Wards (TTW 2013), Nasogastric Tube Insertion Practical Session, 1 to 5pm, Faculty, JHOC Simulation Center, Baltimore, MD
02/28/2013	Faculty for Transition to the Wards (TTW 2013), Examiner of medical students on intravenous catheter placement technique, 1 to 3pm, JHOC Simulation Center, Baltimore, MD
10/15 to 10/17/2013	Faculty for the Year 3 and 4 Metabolic Intersession 2013, One hour lecture on Why bariatric surgery works and small group sessions 1.5 hours x 2, The Johns Hopkins University School of Medicine, Baltimore, MD

CME Instruction

05/8 to 9/2006	SAGES Advanced Foregut Resident Course, Invited Faculty (16 hour instruction), Ethicon Endo-Surgery, Cincinnati, Ohio
05/21/2006	US Surgical Workshop: Endostitch and Intracorporeal Suturing Training Course, Faculty, Blalock 12th floor MISTC, Baltimore, MD.
03/8 to 9/2007	SAGES Advanced Laparoscopic Hernia Surgery Resident Course, Invited Faculty (16 hour instruction), US Surgical Compound, Norwalk, CT
06/18/2012	Laparoscopic Suturing and Skills Course, the Association of Metabolic and Bariatric Surgery (ASMBS) Annual Conference 2012, Core Faculty, (4 hour course for International Surgeons), University of San Diego, Minimally Invasive Simulation Labs, San Diego, California.

Workshops/Seminars

03/21/2008	Perioperative Care of the Bariatric Patient: Surgical Nursing In-service, Faculty, 6th Floor Surgery, Johns Hopkins Bavyiew Medical Center, Baltimore, MD
02/27/2009	Importance of Ambulation and Incentive Spirometry in the Bariatric Patient, In-service Faculty, 6th Floor Surgery, Johns Hopkins Bayview Medical Center, Baltimore, MD
02/07/2012	Welch Center Journal Club/Seminar, The Johns Hopkins Bloomberg School of Public Health MPH and PhD program, noon conference. Invited expert for article presented: Sjostrom L, et al. Bariatric Surgery and Long-term Cardiovascular Events. JAMA 2012;307(1) 56-65., Whelton Conference Room, Welch Center, The Johns Hopkins Bloomberg School of Public Health and School of Medicine, Baltimore, MD.
02/20/2012	Miller-Coulson Academy of Clinical Excellence (MCACE) and the Residency Program Clinical Pathology Conference (CPC), invited by Scott Wright MD, Director of Miller-Coulson Academy, Faculty Johns Hopkins Bayview Medical Center, Baltimore, MD

Clinical Instruction

07/2005 to present per week	Outpatient surgical service/clinic, surgical attending ½ to 1 session
07/2005 to present	Inpatient surgical service/operating room, surgical attending, on average 3.5 days per week

Mentoring

2005 to present	I have mentored numerous medical students (The Johns Hopkins University School of Medicine and international students including students from Japan, Egypt, India and Greece), nurse practitioners, engineers and surgical residents.

Examples of student mentees:

Kendra Harris MD, MHS, Johns Hopkins SOM 2007-2008, went on to radiation oncology residency at JHH.
Michael Brinkley, MD, Johns Hopkins SOM 2007-2008, mentored Michael and helped him earn the Doris Duke Award and Fellowship.
Sam Hsieh, Royal College of Surgeons, Ireland, Ireland, 2008 to 2009, awarded MD degree
Konstantinos Economopoulos, medical student from Greece, Dec. 2008, completed sub-internship rotation with me as his supervisor.
Hyaehwan Kim, Thomas Jefferson University, medical student, Feb. 2008, completed sub-internship rotation with me as her supervisor.
Luis Carlos Cajas-Monson, MD, MPH, Johns Hopkins SOM 2010-2011, awarded MD degree and went on to UCSD for surgical residency.
Katie Schlafer, Dickinson College, BSc. (pre-med), 2010-2011
Stephanie Baltch, Gaucher College, Baltimore, MD (pre-med program), 2012-2013
Elizabeth Goutha, Gaucher College, Baltimore, MD (pre-med program), 2013-2014
Anant Subramaniam, CBID Biomedical Engineering, Johns Hopkins University, September 2013, provided mentorship on school team project - the need to prevent or diagnose anastomotic dehiscence following GI/bariatric surgery
Gamal Abdalla, medical student from Ains Shams University, Egypt (completing a 3 month research elective with me), Jan.to April 2014

2006 to present	The Johns Hopkins Minimally Invasive Surgical Fellowship; training fellows in minimally invasive and bariatric surgery Covidien and Ethicon Fellowship grant funded $75,000. I have been involved in training and mentoring the following fellows: 2006-2007: Molly Sebastian, MD 2007-2008: Hien Nguyen, MD 2008-2009: Jerome Lyn-Sue, MD 2009-2010: Hamilton Le MD, and Kevin Tymitz, MD 2010-2011: Marianne Franco MD, and Tejwant Datta, MD 2011-2012: Kathyrn Lamond, MD 2012-2013: Kashif Zuberi, MD 2013-2014: Erin Moran-Atkin, MD

2006 to present	Johns Hopkins Faculty-Instruction and mentoring of laparoscopic approach to gastric bypass, adjustable gastric band, sleeve gastrectomy, foregut surgery including Nissen Fundoplication and Paraesophageal Hernia Repair, colon resection, hernia (ventral and inguinal) repair and splenectomy, trauma call and general surgery call.
05/2010 to present	First year medical student shadowing, The Johns Hopkins first year medical students elect to shadow a surgeon for a period of time. Generally, 1 to 2 weeks.
07/2012 to 06/30/2013	*Estefania De La Paz Nicolau, MD, MPH,* physician from Mexico who completed her capstone MPH project under my supervision, The Johns Hopkins Bloomberg School of Public Health. Do Antibiotics Change the Microbiota of Bariatric Patients?
09/2012 to present	Taylor Beauregard RN and Nicole Shacochis-Edwards RN, CUSP Safety project initiated by the 6 Surgical Nursing Staff at Bayview Medical Center: Mentoring the nursing staff on a bariatric safety project. Perioperative Education Interventions for the Bariatric Surgical Patient. Chosen by the Department of Surgery for the Johns Hopkins Women's Board Grant application submission this year.

Educational Program Building

2007 to present	Developed and implemented surgical minimally invasive lab curriculum for The Johns Hopkins Department of Surgery residency program.
2007 to present	Developed and implemented surgical minimally invasive lab curriculum for The Johns Hopkins Surgical Clerkship for the second to fourth year medical students.
2009 to present	PRECEDE faculty- developed a curriculum for The Johns Hopkins medical students clerkships.
2008 to present	Instrumental in developing an hour long informational session for The Johns Hopkins Center for Bariatrics. Website and in-person based. (Goal is to educate potential patients who are interested in bariatric surgery)
01/2010 to present	Duke University surgical residency program utilizes the minimally invasive surgical curriculum that I developed.

CLINICAL ACTIVITIES

Licensure

2000 to 2005	Pennsylvania training license
2005 to present	State of Maryland D62897

Certifications

02/2006	American Board of Surgery Certificate #51053
2002 to present	Advanced Trauma Life Support Instructor
1999 to present	Advanced Cardiac Life Support
1998 to present	Basic Life Support
2006 to present	Fundamentals of Laparoscopic Surgery (FLS)

Clinical Service Responsibilities

Since 2005, I have taught medical students, general surgery residents and fellows at the Johns Hopkins University School of Medicine and surgery residents from Sinai Hospital of Baltimore. Teaching occurred on the surgical wards, conferences and in the operating room.

Weekly surgical clinic, one and one-half days of operating/surgical procedures, on average one hour of rounding on the surgical floor, trauma and general surgery call.

Clinical Program Building

Since 2006, I have been involved in developing The Johns Hopkins Center for Bariatric Surgery program.

Since 2009, I have been involved and on the committee for planning an Obesity and Metabolic Center at Johns Hopkins Institution.

Since 2009, I have been Director and program builder of the Adolescent Bariatric Surgical Program at The Johns Hopkins Center for Bariatric Surgery.

ORGANIZATIONAL ACTIVITIES:

Institutional Administrative Appointments

External Committees

2004 to 2006	Resident Liaison, Executive Council for Central Pennsylvania, American College of Surgeon Keystone Chapter
2007 to present	Society of American Gastrointestinal Endoscopic Surgeons membership committee

2008 to present	Association of Surgical Education- Surgical Simulation and Education committee
2009 to present	American Society of Metabolic and Bariatric Surgery Research and Education committee

Internal Committees

2000 to 2003	General Surgery Resident Class Representative Committee, Penn State College of Medicine
2007 to 2008	Data Safety Monitoring Board (DSMB) Johns Hopkins University School of Medicine
2008 to present	Surgical Resident Education Committee Johns Hopkins University
2009 to present	Johns Hopkins Bariatric Surgery Center of Excellence Committee
2009 to 2010	PRECEDE Medical Student Curriculum Committee
2009 to 2010	Operating Room Task Force Committee, Johns Hopkins Bayview Medical Center. Promoting a better work environment in the operating theater.
2011 to 2012	**Prevention of Venothromboembolism (VTE) at Johns Hopkins Bayview Medical Center Working Committee**.
2011 to present	Data Safety Monitoring Board (DSMB). GSK Investigator Initiated DVT Project. Johns Hopkins Bayview Medical Center, Baltimore, MD.

Journal Peer Review Activities

05/2008 to present	Contemporary Surgery
06/2008 to present	Surgical Obesity and Related Diseases (SOARD)
04/2009 to present	Archives of Surgery
05/2009 to present	Saudi Journal of Gastroenterology
02/2010 to present	Brain Research
05/2012 to present	Neuroscience Research
06/2012 to present	JAMA & JAMA Surgery (Archives of Surgery)
04/2013 to present	Annals of Surgery

Advisory Committees and Review Groups

04/09 to present	Association of Metabolic and Bariatric Surgery (ASMBS) Grant Review Committee. Grant Reviewer
02/17 to 19/2009	The Centers for Disease Control and Prevention (CDC), US Medical Eligibility Criteria for Contraceptive Use. Served as expert on panel, discussing recommendations for bariatric patients and contraceptive methods. CDC, Atlanta Georgia.
10/14/2009	The American College of Surgeons Surgical Education I Session- invited discussant. Intensive Laparoscopic Training: The impact of a simplified pelvitrainer curriculum on long term learning in surgical novices. Bonrath et al. Chicago Illinois.
October 18 2013	Requested to serve on NIH committee Special Emphasis Panel (ZRG1 AARR-F(59)). **José H Guerrier, Ph.D.** Scientific Review Officer, National Institutes of Health Center for Scientific Review, Behavioral & Social Science Approaches to Preventing HIV/AIDS, Rm 3190, MSC7852 , 6701 Rockledge Dr., Bethesda MD 20892.

Professional Societies

2003 to 2007	Candidate, American College of Surgeons
2004 to present	Association of Women Surgeons (AWS)
2004 to present Candidate (SAGES)	Society of American Gastrointestinal Endoscopic Surgeons
2006 to present	Association of Surgical Education (ASE)
2006 to present (ASMBS)	American Society of Metabolic and Bariatric Surgery
2007 to present	Fellow, American College of Surgeons (F.A.C.S)
2007 to present	American Academy of Academic Surgeons (AAS)
2010 to 2012	Liaison for the Academy of Academic Surgeons (AAS) to the Association of Women Surgeons (AWS), invited by the president of the AAS, Dr. Kevin Stavely O'Carroll.

Conference Organizers, Session Chair

02/15/2012	The AAS/AWS conference luncheon and plenary session - "Women in Surgical Leadership: Is there more to be done?" Responsible for organizing and chairing the event with invited speakers: Patricia A. Numann, MD (Past President of ACS), Julie Ann Freischlag, MD (Chair Dept. of Surgery Johns Hopkins) and Amalia Cochran, MD

Recognition

Awards and Honors

05/2000	Distinguished Scholar, Valedictorian, GPA 4.0 Ross University School of Medicine.
12/2001	Penn State Hershey Medical Center Peace Tree Book of Honor Award for Outstanding Patient Care by a Physician.
07/2002	Resident Physician Humanitarian Award: in Memory of Jane Witmer Kienle, M.D., Penn State Hershey Medical Center (This was the first time the award was given to a resident from the Department of Surgery)
11/17/2002 to 11/24/2002	Penn State Pediatric Heart Surgical Team, Dr. John L. Myers, Variety Children's Lifeline Hospital de Ninos, Dr. Roberto Gilbert E Quayaquil, Ecuador. (This was the first time a 2nd year surgical resident was asked to accompany Dr. Myers, in general he only brings his cardiothoracic 2nd year fellow)
07/2003	Resident Case Study Challenge Winner PGY3; Penn State College of Medicine Surgical Residents
07/2003 to 2006	AMA Physician Recognition Award in Continuing Medical Education
08/2006	Nominated for Association of Women Surgeons Female Surgical Resident of the Year 2006.
07/16/2008	Shining Star- Excellence in Clinical Care. Johns Hopkins Bayview Medical Center. Baltimore, MD.
06/22/2011	Outstanding Teaching Award, Faculty Teacher. The Basic Surgery Clerkship for the 2010-2011 academic year, Johns Hopkins University School of Medicine, Baltimore, MD.
07/2012	Nominated and chosen to participate in the Office of Women In Science and Medicine 2012 Leadership

Program for Women Faculty (LPWF) Class of 2013, The Johns Hopkins University School of Medicine.

Invited Local Presentations

11/10/2005	Guest lecturer - Essex Community College Paramedic Training Graduate Course -Thoracoabdominal Trauma, Essex, MD.
03/2007	Guest lecturer - Johns Hopkins Bayview Medical Center Research Conference- Brain Dopamine Receptors and Obesity. Asthma and Allergy Conference Hall, Johns Hopkins Bayview Medical Campus, Baltimore, MD.
10/20/2006	Guest lecturer - Nutritional Implications of Obesity and The Disordered Eating Conference. Surgical Procedures for Obesity. The Carroll Auditorium, The Johns Hopkins Bayview Medical Center, Baltimore, MD.
10/19/2007	Guest lecturer - Surgical Weight Loss Surgery. National Dietician Interns Conference. Johns Hopkins Bayview Medical Center, Baltimore, MD.
10/28/2008	Guest lecturer - Obesity and Disordered Eating: Dietetic Internship Joint Class Day. Surgical Management of Obesity. Presented to Dietetic Interns from NIH, UMMS, UMd, VTech, NOVA and Sodexo. Carroll Auditorium, Johns Hopkins Bayview Medical Center, Baltimore, MD.
12/11/2009	Dietician Internship Joint Class Day - Obesity and Disordered Eating. Bariatric Surgery and Nutrition Implications. Carroll Auditorium, Johns Hopkins Bayview Medical Center, Baltimore, MD.
01/09/2010	Guest lecturer - Department of Surgery Annual Retreat 2010. An Update on Research at Johns Hopkins Bayview Medical Center. The Armstrong Medical School Building, Baltimore, MD.
01/28/2010	Invited Speaker - The Johns Hopkins Community Physician Pediatric Division Wyman Park. The Surgical Management of Adolescent Obesity. Wyman Park Medical Plaza, Baltimore, MD.
03/05/2010	Invited speaker -The Johns Hopkins Hospital 2nd Annual DVT Awareness Symposium. The Prevention of Venous Thromboembolism in the Bariatric Surgical Patient. Hurd Hall, Johns Hopkins Hospital, Baltimore, MD.
1/14/2011	Guest panelist - Women in Surgery, medical student meeting with Dr. Julie Ann Freischlag and women faculty. Armstrong Building, The Johns Hopkins University School of Medicine, Baltimore, MD.

5/8/2011	Invited panelist- The Johns Hopkins University Pre-Health Leadership Conference. A Women's Journey: on becoming a surgeon. The Johns Hopkins University, Glass Pavilion, undergraduate campus, Baltimore, MD.
9/8/2011	Invited speaker - Research Symposium. Halsted Society National Meeting. Central dopamine and its relationship to obesity. The Johns Hopkins Hospital-Hurd Hall, Baltimore, MD.
12/5/2011	Dietician Internship Joint Class Day-Obesity and Disordered Eating. The Surgical Management of Obesity. Asthma and Allergy Auditorium, Johns Hopkins Bayview Medical Center, Baltimore, MD.
11/16/2012	Invited faculty and speaker: The Center for Clinical Trials (CCT) and the Graduate Training Program in Clinical Investigation (GTPCI) at the Bloomberg School of Public Health welcomes Dr. Robert M. Califf as a visiting scholar. The Challenges of Clinical Trials: from a clinician's standpoint. The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.
12/10/2012	Invited lecturer, The 2012 Annual Dietetic Joint Intern Conference. The Obesity Epidemic: When surgery is the only option. The Asthma and Allergy Center, The Johns Hopkins Bayview Medical Center, Baltimore, MD.

Invited National Presentations

09/06/01	Invited speaker-"Case Study: Presacral cyst—iatrogenic etiology?", Visiting Professor Presentation for David Schoetz, Jr., Professor of Surgery, Tufts University School of Medicine, Division of Colon and Rectal Surgery, Penn State College of Medicine, Hershey, PA.
11/19/2002	Invited speaker-"Case Study: FAP, desmoid and adrenal incidentaloma", Visiting Professor Presentation for James Fleshman, Washington University School of Medicine, Section Chief, Colorectal Surgery Division of Colon and Rectal Surgery, Penn State College of Medicine, Hershey, PA.
09/11/2003	Invited speaker- "Case Study: Recurrent GI Bleed Secondary to Jejunal Diverticulum", Visiting Professor Presentation for Zane Cohen, Division Chair, University of Toronto, Division of Colon and Rectal Surgery, Penn State College of Medicine, Hershey, PA.
12/03/2003	Invited speaker-"Squamous Cell Carcinoma Case Presentation: An Incidental Finding within a Hemorrhoid" GI/Endoscopy Rounds, Penn State Hershey Medical Center, Hershey, PA.

05/15/2005	Nursing Grand Rounds -"Critical Care Nursing Update" Trauma Critical Care Module for Nurses in Training. Holy Spirit Hospital, Camp Hill, PA.
05/06/2006	Invited speaker - Cleveland Clinic International Video Web Teleconference: Laparoscopic Morgagni Hernia Repair. Presented from The Minimally Invasive Surgical Center at Johns Hopkins Hospital, Baltimore,MD.
10/30/2007	Guest lecturer - Adolescent Obesity: Tools to help clinicians evaluate and treat, CME: Frederick Maryland.
04/2008	Guest lecturer - Safe Access and Trocar Placement in the Previously Operated Abdomen. American College of Surgeons Conference- Minimally Invasive Surgery Course, San Francisco, California.
12/05/2009	Guest lecturer - Pri-med 2010 Conference Plenary Session - Harvard Medical School and The Johns Hopkins University School of Medicine. The Surgical Management of Obesity. The Baltimore Convention Center, Baltimore, MD.
05/05/2010	Meet the Professor-55th Annual Philip A. Tumulty Topics in Clinical Medicine Course. Case presentations/Question and Answer seminiar on bariatric patients. Turner Auditorium, The Johns Hopkins University School of Medicine, Baltimore Maryland.
05/05/2010	Invited speaker - 55th Annual Philip A. Tumulty Topics in Clinical Medicine. Weight loss Surgery 101: for the primary care physician. Turner Auditorium, The Johns Hopkins University School of Medicine, Baltimore Maryland.
5/4/2011	Meet the Professor-56th Annual Philip A. Tumulty Topics in Clinical Medicine Course. Seminar on what every primary care physician needs to know about bariatric patients. Turner Auditorium, The Johns Hopkins University School of Medicine, Baltimore Maryland.
02/15/2012	Moderator for Association of Women Surgeons Luncheon-Women in Surgical Leadership: Is there more to be done? Organized the event with invited speakers including Drs. Patricia J Numann (President of the American College of Surgeons), Julie Ann Freischlag and Amalia Cochran. The Association of Academic Surgeons (AAS) Annual Surgical Conference Feb. 13-17 2012, Las Vegas, ND.
5/10/2012	Meet the Professor - 57th Annual Philip A. Tumulty Topics in Clinical Medicine Course. A Question and Answer Session - A Primer on Bariatric Surgery for the Primary Care Physician. The Johns Hopkins University School of Medicine, Baltimore Maryland.

10/05/2012	Invited speaker at the plenary session for the 2012 Annual Meeting of The North American Menopause Society (NAMS). Obesity: When surgery is the only option. Gaylord Palms Convention Center, Orlando Florida.
10/05/2012	Meet The Professor for the 2012 Annual Meeting of The North American Menopause Society (NAMS). Obesity Surgery: A primer for the primary care physician. Gaylord Palms Convention Center, Orlando Florida.
11/12/2013	ASMBS 2013 Obesity Week – Bariatric Research – Faculty. Research Assessment Methods – How They Differ from What is Recorded for Clinical Care. Atlanta, GA.

Invited International Presentations

3/19/08	Johns Hopkins International Lecture Series: Bariatric Surgery- Procedures and Complications. Presented to Al Mishari Hospital in Riyadh, Saudi Arabia Teleconference, Johns Hopkins Medicine Telehealth. Johns Hopkins Hospital, Baltimore, MD.
3/17/09 to 3/20/09	Invited lecturer- Gastroenterology and Hepatology Viva La Vida Conference. Lecturing on 2 subjects: a) The Management of Bariatric Patients and b) The Surgical Management of Crohn's Disease. The Ritz Carlton Convention Center, San Juan, Puerto Rico.
6/1/2012	3rd Annual International Women in Surgery Career Symposium. Faculty for the medical students and resident plenary session. Pregnancy in Surgical Residency: how to make it work. Hyatt Regency Convention Center, Baltimore, Maryland.

Grand Rounds

03/18/2008	Grand Rounds, Johns Hopkins Community Physicians: Surgical Weight Loss for the Primary Care Physician: What we need to know. Presented to Johns Hopkins Community Physician Group, Burton Pavilion, Johns Hopkins Bayview Medical Center, Baltimore, MD
06/04/2010	Internal Medicine/Multidisciplinary Grand Rounds, Harbor Hospital: The Surgical Management of Obesity: What the primary care physician needs to know, Harbor Hospital, Baltimore, MD.
6/10/2011	Internal Medicine Grand Rounds: Surgical Weight Loss Complications, Harbor Hospital, Baltimore, MD.

12/5/2011	Sleep Medicine Grand Rounds: Weight Loss Surgery and the Effects on Sleep Apnea, Asthma and Allergy, Rm4B44 Conference Hall, The Johns Hopkins Bayview Medical Center, Baltimore MD.
09/28/2012	Pediatric Grand Rounds at Mercy Medical Center: Childhood Obesity: When is surgical intervention an option? Mercy Medical Center, Baltimore, MD
12/07/2012	Grand Rounds, Department of Surgery: Childhood Obesity: When is surgical weight loss appropriate? The Johns Hopkins Bayview Medical Center Department of Surgery, Baltimore, MD
05/22/2013	Grand Rounds: Bariatric Mini-Symposium, Department of Endocrinology, Central Dopamine and the Effect of Weight loss and Taste/ Appetite, Marburg Conference Room, The Johns Hopkins Hospital, Baltimore, MD

Other Professional Accomplishments

Community Service

1994 to 1995	Note taker for students with disabilities University of Toronto Volunteer Service for the Department of Special Services, Toronto, Ontario, Canada
January 1995	Special Guest: Ice Skating Performance for the Canadian Association of Muscular Dystrophy, Maple Leaf Gardens, Toronto, Ontario, Canada
2009 to 2010	Washington Hill Community Board Member, citizens in the community cleaning-up Washington Hill, Improving our city, Baltimore City, MD.

Personal Achievements

1983 to 1990:	Member of the Canadian National Ice Dance Center and Granite Figure Skating Club, National Competitor, Toronto, Ontario, Canada.
1991 to 1992	German National Bavarian Ice Dance Champion, Oberstdorf, Germany
1992 to 1994	International Carded Athlete, member of the German National Figure Skating Team (Ice Dancing). Olympic Team Member 1994

D. Brief Biosketch

Dr. Steele was born in Oakville, Ontario Canada. She remained in Ontario throughout her elementary and high school years. She then attended the University of Toronto to obtain her Bachelor of Science degree with High Honors.

Early Years

As a young adult, Dr. Steele never really imagined that she would choose surgery as her career. For most of her 20s, she was competing full-time on an international level as an ice dancer. An ice dancer attains perfection of movement and form through countless hours of practice on the ice. The shift to medicine came after an injury ended her skating career. She since found that medicine, and surgery in particular, shares a great deal with competitive skating. The dedication, determination and persistence required to be an elite athlete carried forward as she pursued a career in medicine. She took an unorthodox approach to medicine and returned to her academic studies to earn her MD degree as a distinguished scholar and valedictorian from Ross University School of Medicine in 2000. Despite the parallels that in retrospect seem obvious, she was not drawn to surgery at first. Indeed, her initial impression of surgeons was that they were technically skilled but somewhat cold, and not especially interested in research or spending time one-on-one with the non-anesthetized patient. Her impressions were changed, however, by her surgical teacher and mentor in medical school, Dr. Anna Kobylecky. Dr. Kobylecky did it all. In the O.R. she was in control: confident, calm, meticulous, and technically astute. She was a dedicated teacher who expected a high level of performance from everyone,

and for whom complete knowledge of the patient and procedure was an essential prerequisite to operating. Most importantly she encouraged Dr. Steele to ask questions and be curious about the causes and consequences of disease. It was her mentoring that inspired Dr. Steele to pursue an academic career path where she could make a difference clinically, by teaching and through research. Dr. Steele completed her general surgery residency training at Penn State University School of Medicine in Hershey Pennsylvania from 2000 to 2005 and was the first surgical resident to earn the prestigious Kienle Humanitarian Award for outstanding clinical skills and compassionate care of her patients. She was nominated by the faculty for the Association of Women Surgeons Female Surgical Resident of the Year, and had the rare opportunity as a second year resident to travel to Ecuador, where she accompanied the chief of pediatric cardiothoracic surgery to perform delicate and complicated pediatric heart procedures. From 2005 to 2006 she completed a minimally invasive and bariatric surgery fellowship at the Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center. After completing her fellowship, she was actively recruited to The Johns Hopkins Center of Bariatric Surgery where she has established a busy surgical practice. In 2009, after having been in practice only two years, she was asked to serve as a national expert on the effect of bariatric surgical procedures on contraception at the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. That same year, she was named Director of the Adolescent Bariatric Surgical Program, taking on the task of developing the only program in Maryland to offer safe surgical options for the morbidly obese adolescent. In establishing this center, she assembled a multidisciplinary team involving faculty and staff from pediatric gastroenterology, psychiatry, nutrition and the Mount Washington Weigh Smart

Program and together they have obtained IRB approval for a longitudinal study of bariatric surgical outcomes in adolescents. She has also played a key role in the development of the internationally recognized Johns Hopkins Center for Bariatric Surgery Adult Program.

In her first year as faculty, despite being clinically busy, she volunteered to precept the medical students who were completing their surgical clerkship. She was so well received by the students and the program director that she was asked to take on the role of Associate Director of the Surgical Clerkship in the same year, 2006. Not only did she teach various components within the surgical clerkship including labs, didactic sessions and in the operating room, she helped with administrative duties, mentored medical students (both from Hopkins and abroad) that went on to become surgical residents, took on sub-interns, developed and taught a laparoscopic curriculum that continues to be utilized today and helped develop and teach the PRECEDE medical student surgical curriculum and the surgical resident minimally invasive curriculum having authored 8 modules that have been used in Duke Universities surgical curriculum. In 2011, she received the Outstanding Teachers Award for the Surgical Clerkship. Dr. Steele is presently working on an educational study involving students and trainees, evaluating the importance of warm-up prior to going to the operating room to perform a surgical procedure. In addition to making a large contribution to teaching within the institution, she has accumulated an impressive amount of educational scholarship outside the institution. She is committed to the education of medical students and serves on the Association of Surgical Educations medical student education committee. She has authored numerous book chapters, been invited faculty to numerous SAGES national

courses and most recently was faculty at a laparoscopic suturing course at the annual ASMBS meeting, where she had the privilege of teaching surgeons from around the world.

Inspiration to become a surgeon scientist

Although, Dr. Steele very much enjoys her clinical work and teaching, she now understands that she cannot make scientific contributions unless she can devote her professional time towards developing a research career. This became abundantly clear three years ago when she received the KL2 award and more recently the Clinician Scientist Award in 2013. The KL2 has provided Dr. Steele with the academic basis of scientific and research knowledge, and allowed her to explore many of her unanswered questions about her patient population – namely morbidly obese surgical patients, the prevention and treatment of blood clot formation. As well, the academic environment at Johns Hopkins has inspired her to move from clinician to clinician researcher, actively seeking answers and explanations to the causes and consequences of blood clot formation in the obese surgical patient. Bariatric surgical patients present us with a uniquely valuable resource to determine many of our questions regarding DVT prophylaxis, prevention and treatment.

Taken together, Dr. Steele's ongoing clinical studies, education, and passion regarding bariatric research have motivated her aims for this thesis project.

Opportunities

Enrollment in the PhD program has given her the opportunity to do much collaboration with accomplished researchers including Mechanisms of Sleep Apnea in Severe Obesity (R01 HL050381), Principle Investigator Alan Schwartz, M.D. and Improving Diabetes through Lifestyle and Surgery (IDeaLS) (R01 DK089557-01), Principal Investigator Jeanne Clark, M.D. As well, she is a co-investigator on numerous multidisciplinary projects investigating obesity related topics, involving investigators from psychiatry, obstetrics and gynecology, pulmonology, urology, gastroenterology, radiology and pediatrics. *Her overarching career goal is to use her training and experience in clinical research to earn a position as an independently funded clinical investigator with the intention of being a leader in obesity research and weight loss surgery.*

Final Thoughts

On a personal note: Dr. Steele could not have completed this this work without the love, support and extreme patience from her amazing husband Greg Prokopowicz and their two sons Michael and Matthew.