

***Efficacy and Safety of Pharmacological  
Thromboprophylactic Agents for the Prevention of  
Venous Thromboembolism after Major Abdominal  
Surgery***

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## ***Abstract***

### ***Statement of the problem:***

The type and duration of pharmacological thromboprophylaxis post major abdominal surgery remains controversial.

### ***Methods of investigation:***

A systematic review and pooled analysis of literature was performed to assess the risk benefit ratio of the different pharmacological thromboprophylaxis agents compared to placebo or no thromboprophylaxis post major abdominal surgery. A survey of the clinical practice among both general surgeons and thrombosis expert was conducted.

### ***Results:***

The systematic review demonstrated that all five pharmacological thromboprophylaxis regimens were associated with similar rates of overall VTE. The 95% CI of the different estimates overlapped indicating no statistically significant difference between any of the pharmacological interventions and placebo. While all the surgeons and thrombosis experts recommended thromboprophylaxis post major abdominal surgery, over 70% of them recommended it during hospitalization only.

### ***Conclusion:***

Pharmacological thromboprophylaxis was not associated with a significant benefit in reducing the rate of overall VTE events post major abdominal surgery. There is an agreement between general surgeons and thrombosis experts in using LMWH for thromboprophylaxis post major abdominal surgery. However, there is still equipoise around the use of pharmacological thromboprophylaxis post discharge.

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## Table of Contents

Efficacy and Safety of Pharmacological Thromboprophylactic Agents for the Prevention of

Venous Thromboembolism after Major Abdominal Surgery.....	1
Abstract.....	ii
Acknowledgements.....	iii
SECTION 1: Introduction, Background and Overall Aim .....	1
Introduction.....	1
Background.....	3
Post-operative Thromboprophylaxis.....	3
Overall Aim .....	12
SECTION 2: Systematic Review.....	13
Rationale for the Systematic Review.....	13
Systematic Review Methods.....	14
PICOS Question and Objectives.....	14
Data Sources and Searches .....	17
Study Selection .....	17
Outcome Measures.....	22
Data Extraction and Quality Assessment.....	24
Data Synthesis and Analysis.....	24
Results of Systematic Review.....	26
Result of the literature search .....	26

Baseline Characteristics of Included Studies .....	26
Quality Assessment.....	36
Reporting and Publication Bias Assessment.....	40
Summary of pooled analysis.....	41
Pooled Proportions of Venous Thromboembolic Events.....	42
Pooled Proportions of DVT Events .....	49
Pooled Proportions of Pulmonary Embolism Events.....	58
Pooled Proportions of Major Bleeding Events .....	66
Pool Proportion for Secondary Outcomes .....	73
Subgroup Analysis.....	73
Discussion of the Systematic Review and Pooled analysis .....	76
Summary of main results .....	76
Other thromboprophylaxis regimens .....	79
Length of Intervention .....	79
Limitations .....	80
Quality of the evidence .....	84
Conclusion .....	85
SECTION 3: Cross Sectional Survey of Thrombosis Experts and General Surgeons. ....	87
Rational for the Survey .....	87
Cross Sectional Survey methods.....	88

Survey population .....	88
Survey Design and Implementation.....	88
Survey Contents .....	89
Survey Analysis .....	89
Survey results.....	89
Survey Discussion.....	92
Survey Limitation .....	93
Survey Conclusion .....	94
Thesis Conclusion.....	95
Bibliography .....	96
Appendixes .....	103
Appendix 1: The Cochrane Collaboration’s tool for assessing risk of bias.....	103
Appendix 2: Newcastle - Ottawa Quality Assessment Scale for Cohort Studies.....	109
Appendix 3: Grey literature search.....	112
Appendix 4: Reporting and Publication Bias Assessment.....	115
Venous Thromboembolic Events.....	115
Deep vein thrombosis Events.....	121
Pulmonary Embolism Events.....	126
Major Bleeding Events .....	131
30 days Mortality .....	137

30 Days Re-Operation Rate .....	142
Pooled Proportions of wound infection .....	147
Wound oozing.....	149
Subgroup Analysis.....	153
Appendix 5: Pooled Proportions for Secondary Outcomes .....	170
Pooled Proportions of 30 days Mortality .....	170
Pooled Proportions of 30 Days Re-Operation Rate .....	177
Pooled Proportions of wound infection .....	183
Pooled Proportion of wound oozing .....	187
Appendix 6: Subgroup Analysis for Laparoscopic Surgery .....	192
Fondaparinux (2.5mg s/c daily) .....	192
High thromboprophylactic dose of low molecular weight heparin ( $\geq 4000$ IU) .....	192
High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours) .....	194
Low prophylactic dose of low molecular weight heparin ( $< 4000$ IU) .....	195
Placebo, non-pharmacological thromboprophylaxis or no treatment.....	198
Appendix 7: Subgroup Analysis for Bariatric Surgery Surgery .....	200
Fondaparinux (2.5mg s/c daily) .....	200
High thromboprophylactic dose of low molecular weight heparin ( $\geq 4000$ IU) .....	200

High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)	209
Low prophylactic dose of low molecular weight heparin (<4000 IU)	209
Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)	209
Placebo, non-pharmacological thromboprophylaxis or no treatment	209
Appendix 8: Subgroup Analysis for Bariatric Surgery Surgery	210
Fondaparinux (2.5mg s/c daily)	210
High thromboprophylactic dose of low molecular weight heparin ( $\geq$ 4000 IU)	212
High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)	216
Low prophylactic dose of low molecular weight heparin (<4000 IU)	220
Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)	224
Placebo, non-pharmacological thromboprophylaxis or no treatment	227
Appendix 9: Contact email send for Survey Participants	231
Appendix 10: The Survey	234
Survey sent to the Thrombosis Canada	234
Survey sent to the Canadian Association of General Surgeons	238

## ***SECTION 1: Introduction, Background and Overall Aim***

### ***Introduction***

Venous thromboembolism (VTE) is a condition associated with an increased morbidity and mortality among hospitalized medical and post-surgical patients. The most common presentations of venous thrombosis are deep vein thrombosis (DVT) of the lower extremity and pulmonary embolism (PE) [1]. Asymptomatic (usually calf veins, also named distal or below knee) DVTs are more common than symptomatic (usually thigh veins or proximal) DVTs, and most of these DVTs require no treatment as they resolve spontaneously without any sequelae [1]. However, the thrombus may propagate and lead to symptoms of venous occlusion (including calf pain and swelling), or dislodge and travel to the lungs, resulting in a pulmonary embolism (PE) [1]. Pulmonary embolism remains the most common preventable cause of hospital death despite the significant advances in the prevention and treatment of VTE [2] [3] [4] [5] [6]. More than 90% of acute cases of PE are due to proximal DVTs [7] [8]. PE account for more than 15,000-20,000 hospital death in the United States every year [9] [10]. Thus, it is not surprising that the Agency for Healthcare Research and Quality (AHRQ) considers VTE prevention as the number one strategy to improve inpatients safety [11].

Contrast venography has long been considered the reference test for the diagnosis of DVT [12] [13]. However, venography is not recommended as an initial test due to patient discomfort and difficulty in obtaining an adequate study. Noninvasive tests with nearly equivalent diagnostic accuracy for DVT (e.g. compression ultrasonography) have drastically reduced the need for

venography. Venography is currently reserved for situations in which compression ultrasonography is not feasible, when noninvasive studies are equivocal, or when noninvasive studies are discordant with a clinical impression [14]. Pulmonary angiography is the definitive diagnostic technique or "gold-standard" in the diagnosis of acute PE. However, CT pulmonary angiography (or CTPA) is currently the most widely used non-invasive test to diagnose PE with 98% diagnostic accuracy [15].

The causes of VTE can be divided into two groups: unprovoked and provoked events. Provoked VTE are often triggered by surgeries; particularly orthopedic, major vascular, neurosurgery, and cancer surgery. This is thought to be due to a combination of stasis of venous blood flow from reduced mobility and from venous injury secondary to surgery [16]. Orthopedic surgeries including elective total hip replacement (THR), elective total knee replacement (TKR), and hip fracture surgery (HFS) are particularly associated with an increased risk for VTE. The cumulative incidence of nonfatal, symptomatic VTE rates after major orthopedic surgery without thromboprophylaxis has been estimated to be 4.3% (PE 1.5%, DVT 2.8%). As a result, it has become standard practice that patients undergoing major orthopedic surgery receive pharmacological thromboprophylaxis in the post-operative period [15]. Traditionally, a prophylactic dose of low-molecular-weight heparin (LMWH) or direct oral anticoagulant (DOAC) has been used as the pharmacological thromboprophylaxis of choice in the post-operative period [16]. Interestingly, a number of studies, and a recently conducted randomized controlled trial have shown that aspirin was non-inferior to LMWH in patients post THR for the prevention of VTE [17]. Therefore, the latest edition of the American College of Chest Physicians (ACCP) guidelines states that LMWH, DOAC or aspirin for 10 to 35 days are all reasonable pharmacological thromboprophylaxis options for patients undergoing THR or TKR.

## ***Background***

Patients undergoing major abdominal surgery are also at high risk of developing a VTE complication in the post-operative period. Their VTE risk depends on both patient-specific and procedure-specific factors [18]. Older age, previous VTE, cancer, obesity and prolonged immobilization post-surgery are examples of high-risk patient-specific factors. Examples of high-risk procedures include open abdominal and pelvic surgeries, abdominal-pelvic cancer surgery and bariatric surgery. The longer the duration of the general anaesthesia (and surgery), the higher the risk for VTE. Based on those risk factors, the estimated baseline risk for VTE post major abdominal surgery in patients with risk factors for VTE is approximately 6% [18].

## ***Post-operative Thromboprophylaxis***

There are different options for thromboprophylaxis available post major abdominal surgery. Roughly, they can be divided into two groups; pharmacological or non-pharmacological thromboprophylaxis. They can be used alone or in combination. Non-pharmacological thromboprophylaxis include graded elastic stockings (GES) or intermittent pneumatic compression (IPC) devices, whereas recommended pharmacological thromboprophylaxis include low-dose unfractionated heparin (LDUH), LMWH and fondaparinux. There are currently no recommendations for using DOAC or aspirin in the post-operative period of a major abdominal surgery.

## ***Graded Elastic Stockings (GES)***

Most of the clinical trials that evaluated GES are older and have low methodological quality. A Cochrane review of 8 RCTs (Only four were general surgery trials) that compared GES to no prophylaxis found that GES reduce the odds of overall DVT (including distal and asymptomatic

DVT) by 65% [19]. A recent update of the same systematic review included a total of 19 RCTs (including 9 general surgery RCTs) comparing GES (+/-pharmacological thromboprophylaxis) to no GES (+/-pharmacological thromboprophylaxis). Overall, GES reduced the odds of DVT by 67%, proximal DVT by 74% and PE by 62% during the post-operative period. However, when the analysis was limited to general surgery alone, the reduction in proximal DVT and PE were no longer statistically significant [20]. These studies had important methodological limitations, including the use of fibrinogen leg scanning to identify asymptomatic DVT. Recent RCTs that looked into GES for prevention of VTE in hospitalized patients with acute stroke, failed to show a reduction in fatal or non-fatal PE and symptomatic proximal DVT, while increasing skin complications fourfold [21].

### **Intermittent pneumatic compression (IPC) devices**

IPC enhances blood flow in lower limbs deep veins, therefore reduces venous stasis. The evidence behind the use of IPC alone in the post-operative period is limited. A systematic review and meta-analysis of the literature including 16 RCTs (of which 4 were general surgery) comparing IPC to no prophylaxis, IPC was associated with a 60% reduction in DVT (including asymptomatic and distal DVT) [22]. However, it was not reported if IPC was associated with a reduction of proximal DVT or PE. A number of small RCTs and meta-analyses have reported that IPC might be associated with a greater benefit when compared to GES. A systematic review that included 10 clinical trials (9 in surgical patients) comparing IPC to GES, reported rates of DVT of 2.8% and 5.9% in the IPC and GES groups, respectively [23]. Therefore, IPC might be the best mechanical thromboprophylaxis option for patients post- major abdominal surgery who are at high risk of bleeding or in whom pharmacological thromboprophylaxis is contraindicated. The American College of Chest Physicians (ACCP) clinical practice guidelines, published in

2012, gave a grade 2C recommendation for the use of IPC in patients at high-VTE-risk post general and abdominal-pelvic surgery who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly important [18]. However, it is important to remember that optimal adherence to IPC is difficult. For example, IPC has to be removed every time the patient is ambulating. One study showed that optimal compliance with IPC was only 19% in post-operative patients [24]. Furthermore, IPC is contraindicated in patients with significant peripheral vascular disease and it is of limited efficacy in amputees or in patients with burns or significant skin lesions affecting lower limbs [25].

### **Unfractionated Heparin (UFH)**

UFH is usually given subcutaneously at a dose of 5000 units every 8 to 12 hours. In a landmark international multi-center RCT (the International Multicenter Trial), over 4000 patients undergoing a variety of major surgical procedures (including vascular and orthopedic surgery) were randomized to UFH every 8 hours or control (no placebo). UFH significantly reduced the rate of post-operative fatal PE from 0.7 % in the control group to 0.1 % in the UFH group. There was also a significant reduction in the rate of DVT from 24.6 % to 7.7%. These findings were confirmed in a systematic review of 69 RCTs assessing the efficacy of UFH following general, orthopedic and urological surgery [26]. Re-analysis of the data demonstrated that UFH was associated with an 18% reduction in the odds of death from any cause, a 47% reduction in the odds of fatal PE, and a 41% reduction in the odds of nonfatal PE, along with a 57% increase in the odds of nonfatal major bleeding [18]. UFH has the advantages of a low side effects profile, and of being relatively non-expensive and easy to administer. However, it is still parenterally administered, requiring subcutaneous self-injections twice or three times daily, making them less

convenient especially for extended post discharge thromboprophylaxis. In addition, UFH is associated with a 2.6% risk of heparin-induced thrombocytopenia (HIT), a rare but potentially serious adverse reaction causing low platelets with paradoxical thrombosis and tissue necrosis [18].

### **Low-molecular-weight heparin (LMWH)**

LMWH is given subcutaneously once or twice daily. There are different preparations of LMWH available (enoxaparin, dalteparin, tinzaparin, parnaparin, semuloparin (ultra-LMWH) and bemiparin). The efficacy of LMWH in post-operative thromboprophylaxis has been previously studied. A meta-analysis of 8 RCTs evaluated 5 different preparations of LMWH compared to no prophylaxis in patients post general or abdominal surgery. Compared to control, LMWH reduced the rate of asymptomatic DVT by 72%, rate of clinical PE by 75% and rate of clinical VTE by 71%. However, LMWH was associated with a twofold increase in major bleeding events and wound hematomas [27]. When LMWH was compared to UFH in the same meta-analysis, there was a 30% reduction in clinical VTE in favor of LMWH. However, this trend was lost when the analysis was restricted to blinded trials. LMWH has several advantages over UFH. LMWH is less likely to cause HIT (0.2% compared to 2.6% with UFH). Although it is also given subcutaneously, it is usually given less frequently (once daily in most cases), available in pre-filled syringes and therefore easier to use over UFH for extended post discharge thromboprophylaxis. Yet, LMWH is more expensive and is contraindicated in patients with significant renal impairment or on dialysis.

## **Fondaparinux**

Fondaparinux is a synthetic pentasaccharide that causes an antithrombin mediated selective inhibition of factor Xa. It is given subcutaneously once daily at a dose of 2.5mg. There is more evidence for its use in orthopedic surgery than in other surgeries. A single RCT assessed the efficacy and safety of fondaparinux compared to LMWH in patients post major abdominal surgery. Fondaparinux was non-inferior and was associated with a 25% reduction in symptomatic and asymptomatic DVT, compared to LMWH. However, fondaparinux showed a trend of possible increase in non-fatal major bleeding [28].

## **Low Dose Aspirin**

In the recent years, there has been renewal of interest for aspirin in the primary prevention of VTE. Aspirin irreversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, via acetylation, which results in decreased formation of prostaglandin precursors; irreversibly inhibits formation of prostaglandin derivative, thromboxane A<sub>2</sub>, via acetylation of platelet cyclooxygenase, thus inhibiting platelet aggregation [29]. Aspirin is highly effective in the primary and secondary prevention of arterial thrombosis in patients who are at high risk for myocardial infarction, stroke and peripheral vascular disease. Aspirin was also shown to be an effective secondary prevention agent in patients with previous VTE [30] [31].

The post-operative use of aspirin for VTE prevention was evaluated in an international multicenter RCT. Low dose aspirin (160mg daily for 35 days) was compared to placebo in patients post orthopedic surgery (HFS and elective arthroplasty). Aspirin was associated with a significant 43% and 29% reduction in PE and symptomatic DVT, respectively [32]. More recently, aspirin was found to be non-inferior to LMWH in thromboprophylaxis post THA [17].

However, its efficacy in prevention of VTE in other surgical populations is still unclear. There are no known RCTs that directly compared low dose aspirin to either placebo or other pharmacological thromboprophylaxis post major abdominal surgery.

The only systematic review and meta-analysis that investigated the role of aspirin in primary prevention of VTE was the Antiplatelet Trialists' Collaboration meta-analysis (APTC, 1994) [33]. The APTC looked into all randomized trials of all antiplatelet agents in the primary prevention of VTE in both surgical and medical patients, published before 1990. Aspirin was associated with 20% reduction in DVT and 69% reduction in PE when compared to control. However, the APTC had several methodological issues. First, many of the trials included in the meta-analysis had an open-label design. Second, it only compared antiplatelet agents to placebo or no treatment and excluded trials that included heparin. Third, the methods used for the diagnosis of VTEs had low sensitivity and specificity compared to more current highly sensitive and specific methods. Fourth, the doses of aspirin used in those clinical trials were high and not reflective of the current clinical practice. Fifth, many of the trials combined aspirin with other antiplatelet agents. Sixth, almost all the other antiplatelet agents used in the trials are not currently being used in clinical practice as antiplatelet agents. Lastly, 25 years have elapsed since the last trial included in this analysis was published and therefore, an updated systematic review and meta-analysis is desperately needed.

### **Other thromboprophylaxis**

Other oral anticoagulants are available [warfarin and DOACs (rivaroxaban, dabigatran and apixaban)] but they have significant downsides limiting their utility in the post-operative period. Warfarin (the most widely used long -term anticoagulant) has a slow onset and offset of action, a

narrow therapeutic window, and non-predictable patient response, which is influenced by factors such as genetic variations, food (relevant in the post-operative period) and drug interactions. Therefore, patients receiving warfarin require anticoagulation monitoring and dose adjustment [34]. The DOACs are dependent on good mucosal integrity for absorption, which potentially limits their efficacy in the post-operative setting. Although they are now approved for post-orthopedic surgery thromboprophylaxis, they have not been evaluated in other surgical procedures, in particular post major abdominal surgery, and thus they are not approved for this indication. Furthermore, apart from dabigatran, there are no available antidotes for reversing their anticoagulation effect, which may be concerning in patients that just underwent major abdominal surgery.

### **Risk associated with pharmacological thromboprophylaxis**

Any potential benefit from a medication needs to be balanced with its potential risks. The major complication associated with the use of pharmacological thromboprophylaxis is major bleeding. Major bleeding events, as defined by the International Society of Thrombosis and Hemostasis include fatal bleeding, and/or symptomatic bleeding in a critical area or organ, and/or bleeding causing a fall in hemoglobin of  $\geq 2$  g/dL or leading to transfusion of two or more units of whole blood or red cells [35]. The estimated baseline risk of major bleeding post abdominal-pelvic surgery in control patients who did not receive pharmacological thromboprophylaxis is approximately 1.2%. However, pharmacological thromboprophylaxis might be associated with a 3-fold increase in the risk of major bleeding events [18]. Procedure-specific risk factors for major bleeding complications post abdominal surgery include male sex, preoperative hemoglobin level less than 13 g/dL, malignancy, and complex surgery defined as two or more procedures, difficult dissection, or more than one anastomosis [36]. Clinicians, therefore, have

to assess the benefit-risk profile of pharmacological thromboprophylaxis prior to their use in post major abdominal surgery.

## **In Summary**

The ACCP Evidence-based consensus guidelines published in 2012 recommend that patients undergoing non-orthopedic surgery at moderate or high risk for VTE (general, abdominal-pelvic or thoracic surgeries) receive routine pharmacological thromboprophylaxis (LMWH, UFH or fondaparinux). The guidelines do not currently recommend the use of aspirin or other oral anticoagulants (warfarin, rivaroxaban, dabigatran or apixaban), either alone or in combination, as prophylaxis against VTE in these surgical populations. Although the efficacy and safety of pharmacological thromboprophylaxis agents have been proven, which agent to use (e.g. UFH vs. LMWH vs. fondaparinux) and at which dose (e.g. UFH 5,000 IU every 8 or 12 hours) remains debatable. Furthermore, the duration of pharmacological thromboprophylaxis (i.e. in-hospital only vs. 7 to 10 days including an outpatient prescription) is unclear. There are significant downsides that limit their use and acceptability for long term thromboprophylaxis (i.e. beyond hospitalization) in the outpatient setting. UFH, LMWH and fondaparinux are administered parenterally, making them less convenient to use following discharge from hospital. Moreover, UFH and to a lesser extent LMWH are associated with HIT, a rare but potentially serious adverse reaction causing low platelets with paradoxical thrombosis and tissue necrosis. Finally, parenteral agents are expensive and not all patients can afford them after discharge from hospital.

## ***Overall Aim***

To determine the efficacy and safety of pharmacological thromboprophylaxis post major abdominal surgery. We aim to establish the risk (i.e. major bleeding) – benefit (VTE) ratio for different pharmacological thromboprophylactic agents and assess the optimal duration of thromboprophylaxis (in-hospital only vs. total of 7 to 10 days) in patients undergoing major abdominal surgery. If equipoise is established, a survey of clinical practice (general surgery) will be conducted in order to decide if a clinical trial is warranted.

## ***SECTION 2: Systematic Review***

### ***Rationale for the Systematic Review***

As detailed above, there are many different options of pharmacological thromboprophylaxis for clinicians to use in the post major abdominal surgery period. Although there were previously published systematic reviews and meta-analyses, all of these reviews were not specific to major abdominal surgeries. Some of these reviews have also included studies that included orthopedic surgery. In addition, clinical guidelines pooled major abdominal surgery with all non-orthopedic surgery. Thus, the recommendation given by these guidelines for non-orthopedic surgeries not specifically for major abdominal surgery. Furthermore, apart from abdomino-pelvic cancer surgery, the guidelines do not give any recommendations to the duration of thromboprophylaxis. Thus far, there is no systematic review and meta-analysis addressing the efficacy and safety of the different types and doses of pharmacological thromboprophylaxis specifically for post major abdominal surgery.

While the 2012 ACCP guidelines recommend the use of LMWH or UFH for thromboprophylaxis in post abdominal-pelvic surgery patients at high risk of VTE, the guidelines gave an equal grade for both agents (Grade 1B). Furthermore, the clinical practice guidelines also gave the same recommendation for fondaparinux and IPC (Grade 2C) in patients in whom LMWH and UFH are contraindicated. Whereas some clinical practice guidelines (e.g. American Society of Clinical Oncology) recommend continuing pharmacological thromboprophylaxis for at least 7 to 10 days (including an outpatient prescription if patients are discharged), others (e.g. ACCP) are not providing recommendations about duration. Therefore, the duration of pharmacological thromboprophylaxis post major abdominal surgery is unclear. A

systematic review reporting the efficacy and safety of the different types and doses (and duration) of pharmacological thromboprophylaxis would be a great asset for policy makers and clinicians to guide them in making the right decision when choosing which intervention to use.

This report reviews the evidence for the clinical effectiveness and safety of pharmacological thromboprophylaxis agents currently being used in clinical practice for the prevention of VTE post major abdominal surgery. The review will help us to determine if there is equipoise around the use of pharmacological thromboprophylaxis in post major abdominal surgery.

A systematic review protocol was designed and approved by the University of Ottawa. The protocol and systematic search strategy of the review is registered on-line (*PROSPERO registry* – *CRD42014013559*).

## ***Systematic Review Methods***

### ***PICOS Question and Objectives***

#### **PICOS Question**

What is the effectiveness and safety of pharmacological thromboprophylaxis agents (Aspirin, UFH, LMWH, fondaparinux, warfarin and the DOACs [dabigatran, rivaroxaban and apixaban] in the primary prevention of VTE (DVT and PE) post major abdominal surgery?

- ***Population:*** Adult (older than 18 years) patients undergoing major abdominal surgery associated with hospitalization, general anesthesia or immobility. This includes any abdominal surgery that is laparoscopic or open, performed under general anaesthesia and lasted for at least 30 minutes.

- **Intervention:** Aspirin, UFH, LMWH, fondaparinux, warfarin and the DOACs (dabigatran, rivaroxaban, apixaban).
- **Outcome (s):**
  - **Primary outcome:** First episode of VTE (all types of DVT [symptomatic and asymptomatic, distal and proximal DVTs) and PE). DVT is diagnosed with compression ultrasound, I-125 fibrinogen leg scan, impedance plethysmography, CT venography. PE is diagnosed with chest CT pulmonary angiography or ventilation perfusion scan (V/Q scan).
  - **Secondary outcome:**
    - Any DVT.
    - PE.
    - Safety outcomes include:
      - Major bleeding defined as: Fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/l or more, or leading to transfusion of two or more units of whole blood or red cells and/or bleeding required reoperation to stop the bleeding (ISTH definition) [37].
      - Safety outcome for surgery:
        - Wound oozing/leakage
        - Wound infection.

- 30-day mortality.
  - 30-day re-intervention rate.
- **Study design:** RCTs and prospective cohort studies.

### **Objectives:**

The primary objective of this review is to determine the rates of overall VTE (effectiveness and major bleeding (safety) associated with the use of pharmacological thromboprophylaxis agents (Aspirin, LMWH, UFH, fondaparinux, warfarin and DOACs) for the prevention of VTE in post major abdominal surgery.

The secondary objectives are to determine the post-operative rates of:

- DVT.
- PE.
- Wound oozing/leakage.
- Wound infection.
- 30-day mortality.
- 30-day re-intervention rate.

## ***Data Sources and Searches***

An electronic search of the following databases was performed: MEDLINE (1946- September 2014), EMBASE (1947- September 2014) and the Cochrane Central Register of Controlled Trials (CENTRAL) (until September 2014) using OVID interface. The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The exact search strategy, using Medical Subject Indexing (MeSH) was modified for each database. The systematic review search strategy is documented in ***Table.1.***

Grey literature was identified by searching the websites of the Canadian Agency of Drugs and Technologies in Health (CADTH) (until July 2015) as well as other specialized databases (such as the University of York Centre for Reviews and Dissemination 'PROSPERO') (until July 2015). Furthermore, scientific meeting abstract publications for the American Society of Hematology (ASH) (2010-2014) and International Society of Thrombosis and Hemostasis (ISTH) (2010-2015) conferences were electronically hand searched. Unpublished clinical trials were screened using *ClinicalTrials.gov* website.

These searches were supplemented by hand-searching the bibliographies of key papers and through contacts with appropriate experts. Articles in English, French, Russian, Italian and Chinese were included in this systematic review. The search was restricted to these languages based on the availability of translators.

## ***Study Selection***

A structured question format was used to aid our literature search strategy to select abstracts of prospective cohort observational studies or RCTs reporting the efficacy and safety of

pharmacological thromboprophylaxis in patients post major abdominal surgeries. We reviewed potentially relevant articles that satisfied all of the following criteria:

1. Adult (older than 18 years) patients undergoing major abdominal surgery associated with hospitalization, general anesthesia or immobility.
2. Post-surgical pharmacological thromboprophylaxis was given. These include at least one of the following pharmacological thromboprophylaxis: Aspirin, UFH, LMWH, fondaparinux, warfarin and the DOACs (dabigatran, rivaroxaban or apixaban).
3. Prospective cohort studies or RCTs.
4. Reporting on at least one of the primary or secondary clinical outcomes.

**Table 1.**

**Database: Embase Classic+Embase <1947 to 2014 September 09>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>  
Search Strategy: September 10, 2014**

- 
- 1 Venous Thromboembolism/ (24605)
  - 2 Thromboembolism/ (76506)
  - 3 exp thrombosis/ (395721)
  - 4 exp pulmonary embolism/ (98479)
  - 5 or/1-4 (502455)
  - 6 Chemoprevention/ (23342)
  - 7 5 and 6 (1102)
  - 8 Venous Thromboembolism/pc (7681)
  - 9 Thromboembolism/pc (16671)
  - 10 exp thrombosis/pc (48429)
  - 11 exp pulmonary embolism/pc (9616)
  - 12 ((vte or dvt) adj5 (prevent\$ or prophyla\$)).tw. (7852)
  - 13 (venous Thromboembol\$ adj5 (prevent\$ or prophyla\$)).tw. (7805)
  - 14 (venous thrombos\$ adj5 (prevent\$ or prophyla\$)).tw. (3604)
  - 15 (thromboembol\$ adj5 (prevent\$ or prophyla\$)).tw. (16613)
  - 16 (deep vein adj5 (prevent\$ or prophyla\$)).tw. (3391)
  - 17 (pulmonary embol\$ adj5 (prevent\$ or prophyla\$)).tw. (3394)
  - 18 (thromboprophyla\$ or thrombo prophyla\$).tw. (7687)
  - 19 or/7-18 (79266)
  - 20 exp Abdomen/su (25840)

21 exp Digestive System Surgical Procedures/ (876829)  
22 exp Hernia, Abdominal/su (28589)  
23 ((abdomen or abdominal) adj5 (surg\$ or operat\$ or resect\$)).tw. (71252)  
24 or/20-23 (955683)  
25 19 and 24 (3342)  
26 Aspirin/ (203474)  
27 (aspirin or Acetylsalicylic acid).tw. (132369)  
28 exp Heparin/ (185496)  
29 heparin.tw. (152840)  
30 lmwh.tw. (9120)  
31 Fondaparinux.mp. (6810)  
32 Warfarin/ (80454)  
33 warfarin.tw. (40780)  
34 exp Anticoagulants/ (703081)  
35 anticoagulant\$.tw. (105898)  
36 (rivaroxaban or dabigatran or apixaban).mp. (10996)  
37 Platelet Aggregation Inhibitors/ (56350)  
38 (platelet adj3 inhibit\$).tw. (35402)  
39 or/26-38 (854004)  
40 25 and 39 (2435)  
41 randomized controlled trial.pt. (387881)  
42 controlled clinical trial.pt. (89783)  
43 placebo.ab. (362378)  
44 clinical trials as topic/ (218510)  
45 trial.ti. (304931)  
46 random\$.tw. (1662489)  
47 exp Cohort Studies/ (1572964)  
48 (cohort or prospective).tw. (1368993)  
49 or/41-48 (4286125)  
50 40 and 49 (686)  
51 animals/ not humans/ (5108962)  
52 50 not 51 (685)  
53 52 use prmz (298) Medline  
54 deep vein thrombosis/ (57639)  
55 exp vein thrombosis/ (97430)  
56 venous thromboembolism/ (24605)  
57 lung embolism/ (66711)  
58 thromboembolism/ (76506)  
59 or/54-58 (237515)  
60 prophylaxis/ or prevention/ (267803)  
61 59 and 60 (9422)  
62 deep vein thrombosis/pc [Prevention] (9995)  
63 exp vein thrombosis/pc (10029)  
64 venous thromboembolism/pc (7681)  
65 lung embolism/pc (5271)  
66 thromboembolism/pc (16671)  
67 or/61-66 (43572)  
68 ((vte or dvt) adj5 (prevent\$ or prophyla\$)).tw. (7852)

69 (venous Thromboembol\$ adj5 (prevent\$ or prophyla\$)).tw. (7805)  
70 (venous thrombos\$ adj5 (prevent\$ or prophyla\$)).tw. (3604)  
71 (thromboembol\$ adj5 (prevent\$ or prophyla\$)).tw. (16613)  
72 (deep vein adj5 (prevent\$ or prophyla\$)).tw. (3391)  
73 (pulmonary embol\$ adj5 (prevent\$ or prophyla\$)).tw. (3394)  
74 (thromboprophyla\$ or thrombo prophyla\$).tw. (7687)  
75 or/67-74 (57859)  
76 exp abdominal surgery/ (597411)  
77 exp abdominal wall hernia/su [Surgery] (13983)  
78 ((abdomen or abdominal) adj5 (surg\$ or operat\$ or resect\$)).tw. (71252)  
79 or/76-78 (652936)  
80 75 and 79 (2554)  
81 acetylsalicylic acid/ (203474)  
82 (aspirin or Acetylsalicylic acid).tw. (132369)  
83 heparin/ (177580)  
84 exp low molecular weight heparin/ (52859)  
85 heparin.tw. (152840)  
86 lmwh.tw. (9120)  
87 Fondaparinux.mp. (6810)  
88 warfarin/ (80454)  
89 warfarin.tw. (40780)  
90 warfarin.tw. (40780)  
91 exp anticoagulant agent/ (703081)  
92 anticoagulant\$.tw. (105898)  
93 (rivaroxaban or dabigatran or apixaban).mp. (10996)  
94 antithrombocytic agent/ (29091)  
95 (Platelet adj3 inhibit\$).tw. (35402)  
96 or/81-95 (843305)  
97 80 and 96 (1884)  
98 random\$.tw. or placebo\$.mp. or double-blind\$.tw. (1975960)  
99 exp cohort analysis/ (1572964)  
100 longitudinal study/ (159448)  
101 prospective study/ (641284)  
102 follow up/ (856900)  
103 (cohort or prospective).tw. (1368993)  
104 or/98-103 (4825238)  
105 97 and 104 (688)  
106 animals/ not humans/ (5108962)  
107 105 not 106 (688)  
108 107 use emczd (547) Embase  
109 53 or 108 (845)  
110 remove duplicates from 109 (697)

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***Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2014>  
Search Strategy: September 10, 2014***

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1 Venous Thromboembolism.hw. (282)  
2 Thromboembolism.hw. (1336)

3 exp thrombosis/ or thrombosis.hw. (5187)  
4 exp pulmonary embolism/ or pulmonary embolism.hw. (685)  
5 ((vte or dvt) adj5 (prevent\$ or prophyla\$)).tw,hw. (489)  
6 (venous Thromboembol\$ adj5 (prevent\$ or prophyla\$)).tw,hw. (605)  
7 (venous thrombos\$ adj5 (prevent\$ or prophyla\$)).tw,hw. (474)  
8 (thromboembol\$ adj5 (prevent\$ or prophyla\$)).tw,hw. (1242)  
9 (deep vein adj5 (prevent\$ or prophyla\$)).tw,hw. (738)  
10 (pulmonary embol\$ adj5 (prevent\$ or prophyla\$)).tw,hw. (157)  
11 (thromboprophyla\$ or thrombo prophyla\$).tw,hw. (463)  
12 or/1-11 (6997)  
13 exp Abdomen/su (19)  
14 exp Digestive System Surgical Procedures/ or Digestive System Surgical Procedure\$.hw. (9875)  
15 exp Hernia, Abdominal/su (115)  
16 ((abdomen or abdominal) adj5 (surg\$ or operat\$ or resect\$)).tw,hw. (4050)  
17 or/13-16 (13642)  
18 Aspirin/ (4100)  
19 (aspirin or Acetylsalicyclic acid).tw,hw. (7264)  
20 exp Heparin/ (3630)  
21 heparin.tw,hw. (7018)  
22 Imwh.tw,hw. (619)  
23 Fondaparinux.mp. (185)  
24 Warfarin/ (995)  
25 warfarin.tw,hw. (1968)  
26 exp Anticoagulants/ (7460)  
27 anticoagulant\$.tw,hw. (4624)  
28 (rivaroxaban or dabigatran or apixaban).mp,hw. (399)  
29 Platelet Aggregation Inhibitors/ (2570)  
30 (platelet adj3 inhibit\$).tw,hw. (3615)  
31 or/18-30 (20354)  
32 12 and 17 and 31 (172)

## ***Outcome Measures***

The primary efficacy outcome was the rate of all VTE defined as:

- Symptomatic DVT.
- Asymptomatic DVT detected by preset screening protocol.
- Proximal DVT (iliac, common femoral, superficial femoral or popliteal vein)
- Distal DVT (peroneal, posterior tibial or anterior tibial vein).
- PE.
- Fatal PE.

Deep vein thrombosis was diagnosed based on the following diagnostic criteria:

1. Compression ultrasonography: non-compressibility of any vein segment from the common femoral vein to the calf veins, or

2. Contrast venography: a persistent intra-luminal filling defect of the iliac, common femoral, superficial femoral, popliteal, posterior tibial or peroneal veins.
3. I-125 fibrinogen legs scan: increase in fibrinogen uptake by 20% or more.
4. Impedance plethysmography: positive test.

Pulmonary embolism was diagnosed based on the following diagnostic criteria:

1. High probability ventilation-perfusion (V/Q) scans.
2. Positive pulmonary angiogram.
3. CTPA: intraluminal filling defect in a vessel larger than a sub-segmental artery.

The primary safety outcome was the rate of major bleeding episodes. Major bleeding was defined as: Fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/l or more, or leading to transfusion of two or more units of whole blood or red cells and/or bleeding required reoperation to stop the bleeding (ISTH definition).

The secondary outcomes were the rates of:

- DVT.
- PE.
- Wound oozing/leakage.
- Wound infection.
- 30-day mortality.
- 30-day re-operation rate.

## ***Data Extraction and Quality Assessment***

Two reviewers (BA and MC) independently screened the title and abstract of all potentially eligible article records and applied the inclusion criteria. Any discrepancies at this level between the two reviewers were handled either by discussion until consensus was reached or by including the discrepant articles in the full-text review. The full text then was retrieved for any article judged to be eligible. The two reviewers (BA and MC) reviewed the full text of all selected articles for inclusion. Any discrepancies at this level were resolved by discussion until consensus was reached.

The two reviewers (BA and MC) independently extracted the data from the selected eligible articles. A structured data extraction Excel spreadsheet was used. Data were compared, and differences between reviewers were resolved by discussion until consensus was reached.

The two reviewers (BA and MC) independently applied the Cochrane Collaboration's risk of bias assessment tool (*Appendix 1*) to assess the quality of the included RCTs. The Newcastle-Ottawa scale (*Appendix 2*) was used to assess the quality of the prospective cohort studies. A structured data extraction Excel spreadsheet was used. The scores were compared, and the differences between reviewers were resolved by discussion until consensus was reached.

## ***Data Synthesis and Analysis***

In order to estimate the rates of VTE and the other secondary outcomes, results from the individual studies were extracted. Pooled proportions using random effect model of the different outcomes stratified by the type of pharmacological thromboprophylaxis agents were generated. The  $I^2$  statistic was calculated to assess for heterogeneity.  $I^2$  statistic of more than or equal to 75% will be considered high, > 50% to 75% moderate and < 50% low heterogeneity. StatsDirect

version 2.8.0 (*StatsDirect Ltd, Cheshire, UK*) was used to compute the statistic of the pooled analysis.

Additional exploration of heterogeneity was done using pre-specified subgroup analysis for the following variables: laparotomy vs. laparoscopic surgery; emergency vs. elective surgery, cancer vs. non-cancer surgery and bariatric vs. non-bariatric surgery.

Funnel plot was used to assess for any potential publication bias.

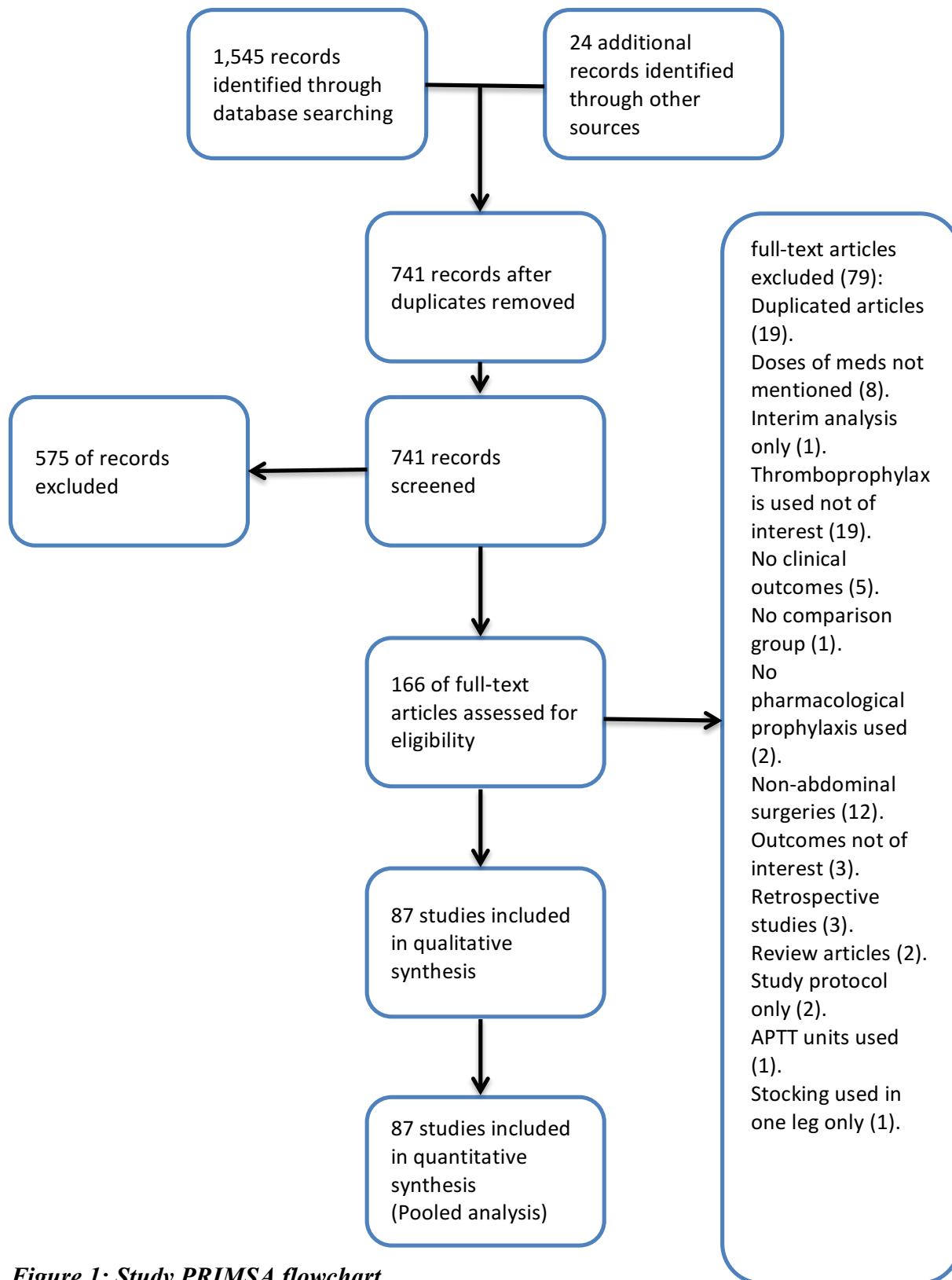
## ***Results of Systematic Review***

### ***Result of the literature search***

Our literature search study identified 1,545 records in addition to another 24 records identified through grey literature search. After removal of duplicate articles, 741 titles and abstracts were available for initial screen. A total of 166 articles were identified as potentially eligible and after review, 87 articles were included in the analysis. (See Figure 1 PRISMA flowchart). Grey literature search is depicted in Appendix 3.

### ***Baseline Characteristics of Included Studies***

A total of 44,681 patients were included in the analyses. Sample size ranged from 52 to 3,809 patients. There were 71 randomized controlled trials and 16 prospective cohort studies. Baseline characteristics of the included studies are depicted in Table 2.



**Figure 1: Study PRIMSA flowchart**

**Table 2: Baseline characteristics of included studies.**

Author	Study	Publication Year	Surgery Type	Treatment 1	Treatment 2	Treatment 3	Treatment Duration
<b>Imberti</b>	RCT*	2013	bariatric surgery	parnaparin sc 4,250 IU <sup>+</sup> /day	parnaparin sc 6,400 IU/day	Na**	14.1±2.4 days
<b>Kakkar</b>	RCT	2014	major laparotomy	semuloparin 20 mg daily	enoxaparin 40 mg daily	Na	7-10 days
<b>Vedovati</b>	RCT	2014	laparoscopic colon cancer	LMWH <sup>++</sup> x 28 days	LWMH X 8 days	Na	28 ± 2 days
<b>Antolovic</b>	RCT	2011	Inguinal, lab chole, colon ca	continuation of ASA	stop ASA 5 before, 5 after	Na	-
<b>Tsutsumi</b>	RCT	2012	colorectal ca	fondaparinux 2.5mg + IPC	IPC	Na	5-7 days
<b>Turpie</b>	RCT	2007	All type	Fondaparinux 2.5mg + IPC	Placebo +I PC	Na	Median 6 days
<b>Hata</b>	prospective cohort	2014	colorectal cancer	Fondaparinux 2.5/1.5mg	Na	Na	Median 4 days
<b>Kakkar</b>	RCT	2010	Abdo/pelvic cancer	bemiparin 3500IU x28 days	bemiparin 3500IUx8 days then placebo x 20 days	Na	28 days

<b>Lozano</b>	prospective cohort	2010	major ambulatory	Bemiparin 3500iu	bemiparin 2500iu	No	7 days
<b>Magee</b>	prospective data-retrospective analysis	2010	laparoscopic bariatric	Dalteparin 5000 IU x 3 week	Dalteparin 5000 IU x 1 week	Na	21 days
<b>Murugesan</b>	RCT	2010	All type	nadroparin 3057 IU	no treatment	Na	7-10 days
<b>Sakon</b>	RCT	2010	Abdo/pelvic cancer	enoxaparin 20mg bid	IPC	Na	14 days
<b>Borkgren-Okonek</b>	prospective cohort	2008	Roux-en-Y gastric bypass	enoxaparin 60 mg bid <sup>###</sup> , BMI<=50	enoxaparin 40 mg bid, BMI>50	Na	bid in hospital, od x 10 after d/c
<b>Brasileiro</b>	Prospective cohort	2007	Roux-en-Y gastric bypass	enoxaparin 40mg	Na	Na	15 days
<b>Raftopoulos</b>	prospective cohort	2008	bariatric	enoxaparin 30mg bid in hospital	enoxaparin 30mg bid in hop+40mg post x10day	Na	in hospital +/- 10days
<b>Kothari</b>	prospective cohort	2007	laparoscopic gastric bypass	enoxaparin 40mg bid	UFH <sup>#</sup> 5000 units TID <sup>¥</sup>	Na	during hospitalization (mean of 2.2 and 2.3 days only)
<b>Gonzalez</b>	prospective data-retrospective analyses	2006	Roux-en-Y gastric	BMI<50 enoxaparin 40mg	BMI >=50 enoxaparin 30mg bid	BMI>=60 enoxaparin 30 bid+10-14 days post discharge	until discharge+/-10-14 days
<b>Rasmussen</b>	RCT	2006	All type	Dalteparin 5000 iu x 4 week	Dalteparin 5000 iu x 1 weeks	Na	28 days
<b>Simonneau</b>	RCT	2006	colorectal cancer	nadroparin 2850 IU	enoxaparin 40mg	Na	7-11 days
<b>Agnelli</b>	RCT	2005	All type	fondaparinux 2.5mg	Dalteparin 5000 IU	Na	5-9 days

<b>Prystowsky</b>	prospective cohort	2005	open and laparoscopic RYGB	UFH 5000 units bid + IPC	Na	Na	during hospitalization (mean was 2.5 days).
<b>Tincani</b>	RCT	2005	Laparoscopic	Dalteparin 5000/2500 IU	no treatment	Na	7 days post discharge
<b>Shepherd</b>	prospective registry	2003	Laparoscopic bariatric	Anti-xa adjusted UFH	no treatment	Na	during hospitalization
<b>Bergqvist</b>	RCT	2003	open abdominal/pelvic cancer	enoxaparin 40mg daily x 4weeks	enoxaparin 40mg x1 week then placebo x 3 weeks	Na	28 days
<b>Schaepkens van Riepst</b>	prospective cohort	2001	laparoscopic cholecystectomy	nadroparin 2850 IU	no treatment	Na	during hospitalization (mean is approx 4 days)
<b>Kalfarentzos</b>	RCT	2001	Roux-en-Y gastric bypass	nadroparin 9500 IU	nadroparin 5700 IU	Na	during hospitalization (mean is 10 days)
<b>McLeod</b>	RCT	2001	Colorectal surgery	enoxaparin 40mg	UFH 5000 units q8h	Na	10 days
<b>Catheline</b>	prospective cohort	1999	laparoscopic	nadroparin 3075/4100 IU	Na	Na	fully mobile (around mean of 5.5 days )
<b>Egger</b>	RCT	2000	All type	weight base nadroparin	sandoparin 3000 units	Na	during hospitalization
<b>Yik-Hong Ho,</b>	RCT	1999	Colorectal	enoxaparin 20mg preop x1-40mg daily post op	no treatment	Na	at least 4 days
<b>Lausen</b>	RCT	1998	All type	tinzaparin 3500 IU x 4 weeks	tinzaparin 3500 IU x 1 week	Na	28 days vs 7 days

<b>Bergqvist</b>	RCT	1997	open abdominal/pelvic cancer	enoxaparin 40mg daily	heparin 5000 units q8h <sup>f</sup>	Na	10 days
<b>Bjerkaset</b>	RCT-Play the winner	1997	All type	enoxaparin 40/20mg post op	enoxaparin 40/20mg pre and post op	Na	7 days
<b>Kakkar</b>	RCT	1997	general and gyne	Clivarine lmwh 1750 IU daily	UFH 5000 IU Q12H <sup>z</sup>	Na	5 days
<b>Bergqvist</b>	RCT	1995	emergency surgeries	tinzaparin 3500 IU	placebo	Na	5 days
<b>Gonzalez</b>	RCT	1996	elective abdo	RO-11(lmwh) 2500 IU	UFH 5000 Q12H	Na	7 days
<b>Bergqvist</b>	RCT	1995	elective general abdo	Dalteparin 5000 IU	Dalteparin 2500 IU	Na	7 days
<b>Wiig</b>	RCT	1995	All type	enoxaparin 40mg daily	dextran 70	Na	fully mobile or 10 doses
<b>Bounameaux</b>	RCT	1992	elective general abdo	Dalteparin 2500 IU	nadroparin 3075 IU	Na	9 days
<b>Gallus</b>	RCT	1993	abdo/thoracic cancer	orgaran 750 u bid	UFH 5000 units bid	Na	6 day
<b>Kakkar</b>	RCT	1993	All type	Dalteparin 2500 u daily	UFH 5000 u q12h	Na	fully mobile and at least 5 days
<b>Marassi</b>	RCT	1993	Cancer surgeries	Seleparina lmwh 3825 IU	no treatment	Na	7 days
<b>Reiertsen</b>	RCT-Play the winner	1993	All type	enoxaparin 20mg daily	dextran 70	Na	fully mobile
<b>Kopenhagen</b>	RCT	1992	All type	Mono-Embolex lmwh 3000 IU	UFH 5000 units tid	Na	7 days
<b>Wille-Jorgensen</b>	RCT	1991	Acute abdomen	UFH 5000 units BID	UFH 5000 units bid + IPC	Dextran 70 + ICP	7 day
<b>Bergqvist</b>	RCT	1990	elective	Dalteparin 5000 IU daily	UFH 5000 units bid	Na	5-8 days

<b>Hartl</b>	RCT	1990	elective	Dalteparin 2500 IU daily	UFH 5000 units bid	Na	7 days
<b>Samama</b>	RCT	1990	general	enoxaparin 60mg od	UFH 5000 units q8h	Na	7 days
<b>Samama</b>	RCT	1990	general	enoxaparin 40mg od	UFH 5000 units q8h	Na	7 days
<b>Samama</b>	RCT	1990	general	enoxaparin 20mg od	UFH 5000 units q8h	Na	7 days
<b>Ockelford</b>	RCT	1989	general	Dalteparin 2500 IU daily	placebo	Na	5-9 days
<b>Gatania</b>	RCT	1988	general	LMWH 7500 IU daily	UFH 5000 units q8h	Na	7 days
<b>Encke</b>	RCT	1988	elective general abdo	fraxiparin 7500 IU daily	UFH 5000 units q8h	Na	7 days
<b>Fricker</b>	RCT	1988	Abdo/ pelvic cancer	Dalteparin 5000 iu daily	UFH 5000 units q8h	Na	10 days
<b>Rasmussen</b>	RCT	1988	All type	UFH 5000 units BID	Graduated compression stocking	Both	fully mobile
<b>Sue-Ling</b>	RCT	1988	elective	stanazolol 10mg 2week preop & 7 days postop	UFH 5000 units Q8H	no treatment (low risk group, not randomized)	7 days
<b>Bergqvist</b>	RCT	1988	elective	Dalteparin 5000 IU daily	UFH 5000 IU BID	Na	5-7 days
<b>Mellbring</b>	RCT	1986	elective	dihydroergotamin e+ UFH (0.5mg+5000 untis) bid	IPC	Na	fully mobile
<b>Onarheim</b>	RCT	1986	elective	Dalteparin 5000 IU daily	UFH 5000 units BID	Na	6 days
<b>Sandor</b>	RCT	1986	elective	dihydroergotamin e+ UFH	UFH 5000 units q8h	Na	7 days

				(0.5mg+5000 units) bid			
<b>Kakkar</b>	RCT	1985	elective	Dalteparin 7500 IU daily	UFH 5000 units bid	Dalteparin 7500 IU daily (open study) no comparison	7-10 days
<b>Wille-Jarrgensen</b>	RCT	1985	elective	UFH 5000 units BID + graded compression stocking	UFH 5000 units bid	Na	7 days
<b>Comerota</b>	RCT	1984	elective	dihydroergotamin e+ UFH (0.5mg+5000 units) bid	UFH 5000 units bid	placebo	5 days
<b>Schmitz-Huebner</b>	RCT	1984	elective	LMWH1 5120 IU bid	LMWH2 6785 IU bid	UFH 5000 iu bid	7 days
<b>Pedersen</b>	RCT	1983	elective	dihydroergotamin e+ UFH (0.5mg+5000 units) bid	UFH 5000 units q8h	Na	4 days
<b>Wille-Jarrgensen</b>	RCT	1983	elective	dihydroergotamin e+ UFH (0.5mg+5000 units) bid	UFH 5000 untis bid	Na	7 days
<b>Zakert</b>	RCT	1982	elective	ASA 0.5gm tid	dihydroergotamin e 2.5mg bid	ASA+ dihydroergotamine	discharge
<b>Immelman</b>	RCT	1979	elective	UFH 5000 units q8h	no treatment	Na	6 days
<b>Kakkar</b>	RCT	1979	elective	UFH 5000 units q8h	dihydroergotamin e 2.5mg bid	dihydroergotamine+ UFH (0.5mg+2500 units) tid	7 day

<b>Plante</b>	RCT	1979	elective	dipyridemol+ASA 50mg/300mg tid	UFH 5000 units BID	no treatment	8 day
<b>Kakkar</b>	prospective cohort	1971	elective inguinal hernia	UFH 5000 units Bid	no treatment	Na	5 days
<b>Borstad</b>	RCT	1988	major gynecological	Dalteparin 500 units daily	UFH 5000 units bid	Na	-
<b>Boncinelli</b>	RCT	2001	Radical retropubic prostatectomy	nadroparin 2850 IU	UFH 5000 units tid	Na	-
<b>Maxwell</b>	RCT	2001	Gynecologic Oncology	Dalteparin 5000 IU	IPC	Na	-
<b>Scholten</b>	prospective cohort	2002	bariatric	enoxaparin 30mg bid	enoxaparin 40mg bid	Na	-
<b>Baykal</b>	RCT	2001	Gynecologic Oncology	enoxaparin 2500 IU (25mg)	UFH 5000 units q8h	Na	-
<b>Nurmohamed</b>	RCT	1998	All type	Enoxaparin 20mg od	UFH 5000 units q8h	Na	-
<b>Clarke-Pearson</b>	RCT	1993	gynecologic oncology	UFH 5000 units q8h	IPC	Na	-
<b>Clarke-Pearson</b>	RCT	1990	gynecologic oncology	UFH 5000 units q8h	UFH 5000 units preop only q8h (2- 9 doses)	control	-
<b>Valle</b>	RCT	1988	General	LMWH (Fluxum) 7500 IU	placebo	Na	-
<b>Clarke-Pearson</b>	RCT	1983	gynecologic oncology	UFH 5000 units q12h	control	Na	-
<b>Joffe</b>	RCT	1976	general	UFH 5000 units q8h	pentosan polysulphate 50mg q12h	control	-
<b>Yang Bl</b>	RCT	2009	open, laparoscopic, transvaginal Gyn surgery	IPC	LMWH (5000 IU daily x 5 days)	Nothing (control)	-

<b>Di Somma</b>	RCT	1990	major abdominal surgery	IV defibrotide (400mg)	subcutaneous calcium heparin (5000 UI) q12h	Na	-
<b>Sciacca</b>	RCT	1991	major abdominal surgery	IV defibrotide (400mg)	subcutaneous calcium heparin (5000 UI) q12h	Na	-
<b>Rzaev</b>	RCT	1989	cholecystitis, stomach and duodenum ulcers	UFH 5000 units q12h	Rheopolyglukin 10ml/kg iv	IPC	-
<b>Sellam</b>	RCT	1999	abdominoplasty	LMWH 40mg/ day	LMWH 40mg/ day + Sigvaris class 2 compression socks	Na	-
<b>Catheline</b>	prospective cohort	1997	various laparoscopic	Nadroparin 3075 IU/day +/- compression socks	Nadroparin 4100 UI/day +/- compression socks	Na	-
<b>Steiner</b>	prospective cohort	1974	all types most common being cholecystectomy (45/100)	calcium heparin sc (Calciparine) q12h	Na	Na	-

\*RCT: Randomized Clinical trial. +IU: International Units. ++LMWH: Low Molecular Weight Heparin. #UFH: Unfractionated Heparin. ##BID: twice per day. ¥TID: three times per day. ≠Q12H: every 12 hours. £Q8H: every 8 hours.

\*\* Na: Not available

## Quality Assessment

The Cochrane Collaboration's tool for assessing risk of bias was used for assessment of the RCTs (See Table 4) and the Newcastle-Ottawa scale was used for assessment of the prospective cohort studies (See Table 5). Overall there was low to intermediate risk of bias for all pooled estimates.

**Table 4 The Cochrane Collaboration's tool for assessing risk of bias of the RCTs.**

Author	Adequate Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Personals	Blinding of Outcome Assessors	free Incomplete outcome data	Free of Selective Reporting	Free of Other Bias	Overall risk of bias
<b>Tsutsumi</b>	unclear	unclear	unclear	Unclear	unclear	unclear	Yes	Yes	unclear
<b>Turpie</b>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
<b>Agnelli</b>	unclear	unclear	Yes	Yes	Yes	Yes	Yes	Yes	unclear
<b>Imberti</b>	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Low
<b>Kakkar</b>	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Low
<b>Sakon</b>	unclear	unclear	No	No	Yes	Yes	Yes	Yes	unclear
<b>Simonneau</b>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
<b>Tincani</b>	Yes	Yes	No	No	Yes	Yes	Yes	No	Low
<b>Kalfarentzos</b>	unclear	unclear	unclear	Unclear	unclear	Yes	Yes	Yes	unclear
<b>McLeod</b>	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Low
<b>Yik-Hong Ho</b>	Yes	Yes	No	No	Yes	Yes	Yes	Yes	High
<b>Bergqvist</b>	unclear	unclear	Yes	Yes	Yes	Yes	Yes	Yes	unclear
<b>Bergqvist</b>	unclear	Yes	Yes	Yes	unclear	Yes	Yes	Yes	unclear

<b>Wiig</b>	unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	unclear
<b>Bergqvist</b>	Yes	unclear	Yes	Yes	unclear	Yes	Yes	Yes	Low
<b>Samama</b>	unclear	unclear	No	No	unclear	unclear	Yes	unclear	High
<b>Gatania</b>	unclear	unclear	unclear	Unclear	unclear	unclear	unclear	unclear	unclear
<b>Encke</b>	unclear	unclear	No	No	unclear	Yes	Yes	Yes	unclear
<b>Fricker</b>	unclear	unclear	No	No	unclear	Yes	Yes	Yes	unclear
<b>Onarheim</b>	unclear	unclear	Yes	Yes	unclear	Yes	Yes	unclear	unclear
<b>Kakkar</b>	Yes	Yes	Yes	Yes	unclear	Yes	Yes	No	unclear
<b>Borstad</b>	unclear	unclear	Yes	Yes	unclear	Yes	Yes	unclear	unclear
<b>Koppenhagen</b>	unclear	unclear	Yes	Yes	unclear	Yes	Yes	unclear	unclear
<b>Sue-Ling</b>	Yes	Yes	unclear	Unclear	unclear	Yes	Yes	unclear	unclear
<b>Sandor</b>	unclear	unclear	unclear	Unclear	unclear	Yes	Yes	unclear	unclear
<b>Pedersen</b>	unclear	unclear	unclear	Unclear	unclear	Yes	Yes	unclear	unclear
<b>Immelman</b>	Yes	Yes	No	No	unclear	Yes	Yes	unclear	High
<b>Imberti</b>	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Low
<b>Murugesan</b>	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Low
<b>Egger</b>	Na	Na	No	No	Na	No	Yes	Yes	unclear
<b>Kakkar</b>	unclear	unclear	Yes	Yes	Yes	Yes	Yes	Yes	unclear
<b>Bergqvist</b>	unclear	Yes	Yes	Yes	unclear	Yes	Yes	Yes	unclear
<b>Gonzalez</b>	unclear	unclear	Yes	Yes	unclear	Yes	Yes	Yes	unclear
<b>Bergqvist</b>	Yes	unclear	Yes	Yes	unclear	Yes	Yes	Yes	Low
<b>kakkar</b>	Yes	Yes	Yes	Yes	unclear	Yes	Yes	Yes	Low
<b>Reiertsen</b>	unclear	NO	No	No	unclear	Yes	Yes	No	High
<b>Hartl</b>	Yes	Yes	Yes	Yes	unclear	Yes	Yes	unclear	Low
<b>Ockelford</b>	Yes	Yes	Yes	Yes	unclear	Yes	Yes	unclear	Low
<b>Gonzalez</b>	unclear	unclear	Yes	Yes	unclear	Yes	Yes	Yes	unclear
<b>Gallus</b>	Yes	Yes	Yes	Yes	unclear	unclear	Yes	Yes	Low
<b>kakkar</b>	Yes	Yes	Yes	Yes	unclear	Yes	Yes	Yes	Low

<b>Wille-Jorgensen</b>	Yes	Yes	unclear	Unclear	unclear	Yes	Yes	No	unclear
<b>Bergqvist</b>	unclear	unclear	Yes	Yes	unclear	Yes	Yes	unclear	unclear
<b>Hartl</b>	Yes	Yes	Yes	Yes	unclear	Yes	Yes	unclear	Low
<b>Rasmussen</b>	unclear	unclear	No	No	unclear	Yes	Yes	unclear	unclear
<b>Onarheim</b>	unclear	unclear	Yes	Yes	unclear	Yes	Yes	unclear	unclear
<b>Kakkar</b>	Yes	Yes	Yes	Yes	unclear	Yes	Yes	No	unclear
<b>Wille-Jarrgensen</b>	unclear	unclear	No	No	unclear	Yes	Yes	unclear	High
<b>Wille-Jarrgensen</b>	Yes	unclear	No	No	Yes	Yes	Yes	No	High
<b>Murugesan</b>	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Low
<b>Sakon</b>	unclear	unclear	No	No	Yes	Yes	Yes	Yes	unclear
<b>Tincani</b>	Yes	Yes	No	No	Yes	Yes	Yes	No	Low
<b>Yik-Hong Ho</b>	Yes	Yes	No	No	Yes	Yes	Yes	Yes	High
<b>Bergqvist</b>	unclear	Yes	Yes	Yes	unclear	Yes	Yes	Yes	unclear
<b>Wille-Jorgensen</b>	Yes	Yes	unclear	Unclear	unclear	Yes	Yes	No	unclear
<b>Ockelford</b>	Yes	Yes	Yes	Yes	unclear	Yes	Yes	unclear	Low
<b>Immelman</b>	Yes	Yes	No	No	unclear	Yes	Yes	unclear	High
<b>Valle</b>	unclear	unclear	Yes	Yes	unclear	Yes	Yes	unclear	unclear

**Table 5 Newcastle-Ottawa scale used for assessment of the prospective cohort studies\***

	Selection				Comparability	Outcome			Total score	overall risk of bias
Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start	Comparability design and analysis	Assessment of outcome	follow-up long enough for outcome	Adequacy of follow up of cohorts		
Hata	a*	c	a*	a*	no	a*	a*	a*	6	Intermediate
Borkgren-Okonek	b*	a*	a*	a*	a*	a*	a*	a*	8	Low
Brasileiro	b*	na	a*	a*	na	a*	a*	a*	6	Intermediate
Kothari	a*	a*	a*	B	no	a*	b	d	4	intermediate
Lozano	a*	a*	a*	a*	ab**	a*	a*	a*	9	Low
Schaepkens van Riepst	a*	a*	a*	a*	a*	a*	b	a*	7	Low
Catheline JM	a*	a*	a*	a*	no	a*	a*	a*	7	Low
Prystowsky	a*	na	a*	a*	na	a*	a*	a*	6	Intermediate
Schaepkens van Riepst	a*	a*	a*	a*	a*	a*	b	a*	7	Low
Hata	a*	c	a*	a*	no	a*	a*	a*	6	Intermediate
Borkgren-Okonek	b*	a*	a*	a*	a*	a*	a*	a*	8	Low
Brasileiro	b*	na	a*	a*	na	a*	a*	a*	6	Intermediate
Kothari	a*	a*	a*	B	no	a*	b	d	4	Intermediate
Scholten	a*	a*	a*	a*	ab**	b*	a*	a*	9	Low

\*Please refer to Appendix 2 for further detail of the Newcastle-Ottawa scale interpretation (meaning of a, b and c)

## ***Reporting and Publication Bias Assessment***

When possible, funnel plots analyses were conducted to assess for reporting bias (See all funnel plots in Appendix 4). A large majority of the forest plots were suggestive of reporting bias.

## Summary of pooled analysis

Table 3 summarizes the pooled proportions for all primary and secondary outcome measures.

**Table 3 Pooled outcome rates according to each prophylaxis regimen**

Intervention	<i>Fondaparinux</i>	<i>LMWH high dose</i>	<i>UFH high dose</i>	<i>LMWH low dose</i>	<i>UFH low dose</i>	<i>Placebo</i>
<b>Overall VTE(number of studies)</b>	1.23 (4)	4.39 (27)	10.1 (14)	3.36 (19)	7.97 (13)	8.64 (12)
95% CI	0.003-4.64	2.74-6.40	6.60-14.23	1.56-5.82	4.37-12.52	4.09-14.66
I <sup>2</sup>	95.1	93.6	90.9	96.8	94.7	91
<b>DVT(number of studies)</b>	0.92 (3)	3.79 (34)	6.86 (21)	3.55 (27)	6.29 (23)	13.83 (21)
95% CI	0.082-4.78	2.46-5.38	4.423-9.78	1.93-5.65	3.84-9.29	8.15-20.71
I <sup>2</sup>	96.8	91.2	90.6	96.7	93.3	93.9
<b>PE(number of studies)</b>	0.24 (3)	0.25 (33)	1.04 (18)	0.31 (24)	1.1 (18)	1.39 (13)
95% CI	0.03-0.64	0.15-0.37	0.48-1.82	0.13-0.56	0.59-1.78	0.60-2.49
I <sup>2</sup>	54.6	12.4	69	71.3	66	52
<b>Major bleeding(number of studies)</b>	1.64 (4)	3.96 (35)	2.44 (16)	2.52 (20)	3.26 (18)	0.98 (17)
95% CI	0.56-3.30	2.70-5.45	0.82-4.87	1.19-4.34	2.01-4.78	0.33-1.96
I <sup>2</sup>	84	91	91.2	95.9	83.9	63.1
<b>mortality(number of studies)</b>	1.13 (3)	1.33 (26)	1.46 (12)	1.14 (14)	1.99 (16)	1.58 (10)
95% CI	0.72-1.62	0.88-1.88	0.48-2.95	0.55-1.95	1.14-3.07	0.56-3.11
I <sup>2</sup>	0	74.6	88.4	84.1	79	63.4
<b>Re-Operation(number of studies)</b>	.	1.03 (13)	0.52 (9)	0.62 (7)	2 (7)	1.3 (5)
95% CI	.	0.67-1.45	0.11-1.21	0.2571-1.15	0.87-3.60	0.08-3.93
I <sup>2</sup>	.	9.8	55.5	0	63.3	63.8
<b>wound infection(number of studies)</b>	.	2.57 (2)	.	6.38 (2)	4.11 (2)	0.8 (2)
95% CI	.	0.74-15.75	.	3.07-10.78	0.12-13.33	0.05-2.44
I <sup>2</sup>	.	.	.	.	.	.
<b>wound oozing(number of studies)</b>	.	4.15 (5)	1.48 (4)	2.83 (2)	10.81 (2)	2.22 (6)
95% CI	.	0.09-13.75	0.0004-5.74	0.01-10.30	7.29-14.92	0.94-4.02
I <sup>2</sup>	.	94.5	84.4	.	.	11.8

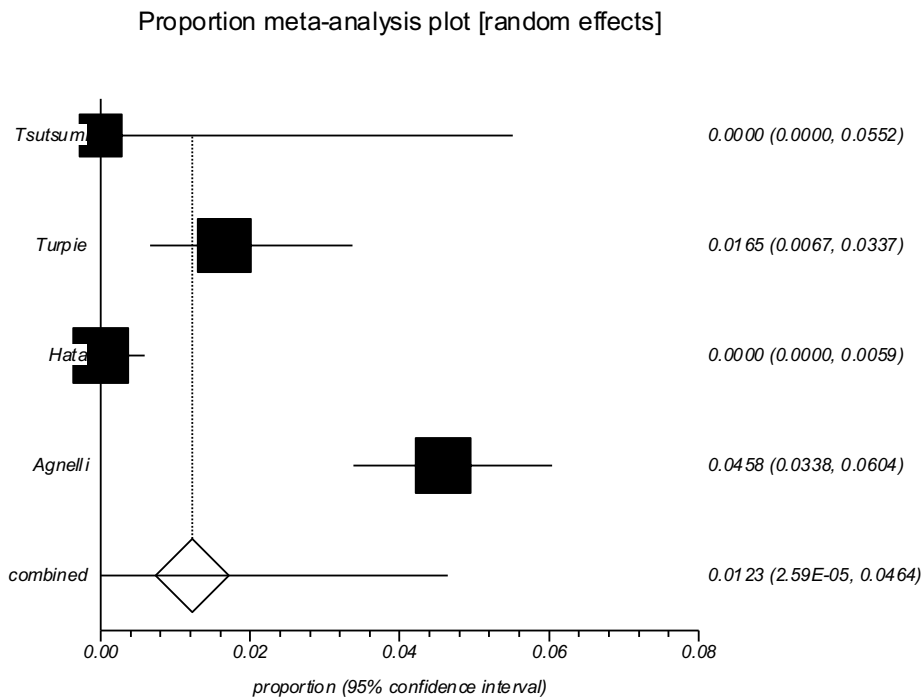
## **Pooled Proportions of Venous Thromboembolic Events**

Details for individual pooled proportions for each type and dose of pharmacological thromboprophylaxis are depicted below

### **Fondaparinux (2.5 mg s/c daily)**

A total of 2135 patients from 3 RCTs and one prospective cohort study were used for this analysis. There were a total of 54 events of venous thrombosis (DVT and PE) corresponding to pooled proportion of 1.23% (95% CI = 0.003 to 4.64) with considerable heterogeneity ( $I^2 = 95.1\%$ ). Figure 2 shows the forest plot of the analysis.

**Figure 2 Forest plot of the pooled proportion of venous thromboembolic events post major abdominal surgery in patients receiving Fondaparinux for 7-10 days post-surgery.**

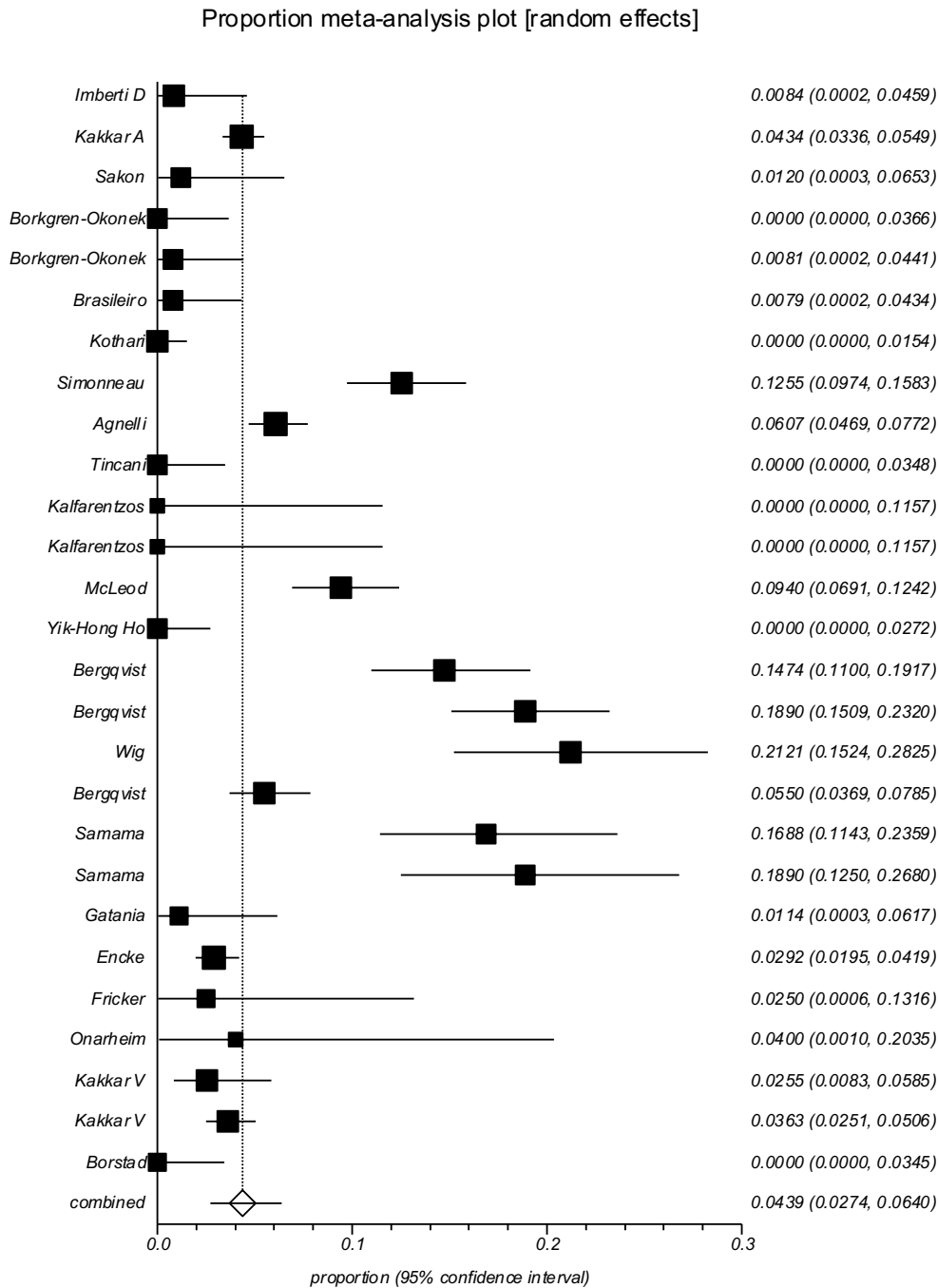


**High thromboprophylactic dose of low molecular weight heparin ( $\geq$  4000 IU)**

A total of 8539 patients from 23 RCTs and 4 prospective cohort studies were used for this analysis. There were a total of 537 events of venous thrombosis (DVT and PE) corresponding to pooled proportion of 4.39 (95% CI = 2.74 to 6.40) with considerable heterogeneity ( $I^2 = 93.6\%$ ).

Figure 3 shows the forest plot of the analysis.

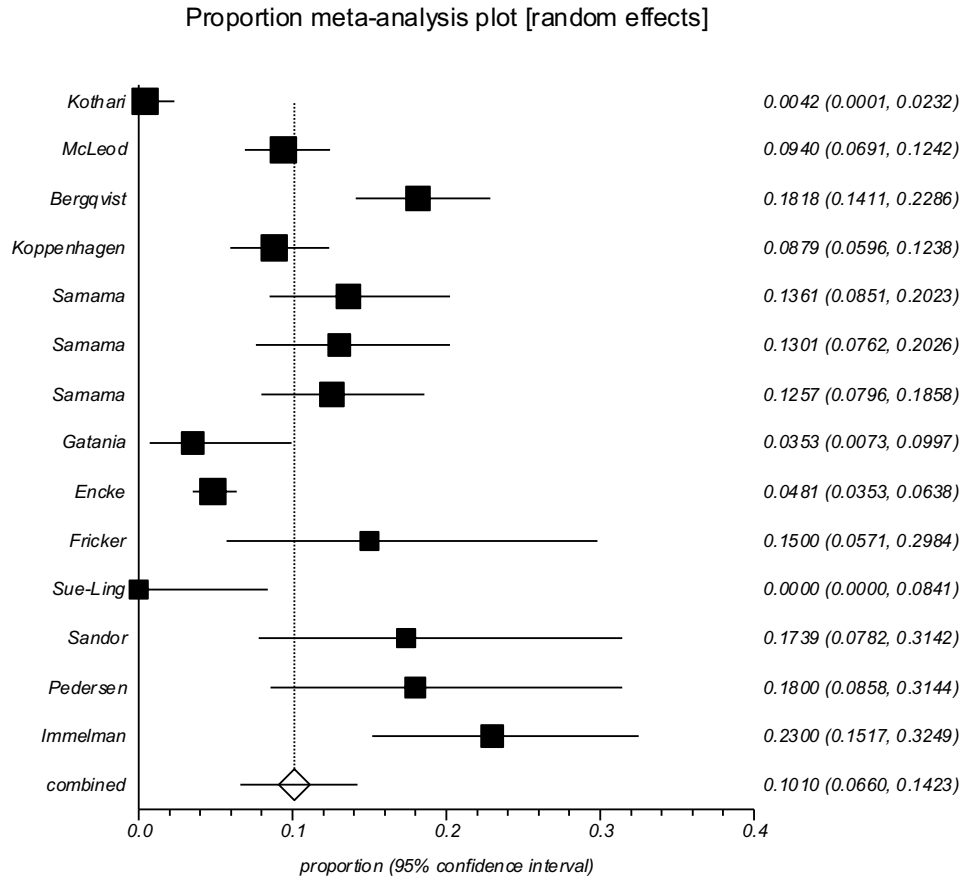
**Figure 3 Forest plot of the pooled proportion of venous thromboembolic events post major abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery.**



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

A total of 3136 patients from 13 RCTs and one prospective cohort study were included in this analysis. There were a total of 283 events of venous thrombosis (DVT and PE) corresponding to pooled proportion of 10.10 (95% CI =6.60 to 14.23) with considerable heterogeneity ( $I^2 = 90.9\%$ ). Figure 4 shows the forest plot of the analysis.

**Figure 4 Forest plot of the pooled proportion of venous thromboembolic events post major abdominal surgery in patient receiving high dose UFH for 7-10 days post-surgery.**

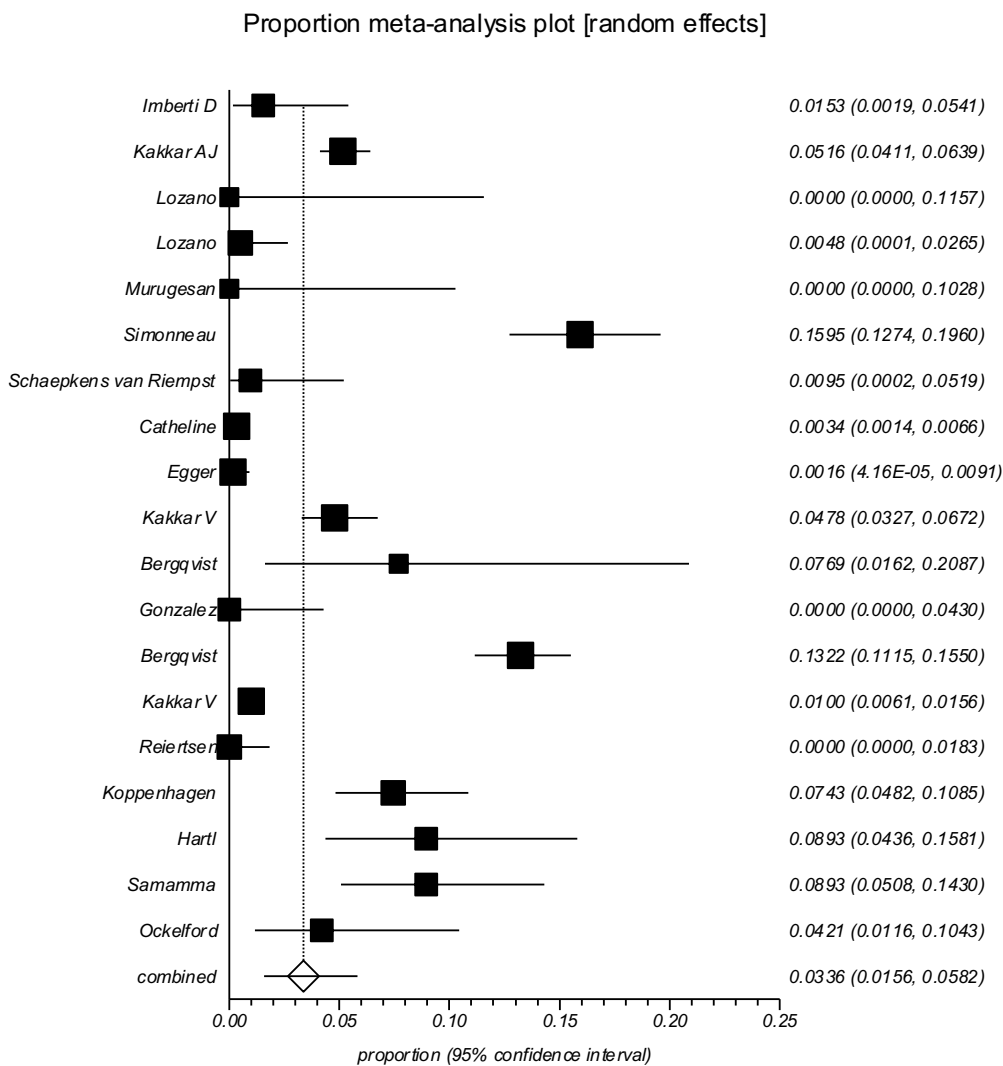


## Low prophylactic dose of low molecular weight heparin (<4000 IU)

A total of 10,035 patients from 16 RCTs and 3 prospective cohort studies were used for this analysis. There were a total of 401 events of venous thrombosis (DVT and PE) corresponding to pooled proportion of 3.36 (95% CI =1.561 to 5.82) with considerable heterogeneity ( $I^2 = 96.8\%$ ).

Figure 5 shows the forest plot of the analysis.

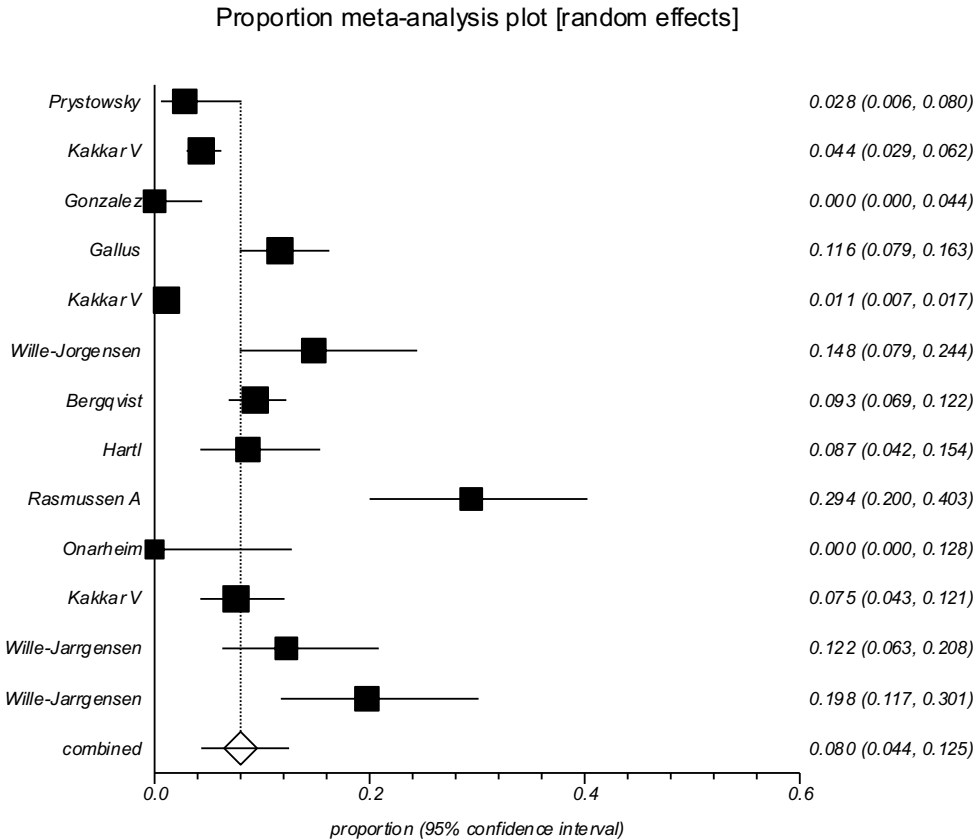
**Figure 5 Forest plot of the pooled proportion of the venous thromboembolic events post major abdominal surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

A total of 4186 patients from 12 RCTs and one prospective cohort study were included in this analysis. There were a total of 218 events of venous thrombosis (DVT and PE) corresponding to pooled proportion of 7.97 (95% CI = 4.37 to 12.52) with considerable heterogeneity ( $I^2 = 94.7\%$ ). Figure 6 shows the forest plot of the analysis.

**Figure 6 Forest plot of the pooled proportion of the venous thromboembolic events post major abdominal surgery in patient receiving low dose UFH for 7-10 days post-surgery.**

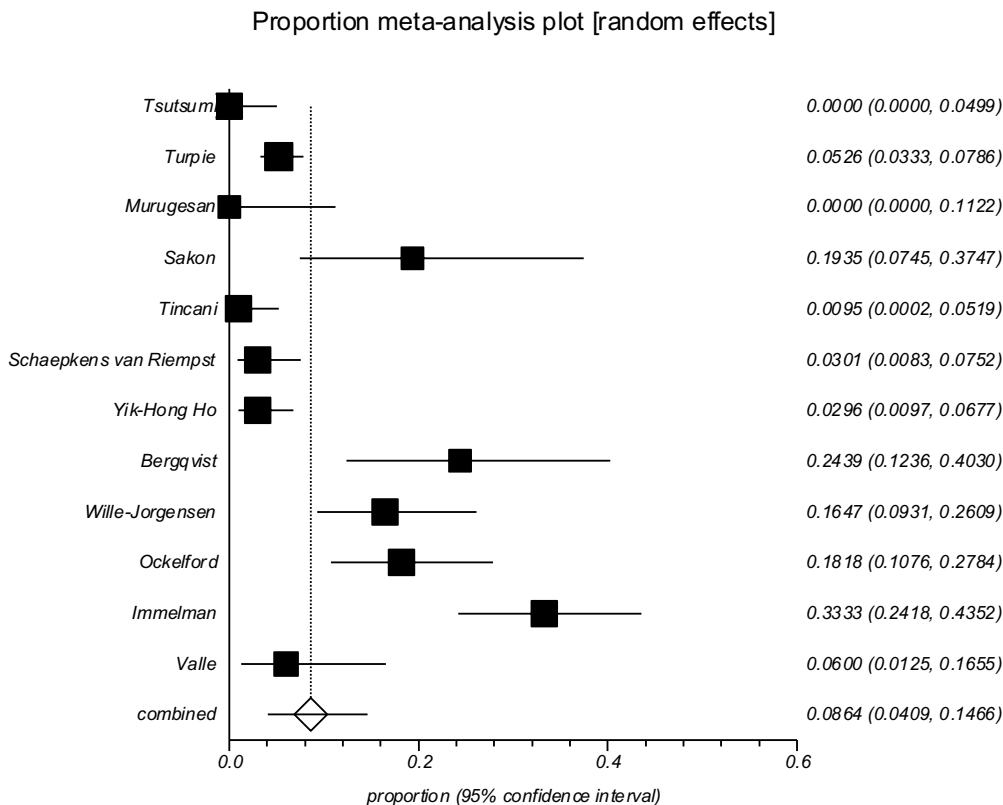


## **Placebo, non-pharmacological thromboprophylaxis or no treatment**

A total of 1322 patients from 11 RCTs and one prospective cohort study were used for this analysis. There were a total of 114 events of venous thrombosis (DVT and PE) corresponding to pooled proportion of 8.64 (95% CI = 4.09 to 14.66) with considerable heterogeneity ( $I^2 = 91\%$ ).

Figure 7 shows the forest plot of the analysis.

**Figure 7 Forest plot of the pooled proportion of the venous thromboembolic events post major abdominal surgery in patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment post-surgery.**

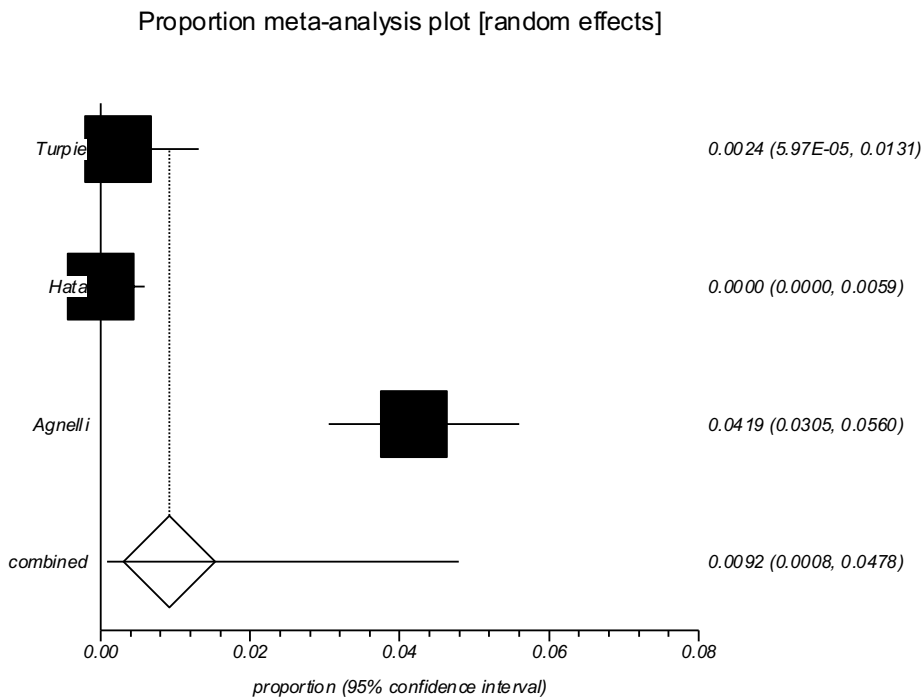


## Pooled Proportions of DVT Events

### Fondaparinux (2.5mg s/c daily)

A total of 2070 patients from 2 RCTs and one prospective cohort study were used for this analysis. There were a total of 44 events of DVT corresponding to pooled proportion of 0.92% (95% CI = 0.082 to 4.78) with considerable heterogeneity ( $I^2 = 96.8\%$ ). Figure 8 shows the forest plot of the analysis.

**Figure 8 Forest plot of the pooled proportion of DVT events post major abdominal surgery in patient receiving Fondaparinux for 7-10 days post-surgery**

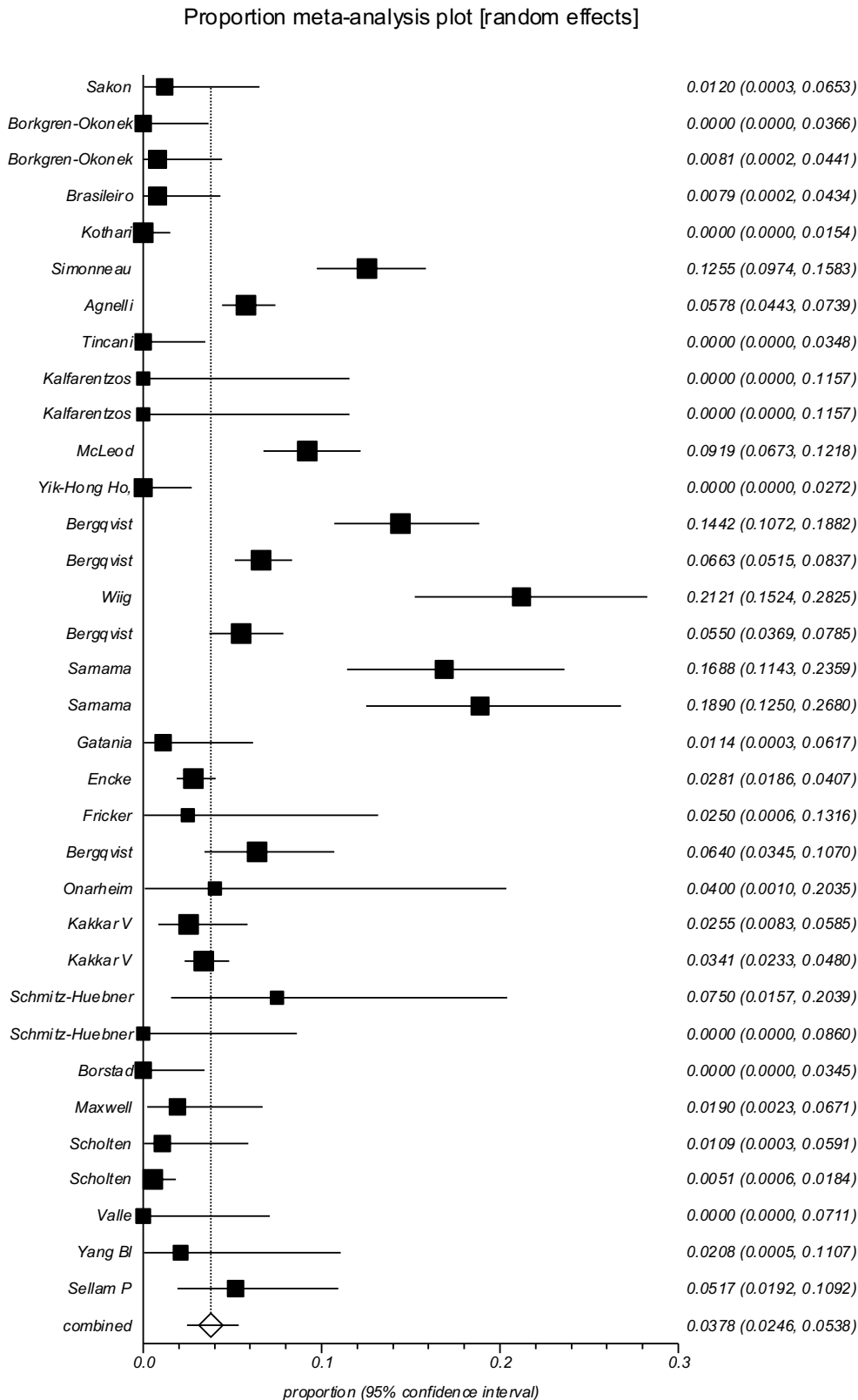


## **High thromboprophylactic dose of low molecular weight heparin**

### **( $\geq 4000$ IU)**

A total of 8605 patients from 30 RCTs and 4 prospective cohort studies were included in this analysis. There were a total of 484 events of DVT corresponding to a pooled proportion of 3.79 (95% CI = 2.46 to 5.38) with considerable heterogeneity ( $I^2$  91.2%). Figure 9 shows the forest plot of the analysis.

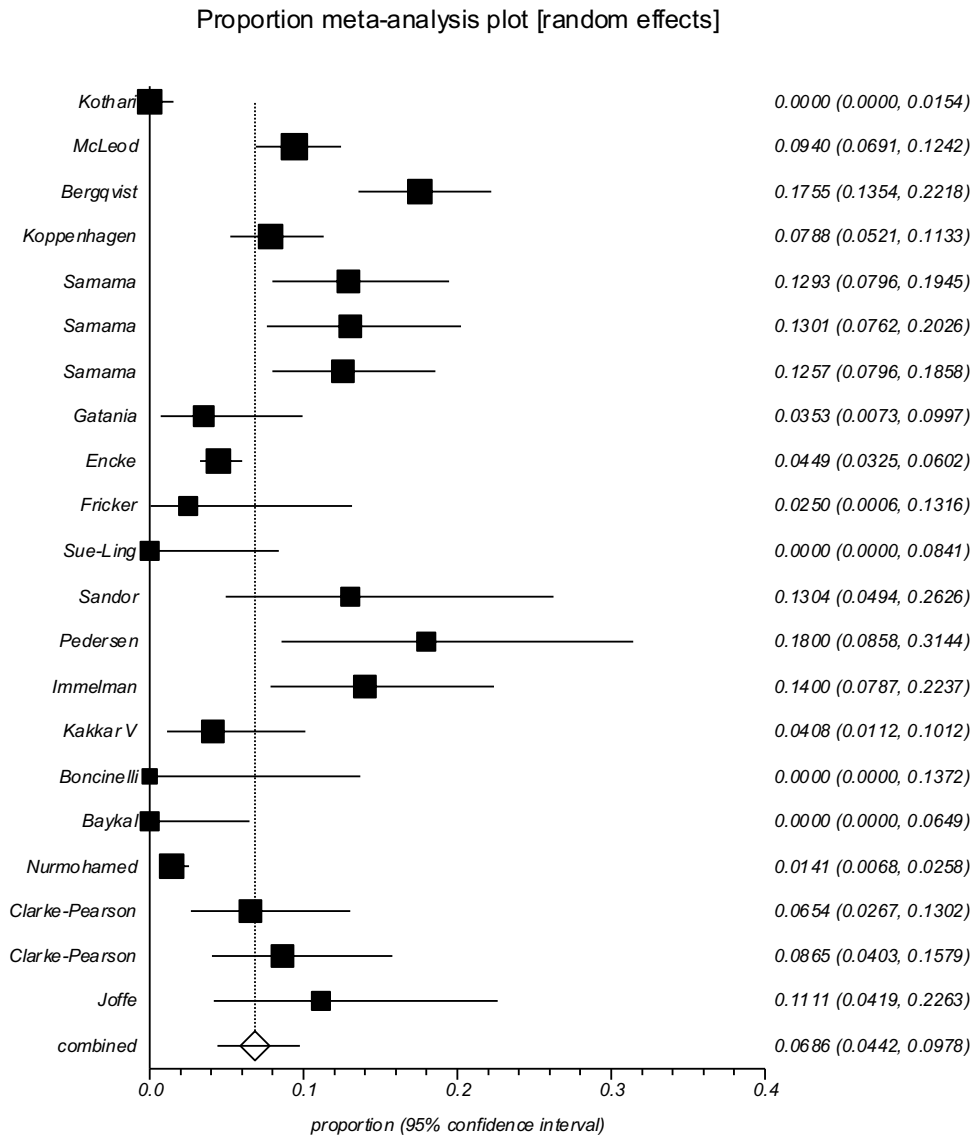
**Figure 9 Forest plot of the pooled proportion of DVT events post major abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery.**



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

A total of 4243 patients from 20 RCTs and one prospective cohort study were used for this analysis. There were a total of 293 events of DVT corresponding to pooled proportion of 6.86 (95% CI = 4.423 to 9.78) with considerable heterogeneity ( $I^2 = 90.6\%$ ). Figure 10 shows the forest plot of the analysis.

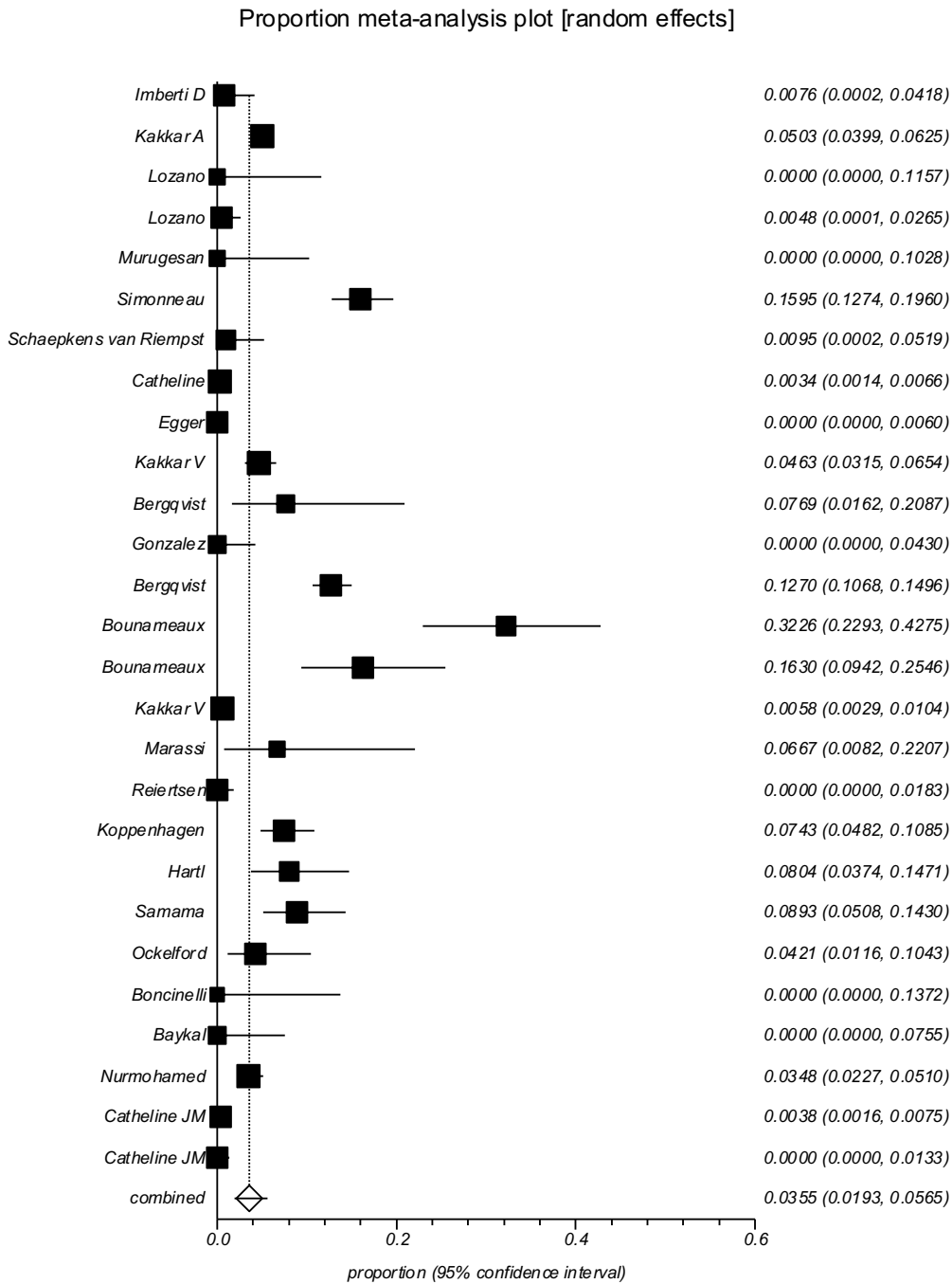
**Figure 10 Forest plot of the pooled proportion of the DVT events post major abdominal surgery in patient receiving high dose UFH for 7-10 days post-surgery.**



**Low prophylactic dose of low molecular weight heparin (<4000 IU)**

A total of 13424 patients from 21 RCTs and 6 prospective cohort studies were used for this analysis. There were a total of 462 events of DVT corresponding to pooled proportion of 3.55 (95% CI = 1.93 to 5.65) with considerable heterogeneity ( $I^2=96.7\%$ ). Figure 11 shows the forest plot of the analysis.

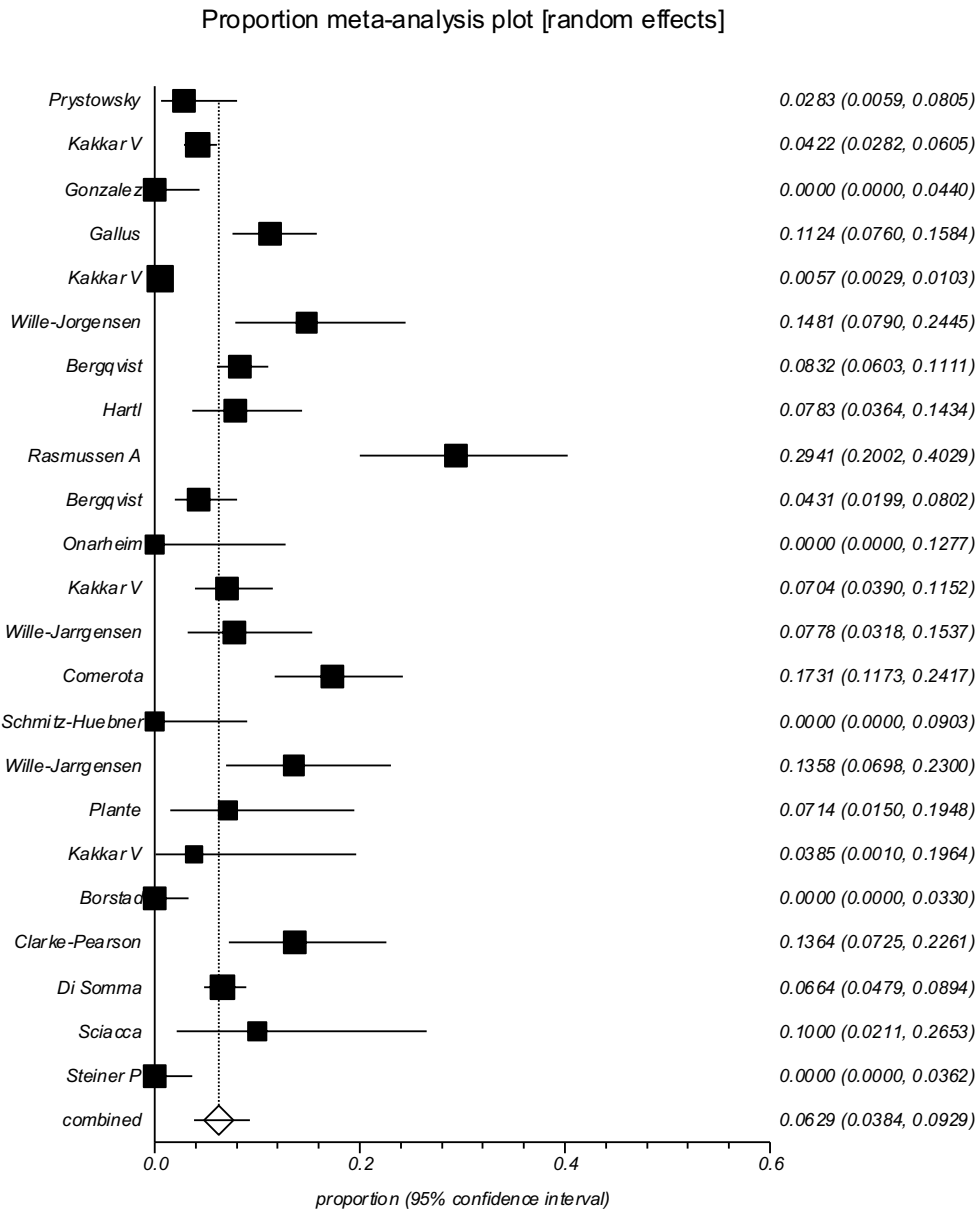
**Figure 11 Forest plot of the pooled proportion of DVT events post major abdominal surgery in patient receiving low dose LMWH for 7-10 days post-surgery**



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

A total of 5588 patients from 20 RCTs and 3 prospective cohort studies were included for this analysis. There were a total of 284 events of DVT corresponding to pooled proportion of 6.29 (95% CI = 3.84 to 9.29) with considerable heterogeneity ( $I^2 = 93.3\%$ ). Figure 12 shows the forest plot of the analysis.

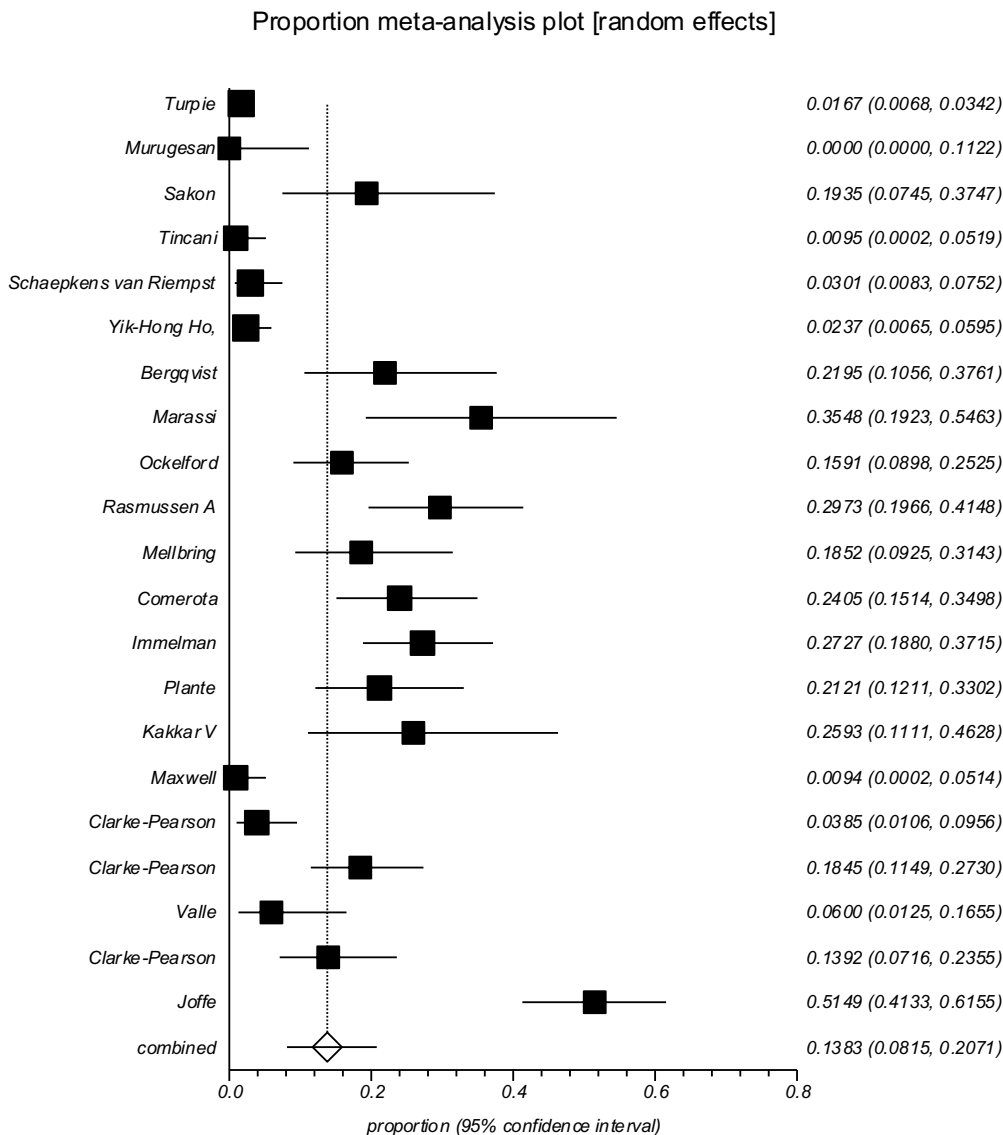
**Figure 12 Forest plot of the pooled proportion of DVT events post major abdominal surgery in patient receiving low dose UFH for 7-10 days post-surgery.**



## Placebo, non-pharmacological thromboprophylaxis or no treatment

A total of 1989 patients from 19 RCTs and 2 prospective cohort studies were included in this analysis. There were a total of 245 events of DVT corresponding to pooled proportion of 13.83 (95% CI = 8.15 to 20.71) with considerable heterogeneity ( $I^2 = 93.9\%$ ). Figure 13 shows the forest plot of the analysis.

**Figure 13 Forest plot of the pooled proportion of DVT events post major abdominal surgery in patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment post-surgery.**

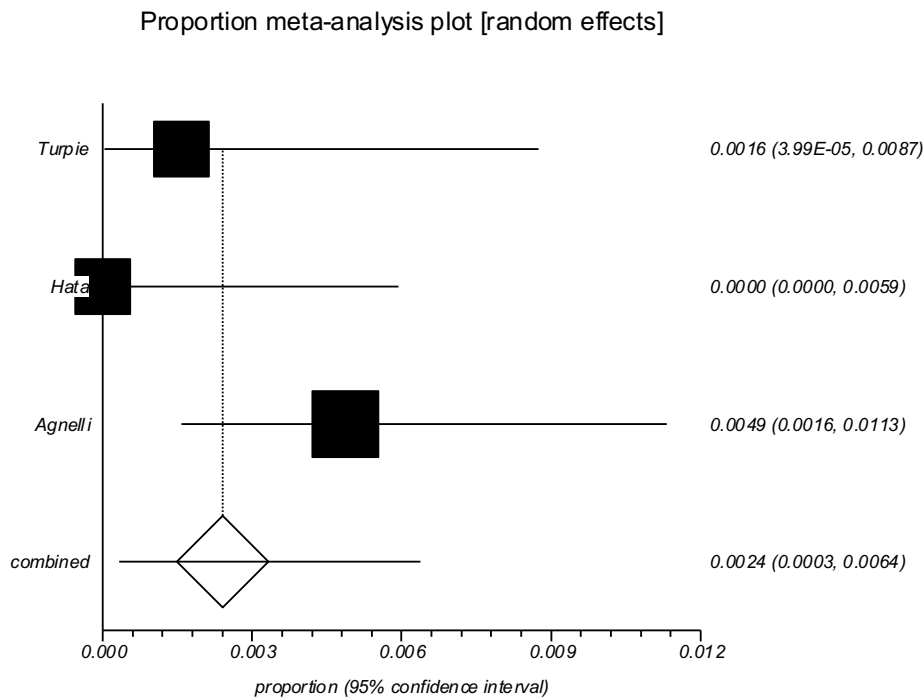


## Pooled Proportions of Pulmonary Embolism Events

### Fondaparinux (2.5mg s/c daily)

A total of 2281 patients from 2 RCTs and one prospective cohort study were used for this analysis. There were a total of 6 events of PE corresponding to pooled proportion of 0.24 (95% CI = 0.03 to 0.64) with moderate heterogeneity ( $I^2 = 54.6\%$ ). Figure 14 shows the forest plot of the analysis.

**Figure 14 Forest plot of the pooled proportion of PE events post major abdominal surgery in patient receiving Fondaparinux for 7-10 days post-surgery**

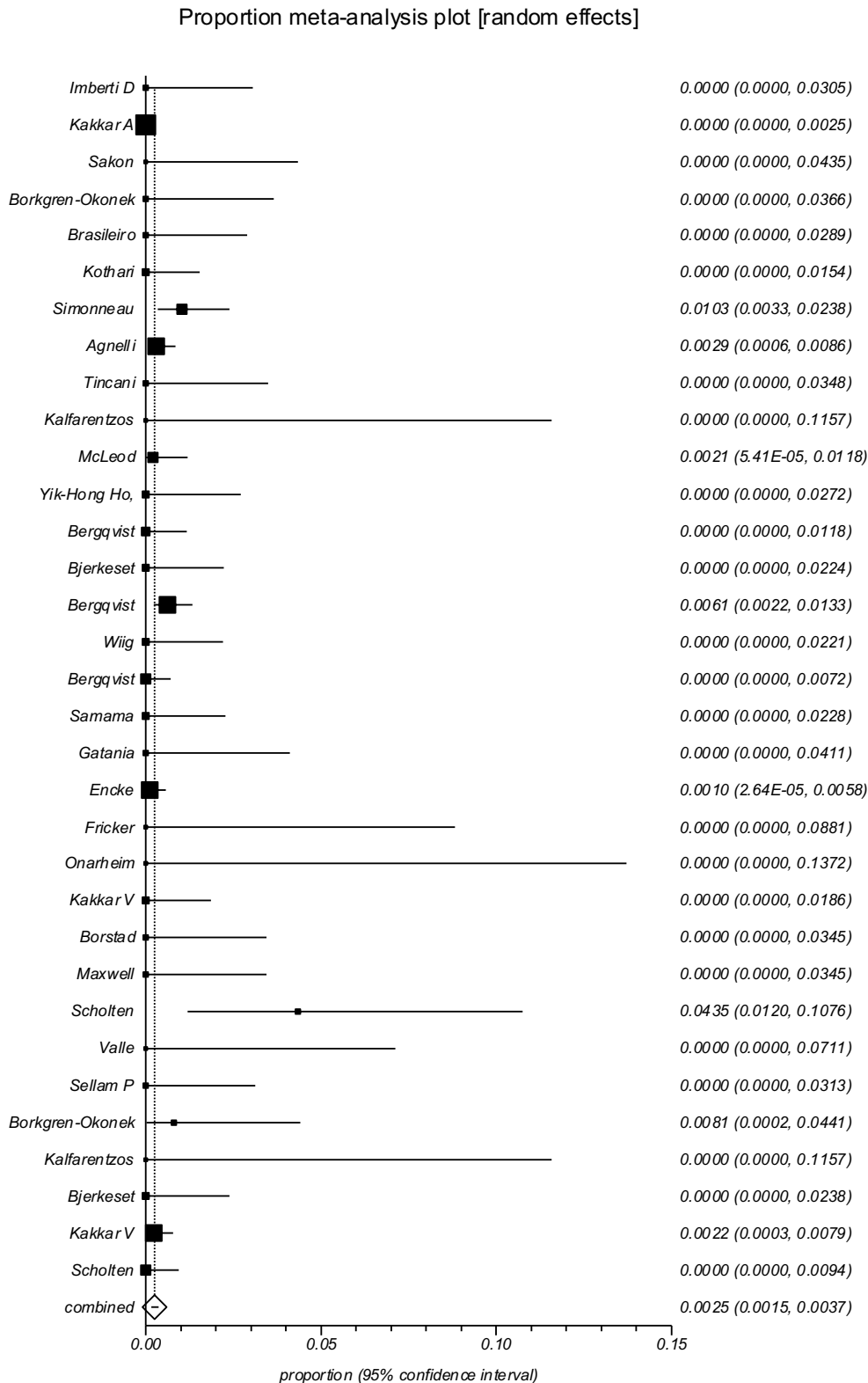


## **High thromboprophylactic dose of low molecular weight heparin**

### **( $\geq 4000$ IU)**

A total of 10081 patients from 27 RCTs and 6 prospective cohort studies were included in this analysis. There were a total of 23 events of PE corresponding to pooled proportion of 0.25% (95% CI = 0.15 to 0.37) with low heterogeneity ( $I^2 = 12.4\%$ ). Figure 15 shows the forest plot of the analysis.

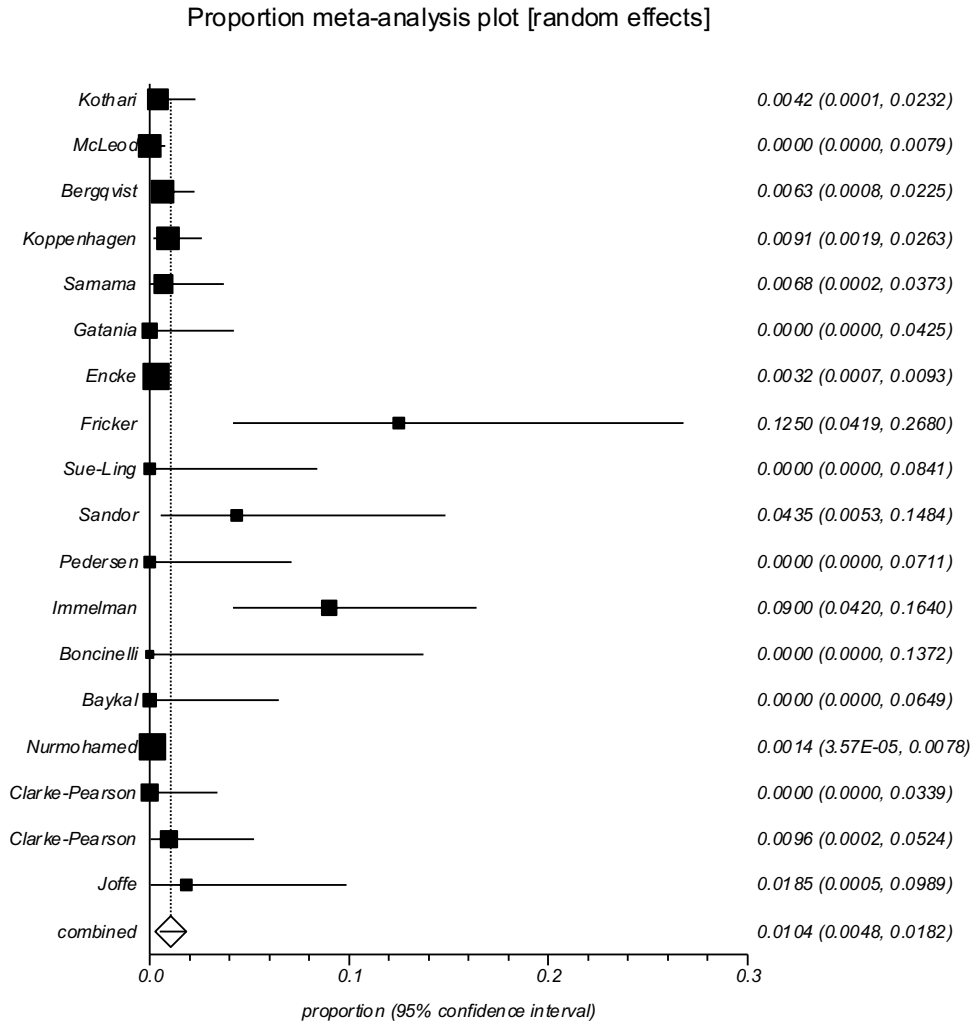
**Figure 15 Forest plot of the pooled proportion of PE events post major abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery**



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

A total of 3855 patients from 17 RCTs and one prospective cohort study were used for this analysis. There were a total of 29 events of PE corresponding to pooled proportion of 1.04 (95% CI = 0.48 to 1.82) with substantial heterogeneity ( $I^2 = 69\%$ ). Figure 16 shows the forest plot of the analysis.

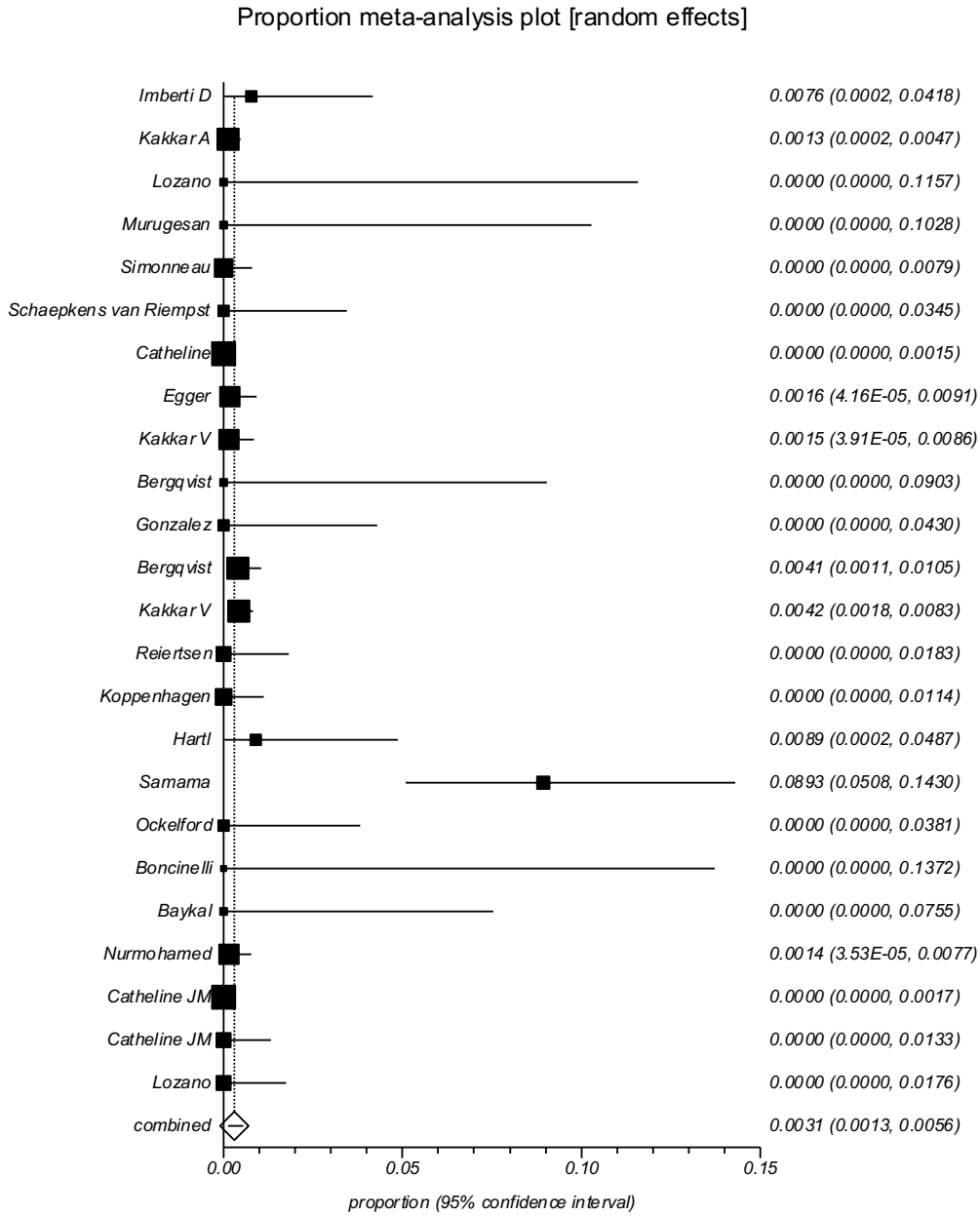
**Figure 16 Forest plot of the pooled proportion of the PE events post major abdominal surgery in patient receiving high dose UFH for 7-10 days post-surgery.**



### **Low prophylactic dose of low molecular weight heparin (<4000 IU)**

A total of 13209 patients from 18 RCTs and 6 prospective cohort studies were included in this analysis. There were a total of 34 events of PE corresponding to pooled proportion of 0.31 (95% CI = 0.13 to 0.56) with substantial heterogeneity ( $I^2 = 71.3\%$ ). Figure 17 shows the forest plot of the analysis.

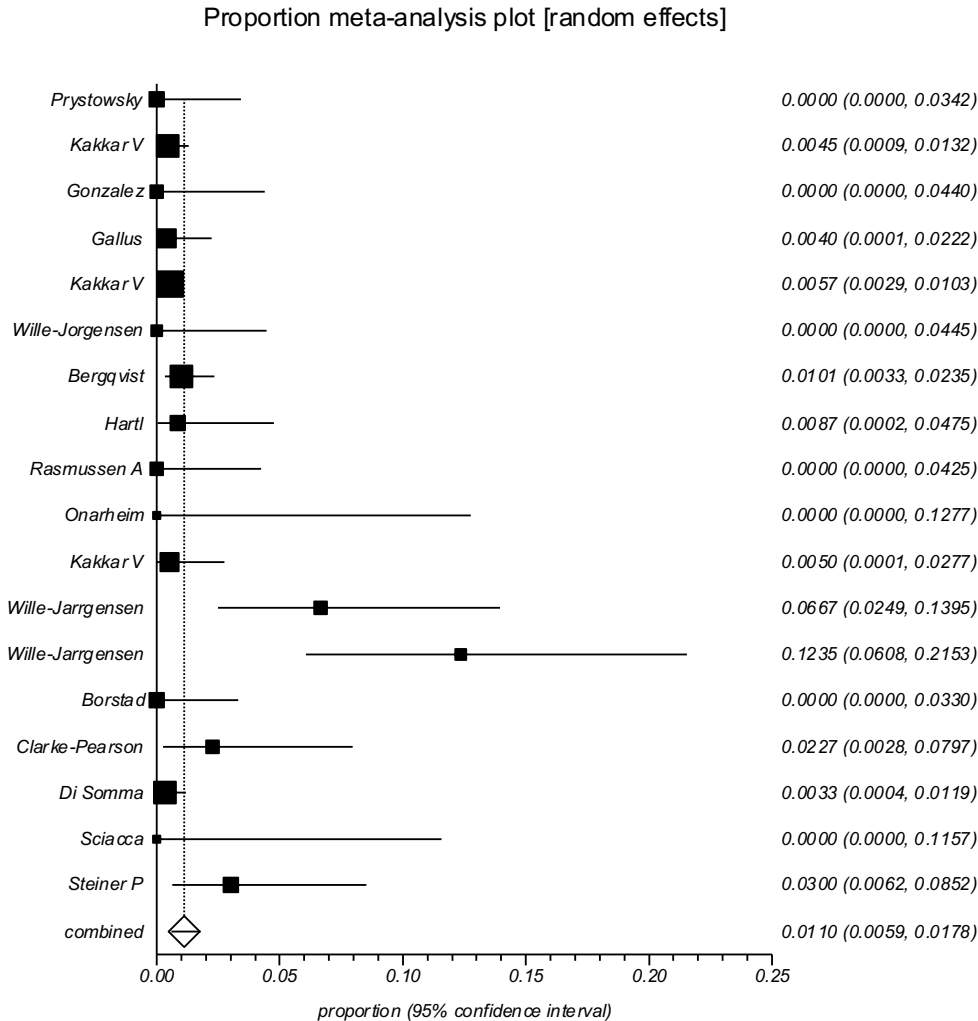
**Figure 17 Forest plot of the pooled proportion of the PE events post major abdominal surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

A total of 5116 patients from 16 RCTs and 2 prospective cohort studies were used for this analysis. There were a total of 45 events of PE corresponding to pooled proportion of 1.10% (95% CI = 0.59 to 1.78) with substantial heterogeneity ( $I^2 = 66\%$ ). Figure 18 shows the forest plot of the analysis.

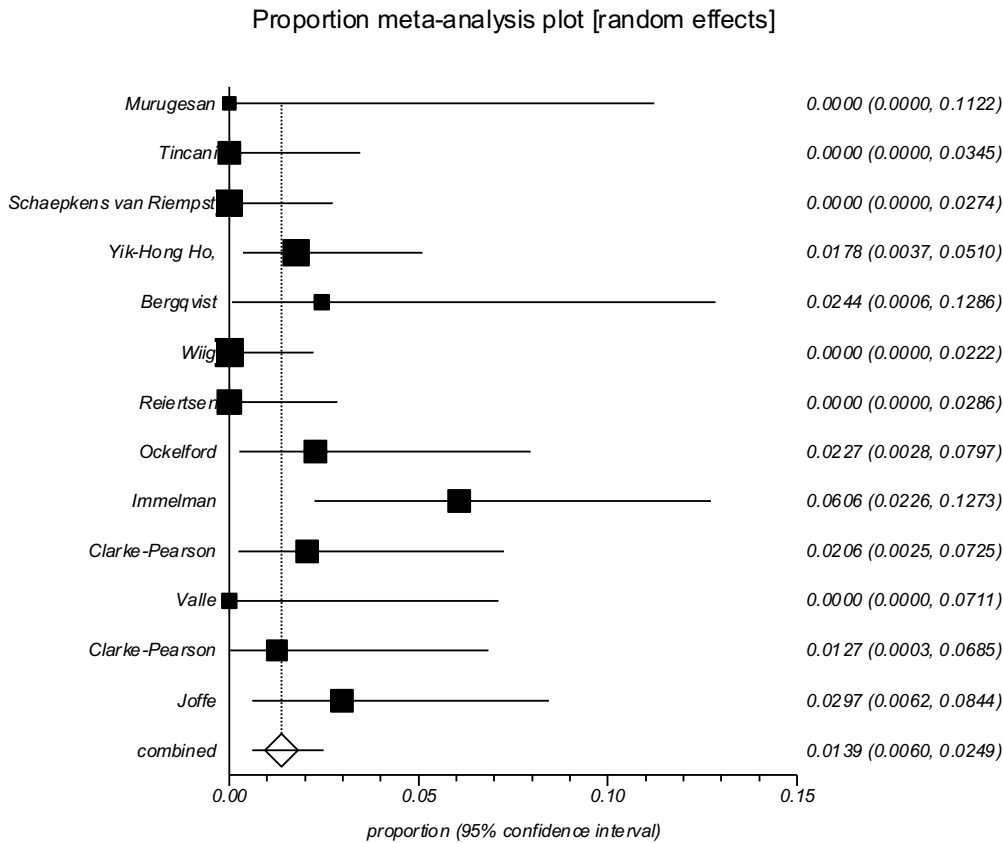
**Figure 18 Forest plot of the pooled proportion of the PE events post major abdominal surgery in patient receiving low dose UFH for 7-10 days post-surgery.**



**Placebo, non-pharmacological thromboprophylaxis or no treatment**

A total of 1284 patients from 19 RCTs and 2 prospective cohort studies were included in this analysis. There were a total of 18 events of PE corresponding to pooled proportion of 13.83 (95% CI = 8.15 to 20.71) with moderate heterogeneity ( $I^2 = 52\%$ ). Figure 19 shows the forest plot of the analysis.

**Figure 19 Forest plot of the pooled proportion of PE events post major abdominal surgery in patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment post-surgery.**

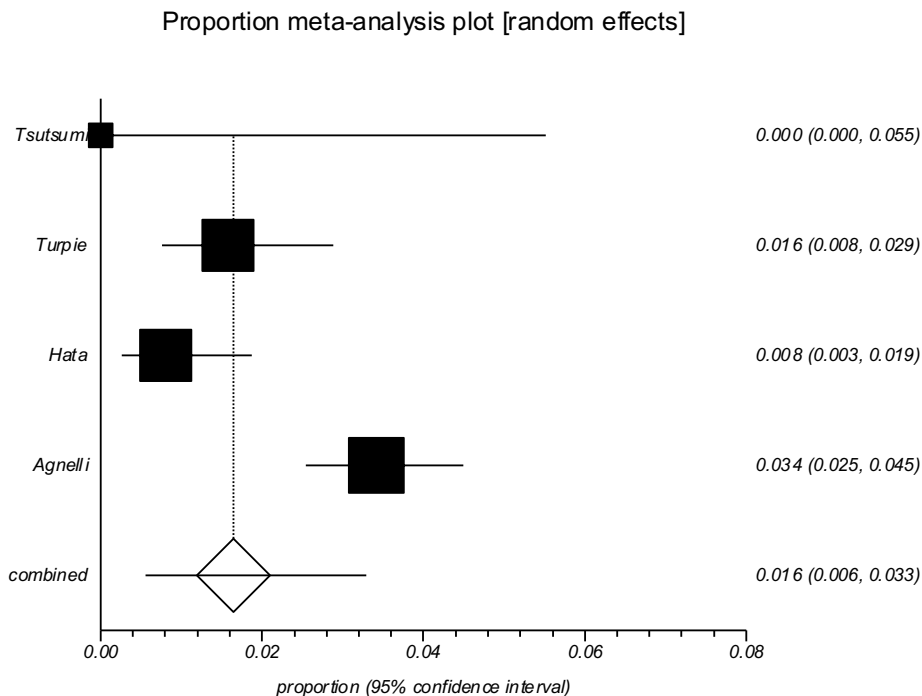


## Pooled Proportions of Major Bleeding Events

### Fondaparinux (2.5mg s/c daily)

A total of 2752 patients from 3 RCTs and one prospective cohort study were used for this analysis. There were a total of 64 events of PE corresponding to pooled proportion of 1.64% (95% CI = 0.56 to 3.30) with substantial heterogeneity ( $I^2 = 84\%$ ). Figure 20 shows the forest plot of the analysis.

**Figure 20 Forest plot of the pooled proportion of major bleeding events post major abdominal surgery in patient receiving Fondaparinux for 7-10 days post-surgery**

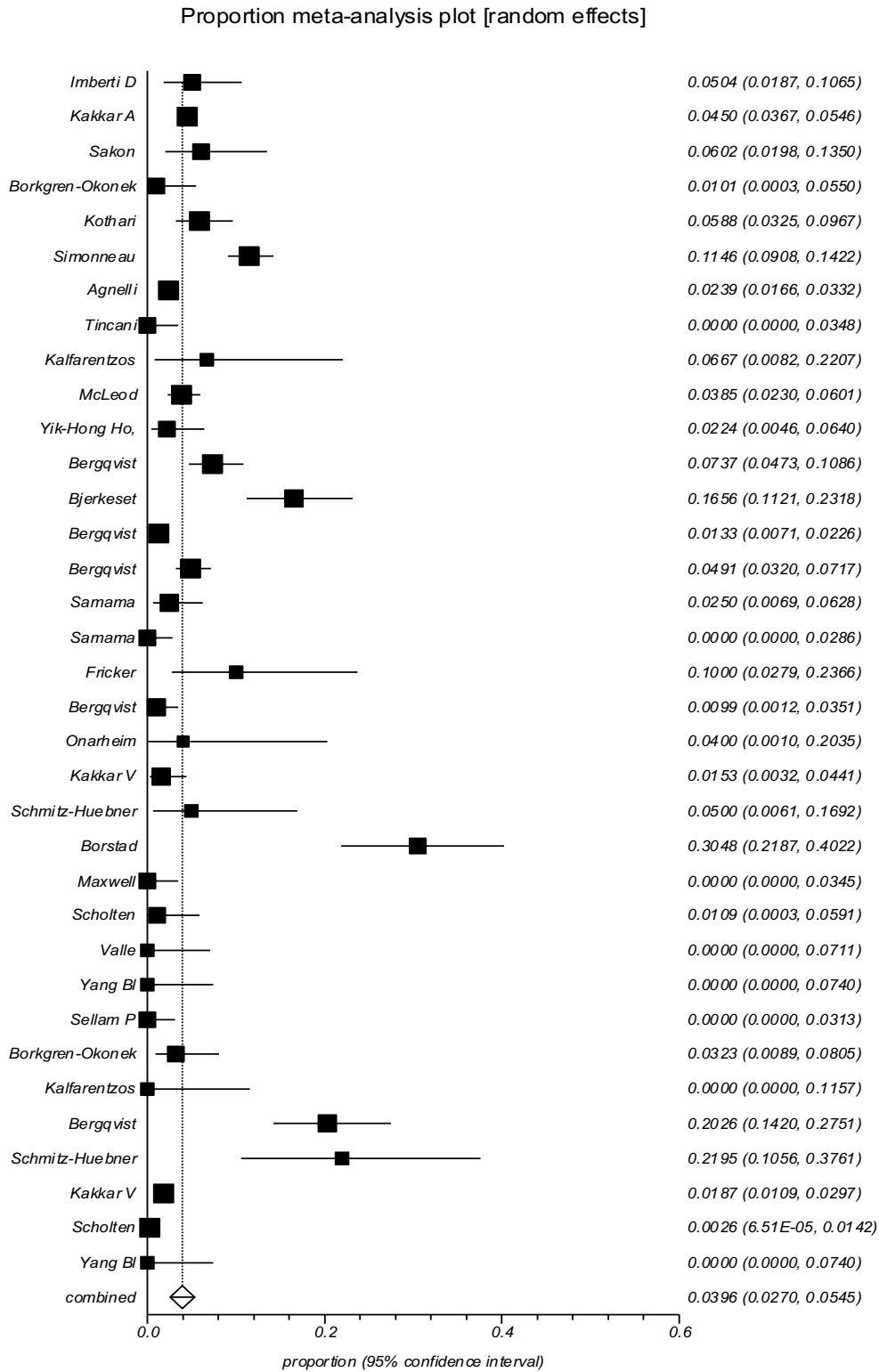


## **High thromboprophylactic dose of low molecular weight heparin**

### **( $\geq 4000$ IU)**

A total of 10472 patients from 31 RCTs and 4 prospective cohort studies were included in this analysis. There were a total of 452 events of PE corresponding to pooled proportion of 3.96 (95% CI = 2.70 to 5.45) with considerable heterogeneity ( $I^2 = 91\%$ ). Figure 21 shows the forest plot of the analysis.

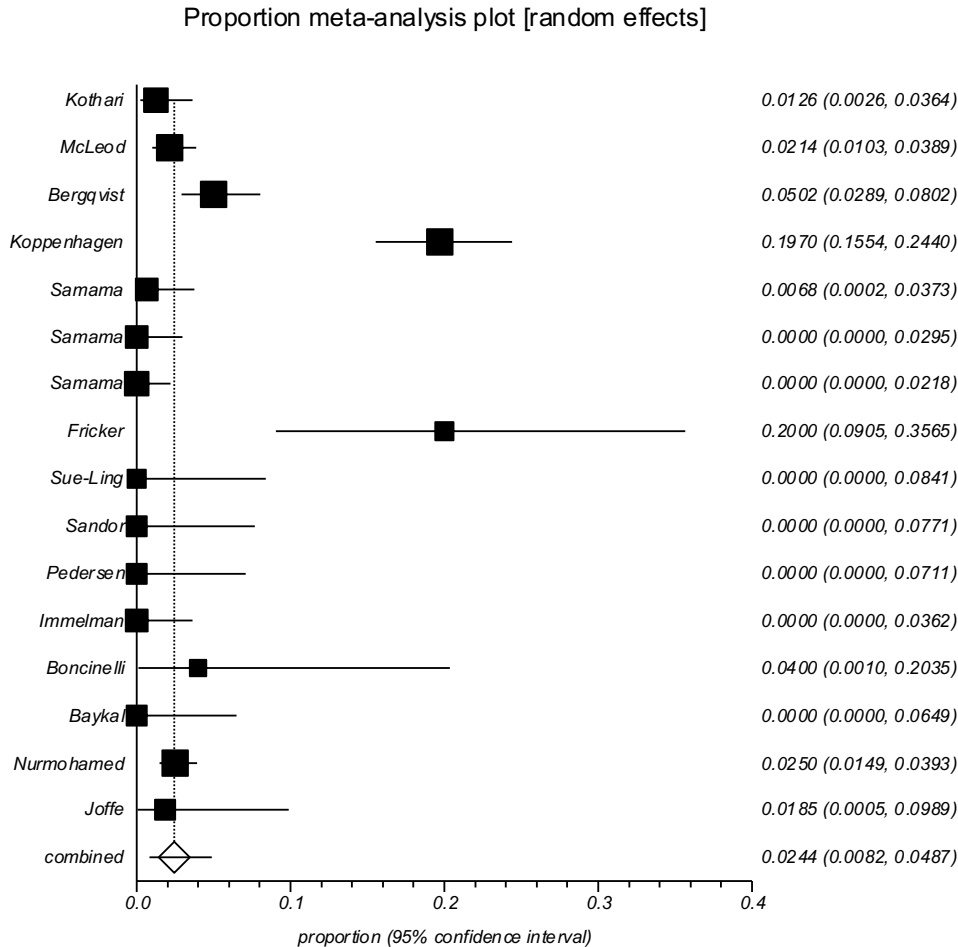
**Figure 21 Forest plot of the pooled proportion of major bleeding events post major abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery**



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

A total of 2923 patients from 15 RCTs and one prospective cohort study were used for this analysis. There were a total of 123 events of PE corresponding to pooled proportion of 2.44% (95% CI = 0.82 to 4.87) with considerable heterogeneity ( $I^2 = 91.2\%$ ). Figure 22 shows the forest plot of the analysis.

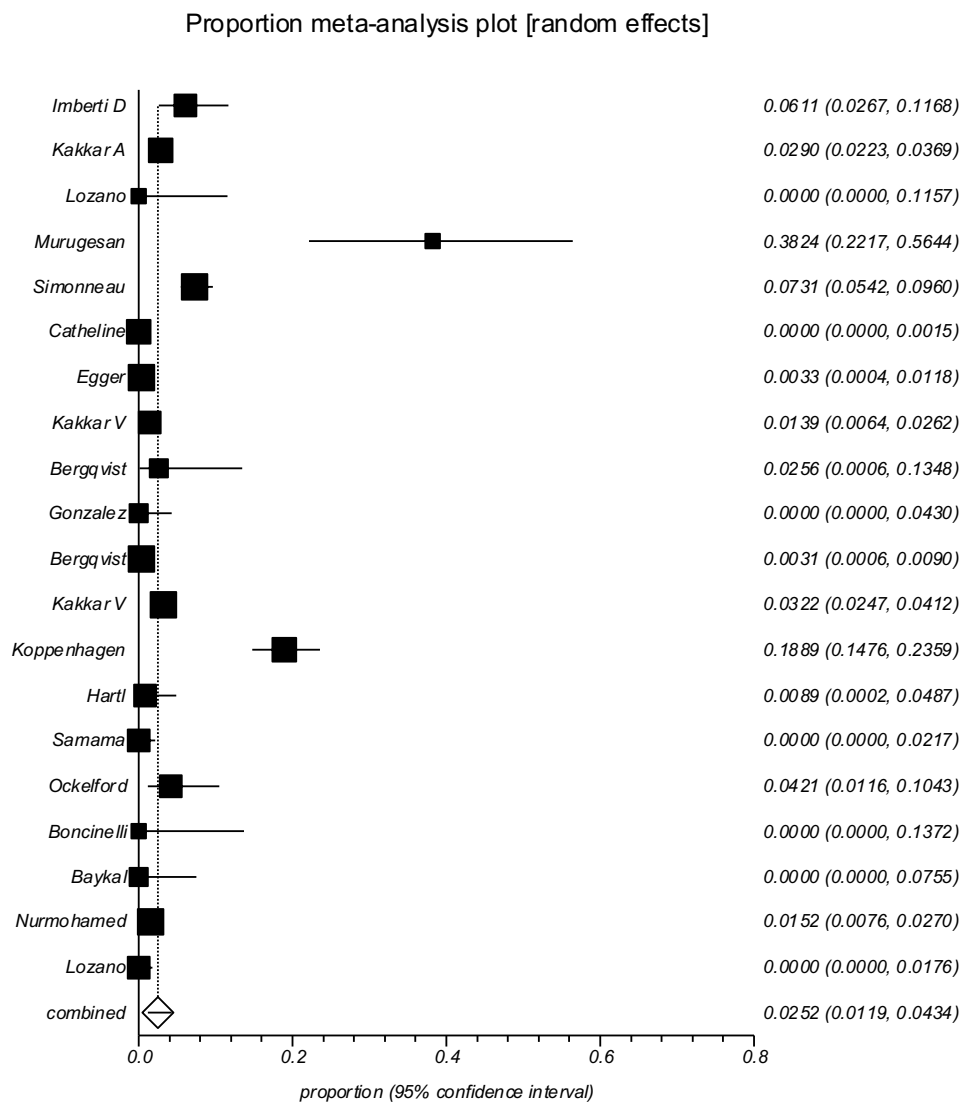
**Figure 22 Forest plot of the pooled proportion of major bleeding events post major abdominal surgery in patients receiving high dose UFH for 7-10 days post-surgery.**



## Low prophylactic dose of low molecular weight heparin (<4000 IU)

A total of 11350 patients from 17 RCTs and 3 prospective cohort studies were included in this analysis. There were a total of 284 major bleeding events corresponding to pooled proportion of 2.52% (95% CI = 1.1866 to 4.34) with considerable heterogeneity ( $I^2 = 95.9\%$ ). Figure 23 shows the forest plot of the analysis.

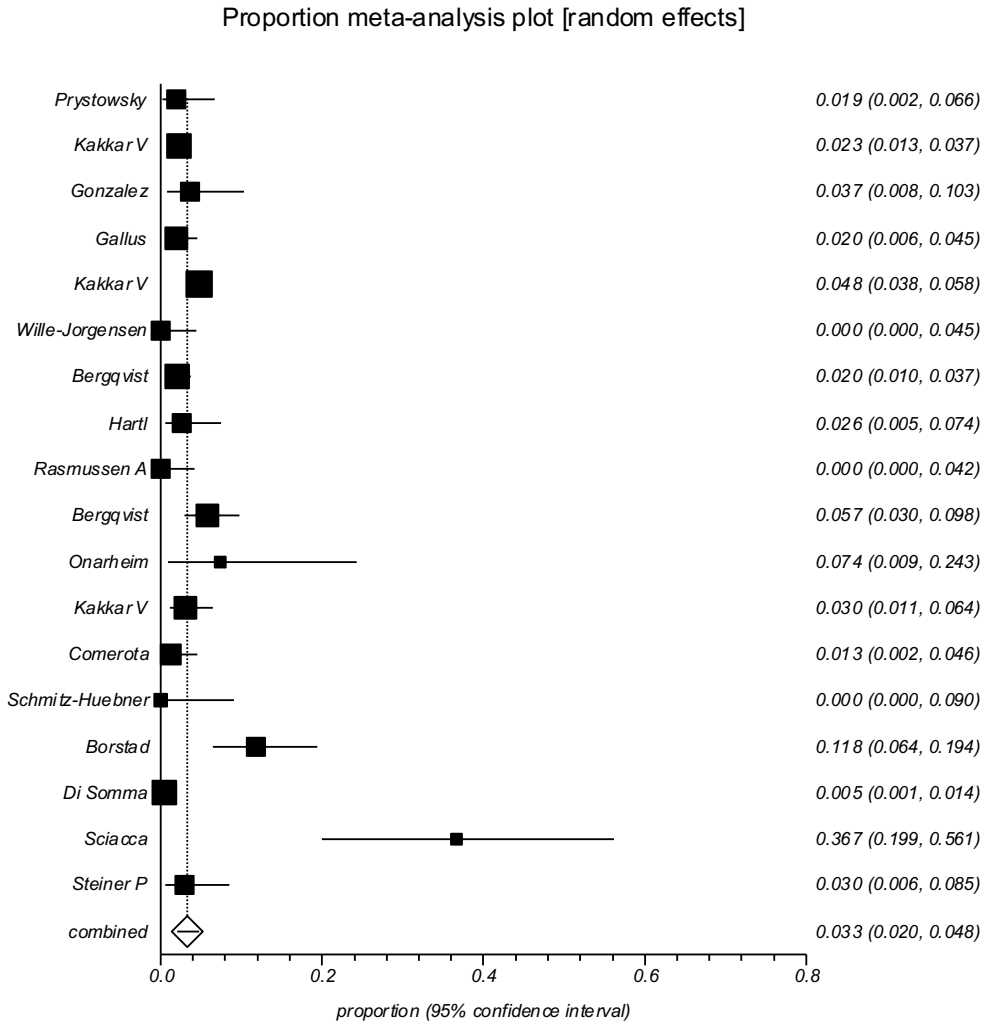
**Figure 23 Forest plot of the pooled proportion of major bleeding events post major abdominal surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

A total of 5268 patients from 16 RCTs and 2 prospective cohort studies were used for this analysis. There were a total of 181 major bleeding events corresponding to pooled proportion of 3.26 (95% CI = 2.01 to 4.78) with substantial heterogeneity ( $I^2 = 83.9\%$ ). Figure 24 shows the forest plot of the analysis.

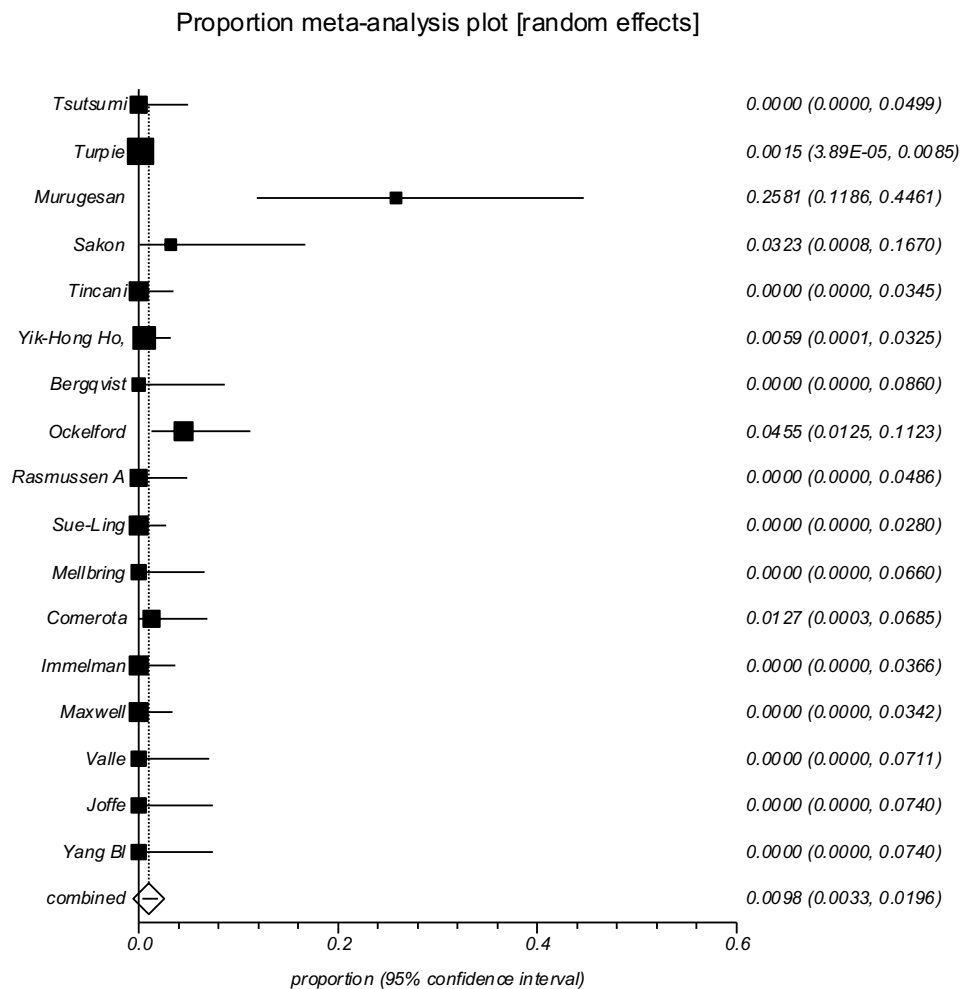
**Figure 24 Forest plot of the pooled proportion of major bleeding events post major abdominal surgery in patient receiving low dose UFH for 7-10 days post-surgery.**



## **Placebo, non-pharmacological thromboprophylaxis or no treatment**

A total of 1875 patients from 17 RCTs were used for this analysis. There were a total of 16 major bleeding events corresponding to pooled proportion of 0.98 (95% CI = 0.33 to 1.96) with moderate heterogeneity ( $I^2 = 63.1\%$ ). Figure 25 shows the forest plot of the analysis.

**Figure 25 Forest plot of the pooled proportion of major bleeding events post major abdominal surgery in patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment.**



## ***Pool Proportion for Secondary Outcomes***

The pooled proportions for 30 days' mortality, 30 days' re-operation rate, wound infection and wound oozing are depicted in [Appendix 5](#).

## **Subgroup Analysis**

### **Laparoscopic Surgery**

#### ***Summary of pooled analysis for laparoscopic surgery***

Table 4 summarized the result of the pooled analyses for laparoscopic surgery. The details of the individual intervention pooled analyses are depicted in [Appendix 6](#).

**Table 4 summary of the pooled analysis for laparoscopic surgery**

<b><i>Intervention</i></b>	<b><i>Fondaparinux</i></b>	<b><i>LMWH high dose</i></b>	<b><i>UFH high dose</i></b>	<b><i>LMWH low dose</i></b>	<b><i>UFH low dose</i></b>	<b><i>Placebo</i></b>
<b><i>Overall VTE(number of studies)</i></b>	.	0.14 (2)	.	0.37 (4)	.	2.37 (2)
<b><i>95% CI</i></b>	.	0.02 to 0.81	.	0.22 to 0.56	.	0.80 to 4.73
<b><i>I<sup>2</sup></i></b>	.	.	.	0	.	.
<b><i>DVT(number of studies)</i></b>	.	0.14 (2)	.	0.37 (4)	.	2.37 (2)
<b><i>95% CI</i></b>	.	0.02 to 0.81	.	0.22 to 0.56	.	0.80 to 4.73
<b><i>I<sup>2</sup></i></b>	.	.	.	0	.	.
<b><i>PE(number of studies)</i></b>	.	0.14 (2)	.	0.02 (4)	.	0.21 (2)
<b><i>95% CI</i></b>	.	0.02 to 0.81	.	0.0002 to 0.07	.	0.03 to 1.18
<b><i>I<sup>2</sup></i></b>	.	.	.	0	.	.
<b><i>Major bleeding(number of studies)</i></b>	.	2.3 (2)	.	0.01 (3)	.	.
<b><i>95% CI</i></b>	.	0.19 to 11.63	.	0.0006 to 0.07	.	.
<b><i>I<sup>2</sup></i></b>	.	.	.	95.9	.	.

## **Bariatric Surgery**

### **Summary of pooled analysis for bariatric surgery**

Table 5 summarizes the pooled analysis for bariatric surgery. The details of the individual intervention pooled analyses are depicted in [Appendix 7](#).

**Table 5 summary of pooled analysis for bariatric surgery**

<b>Intervention</b>	<b>Fondaparinux</b>	<b>LMWH high dose</b>	<b>UFH high dose</b>	<b>LMWH low dose</b>	<b>UFH low dose</b>	<b>Placebo</b>	<b>LMWH high dose-RC</b>
<b>Overall VTE(number of studies)</b>	.	0.98 (13)	.	.	.	.	1.38 (6)
95% CI	.	0.39 to 1.84	.	.	.	.	
$I^2$	.	58.6	.	.	.	.	0
<b>DVT(number of studies)</b>	.	0.61 (13)	.	.	.	.	1.08 (6)
95% CI	.	0.31 to 1.01	.	.	.	.	
$I^2$	.	0	.	.	.	.	0
<b>PE(number of studies)</b>	.	0.52 (13)	.	.	.	.	0.63 (6)
95% CI	.	0.16 to 1.07	.	.	.	.	
$I^2$	.	44.3	.	.	.	.	0
<b>Major bleeding(number of studies)</b>	.	4.47 (12)	.	.	.	.	5.38 (6)
95% CI	.	1.59 to 8.71	.	.	.	.	
$I^2$	.	92.3	.	.	.	.	5.3

## Cancer Surgery

### **Summary of pooled analysis for cancer surgery**

Table 6 summarizes the result of pooled analysis for cancer surgery. The details of the individual intervention pooled analyses are reported in Appendix 8.

**Table 6 summary of the pooled analysis for cancer surgery.**

<b>Intervention</b>	<b>Fondaparinux</b>	<b>LMWH high dose</b>	<b>UFH high dose</b>	<b>LMWH low dose</b>	<b>UFH low dose</b>	<b>Placebo</b>
<b>Overall VTE(number of studies)</b>	0.06 (2)	5.39 (7)	8.06 (7)	4.08 (3)	12.65 (2)	5.2 (6)
95% CI	0.02 to 0.38	1.99 to 10.33	3.99 to 13.40	0.35 to 20.18	9.33 to 16.39	1.50 to 10.95
$i^2$	.	92.1	85.1	92.8	.	84.2
<b>DVT(number of studies)</b>	.	7.17 (6)	6.52 (7)	5.01 (4)	12.07 (2)	11.99 (5)
95% CI	.	3.77 to 11.54	2.92 to 11.43	0.08 to 16.83	8.82 to 15.75	3.41 to 24.82
$i^2$	.	86.3	85.1	89.5	.	89.6
<b>PE(number of studies)</b>	.	0.43 (6)	0.99 (7)	0.1 (3)	1.25 (2)	0.55 (4)
95% CI	.	0.15 to 0.86	0.13 to 2.66	0.01 to 0.54	0.06 to 3.92	0.04 to 1.64
$i^2$	.	6.5	71.5	0	.	0
<b>Major bleeding(number of studies)</b>	0.83 (2)	5.82 (6)	4.72 (5)	2.68 (3)	.	0.71 (3)
95% CI	0.29 to 1.64	2.62 to 10.21	1.57 to 9.45	0.008 to 9.92	.	0.000001 to 2.81
$i^2$	.	89	81.5	79.9	.	30.9

## ***Discussion of the Systematic Review and Pooled analysis***

### ***Summary of main results***

This is the most exhaustive systematic review and pooled analysis performed to date that assessed the efficacy and safety of the different types of pharmacological thromboprophylaxis among patients post major abdominal surgery. We included a total of 71 RCTs and 16 prospective cohort studies in our review. We were able to report the pooled rates of VTE, major bleeding and other adverse events associated with 6 different regimens of pharmacological thromboprophylaxis (Fondaparinux, high and low prophylactic doses of both LMWH and UFH, placebo, non-pharmacological thromboprophylaxis or observation).

All the five pharmacological thromboprophylaxis regimens were associated with similar rates of overall VTE. The 95% CI of the different estimate overlapped indicating no statistically significant difference between any of the pharmacological interventions. Similarly, the different types of pharmacological interventions had similar rate of VTE compared to placebo. However, all the pooled analysis showed statistically significant and considerable heterogeneity with  $I^2$  test more than 90%. For any DVT, the rates between fondaparinux, high/low dose of LMWH were similar and seemed potentially lower compared to patients receiving placebo/observation. Again, however, all the pooled analysis showed statistically significant and considerable heterogeneity with  $I^2$  test more than 90%.

The pooled proportion of PE, including fatal PE, in patients receiving placebo/observation post major abdominal surgery was 1.39% (95% CI =0.60-2.49). Patients receiving any pharmacological thromboprophylaxis regimens seemed to have lower rates of PE complications. This seems to be more pronounced with LMWH (both at a high and low prophylactic dose).

Interestingly, the pooled PE estimates yield lower heterogeneity ( $I^2 < 72\%$ ) compared to that of VTE and DVT pooled analysis ( $I^2 > 90\%$ ). This is especially true for high dose LMWH ( $I^2 = 12.4\%$ ).

The pooled proportion of major bleeding episode was low in patients who did not receive any pharmacological thromboprophylaxis (0.98%, 95% CI= 0.33-1.96). The highest proportions of major bleeding episodes were reported in patients who received high dose LMWH (3.96, 95% CI= 2.70-5.45) or low dose UFH (3.26, 95% CI= 2.01-4.78). However, all the pooled analyses for major bleeding demonstrated statistically significant and substantial heterogeneity with  $I^2$  test (63% to 95%).

The rates of other secondary outcomes including 30-day overall mortality, 30-day re-operation and wound infections were comparable between the different types of pharmacological regimens and in patients receiving placebo/observation. Although, surgical wound infections seem to occur less frequently in patients receiving placebo or non-pharmacological thromboprophylaxis compared to pharmacological thromboprophylaxis. It is important to emphasize that a relatively small number of studies were included in the analyses of surgical wound infections; this led to imprecise estimate with wider CIs. Low dose UFH seems to be associated with an increase rate of wound oozing (10.81%, 95% CI: 7.29-14.92) compared to placebo or non-pharmacological thromboprophylaxis (2.22%, 95% CI: 0.94-4.02). However, this analysis was again done using a limited number of studies and thus these findings are only hypothesis-generating.

## **Summary of sub-groups analyses**

### ***Laparoscopic surgery***

Although both high and low doses of LMWH seemed to be associated with lower rates of overall VTE compared to placebo/observation, our data suggests that only patients receiving low prophylactic dose LMWH had also a lower rate of PE. Low prophylactic dose of LMWH also seemed to be associated with a lower rate of major bleeding in comparison to high dose LMWH or low dose UFH.

### ***Bariatric surgery***

Most of the studies that evaluated thromboprophylaxis post bariatric surgery used high dose LMWH. Accordingly, we were only able to analyze high dose LMWH in this sub-group. We were thus unable to compare it with other possible thromboprophylaxis. However, we can conclude that that pooled proportion of VTE, DVT and PE post bariatric surgery using high dose LMWH was less than 1% and pooled proportion for major bleeding was more than 4%.

### ***Cancer surgery***

Only fondaparinux seemed to be associated with a lower rate of overall VTE post major abdominal cancer surgery compared with placebo and other pharmacological thromboprophylaxis. However, the analysis was based on only two studies with zero events. The analyses of the rest of the interventions showed similar rates between the different types of pharmacological thromboprophylaxis regimens and placebo/observation. Analyses of major bleeding showed that fondaparinux was associated with similar major bleeding events compared to placebo while the rest of interventions reported much higher event rates.

## ***Other thromboprophylaxis regimens***

Our systematic review led only to two studies that evaluated aspirin for thromboprophylaxis post major abdominal surgery. One of these studies (Zakert, 1982) used Aspirin at 0.5g every 8 hours, a dose not currently used in clinical practice. The other study (Antolovic, 2011) was a pilot RCT that randomized patients to either continuing low dose Aspirin versus discontinuation of Aspirin treatment 5 days prior to surgery and resumption on post-operative day 5. There were no VTE events in both groups and there was only one major bleeding event in a patient who continued Aspirin. More research on the utility of aspirin in patients post major abdominal surgery is desperately needed.

Our systematic review found no clinical trial that evaluated the DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) in post major abdominal surgery. Dabigatran, rivaroxaban and apixaban are currently indicated for thromboprophylaxis post major orthopedic surgery but not yet evaluated or indicated post major abdominal surgery.

## ***Length of Intervention***

An important knowledge gap in the use of pharmacological thromboprophylaxis in the post-operative period of patients that have undergone major abdominal surgery is the optimal length of therapy. While some clinical guidelines suggest 7-10 days of intervention [37], others suggest extended duration for a subset of surgical interventions (e.g. cancer surgery) [18] [37], while others do not specify. The majority of clinical trials included in this review evaluated either 7-10 days of prophylaxis, or until discharge. Also, in those trials in which patients received 7-10 days of prophylaxis, it is unclear if this included a post discharge prescription to complete the 7-10 days' duration of prophylaxis or not. An answer to this question is of a great significance given

that the more novel surgical techniques and the scarce health care resources have been resulting in earlier discharge.

## ***Limitations***

### **Heterogeneity**

There were many important differences among the individual trials that might have led to the substantial heterogeneity. First, although most of the trials were RCTs and fewer prospective cohorts, pooling RCT with cohort studies can lead to significant heterogeneity. Non-randomized clinical trials carry a potentially higher risk of biases especially selection and reporting bias. However, in order to minimize these biases, we have only included prospective cohorts' studies. We have included prospective cohort trials in an attempt to gather as much available data in the area without compromising the quality of evidence. While there were a good number of RCTs that examined parenteral thromboprophylactic agents, there were only 2 RCTs for aspirin and no RCT for the DOACs. Hoping for finding more data for aspirin and the DOACs, we have included cohort studies in the review. The initial rationale for including non-randomized studies was to increase the number of events and generate more precise estimates. Second, major abdominal surgery is a broad medical term comprising many different types of surgeries with different risk of VTE complications (e.g. laparoscopy vs. laparotomy) and patient population (e.g. bariatric (obese patients) vs. cancer-related surgeries). We included all kind of abdominal surgeries that met our definition (any abdominal surgery that is laparoscopic or open, performed under general anaesthesia and lasted for at least 30 minutes). Thus, this could have been laparoscopic cholecystectomy or Whipple's resection for pancreatic cancer. Furthermore, many different surgical techniques are used within even more specific sub-categories of major

abdominal surgery. For example, cancer related surgeries included bowel resections for gastrointestinal cancer to nephrectomy to hysterectomies for gynecological malignancies. Similarly, bariatric surgeries included different procedures such as Roux-en-Y gastric bypass, laparoscopic gastric banding and sleeve gastrectomy. These all resulted in important variations in the studies' populations and baseline characteristics and could have contributed significantly to the reported heterogeneity. Sub-group analyses were performed in order to adjust for some of these confounders. This was clearly evident in bariatric sub-group analysis especially for DVT events in which the degree of heterogeneity fell down from over 90% to 0 % for high dose LMWH. However, individual clinical trials assessing one type of pharmacological thromboprophylaxis would be required for each type of procedures in order to account for all these variables. Third, variations in the pharmacological thromboprophylactic regimens might have also contributed to the inconsistency among the trials. The type and dose of LMWH differed from one trial to another. There were at least 6 types of LMWH included into the analyses. These include enoxaparin, dalteparin, tinzaparin, parnaparin, semuloparin and bemiparin. Furthermore, although we divided LMWH into high dose (equivalent to  $\geq$  to 4000 IU of anti-Xa) and low dose LMWH (equivalent to  $<$ 4000 IU of anti-Xa), there were still significant differences in the dosages used within these subgroups. For example, high dose enoxaparin used included 40 mg once daily, 60 mg once daily, 40 mg twice daily, 20 mg twice daily, 60 mg twice daily and 30 mg twice daily. The duration of thromboprophylaxis is also heterogeneous. Pharmacological thromboprophylaxis was administered during hospitalization only, until patients are fully mobile or up to 7-10 days depending on the trial protocol. The timing of administration of the first dose was given either pre (1-24 hours) or postoperatively (4-48 hours). Although it is unlikely that the difference in timing is clinically relevant, it might have

led to some heterogeneity. Finally, the difference in the comparator groups (e.g. observation, placebo, and possible mechanical thromboprophylaxis) might have also led to important discrepancy in the pooled estimates. Including non-pharmacological thromboprophylaxis (graded compression stocking and IPC) under the umbrella of placebo has its own limitation. IPC might be much more effective than placebo and no treatment in preventing venous thrombosis. Lastly, the diagnostic strategies for VTE (primary and secondary outcome measures) have evolved over time. For DVTs, older studies used iodine-125 fibrinogen uptake plus or minus confirmatory test with contrast venography while newer studies used compression ultrasonography. The diagnosis of PE has been more consistent over time (V/Q scan, CTPA), which could account for the lower level of heterogeneity in our PE pooled estimates.

### **Other limitations**

Using all type of DVT events as a component of our primary outcome measure might be a limitation of the analyses. DVT events included proximal and distal, symptomatic and asymptomatic DVTs. The clinical significance of distal and/or asymptomatic DVT is controversial and debatable. Distal asymptomatic DVTs seem to be less likely to extend to proximal DVTs or PEs [38]. This might have overestimated the outcome and yield and overestimate the effect measure of the interventions and potentially biased the results. Most of old studies and a good number of more recent studies did screen for asymptomatic DVTs without reporting the incidence of symptomatic DVTs separately. In addition, very few trials separated DVTs into proximal and distal DVTs. Consequently, it was difficult to analyze a separated pool estimate for symptomatic and/or proximal DVTs.

Another major limitation of this approach is that patients in whom an asymptomatic VTE was detected were most likely treated with anticoagulants, and therefore the actual incidence of symptomatic, clinically relevant outcomes could not be properly assessed and is perhaps underestimated.

We used the total number of patients assessed for our primary outcome measure (i.e. screening diagnostic modality examination required at day 7 or 10), rather than the total number of patients randomized to the different treatment arms. All the included studies reported their event rates based on this modified intention to treat (mITT) rather than an intention to treat (ITT) analysis. For example, if out of the total number of patients randomized in a specific trial, only 70% of them were assessed for VTE, then 30% of the patients are not included in that individual study analyses and therefore also not included in our pooled estimates. Unfortunately, none of the included trials reported the rates of symptomatic VTE only, and therefore ITT rates could not be pooled in our analyses. The mITT might have overestimated the effect estimate of the interventions and biased the result away from the null hypothesis.

Given the span of time of the clinical trials included in this review, many things have changed in patient's management especially post-operative care. Nowadays hospital stay is shorter, surgical technique are shorter and less invasive, and patient is expected to resume normal activities faster. This could alter our results and showed an artificially better outcome rates for most recently tested thromboprophylaxis modalities.

Furthermore, this is not a typical systematic review and meta-analysis were two interventions were compared. This is a pool proportion of a certain interventions regardless of the other interventions they have been compared to or the study arms that they came from. Because of this,

the benefit of randomization has been lost making it harder to interpret and compare the result of the pool estimates. Although, conducting a meta-analysis was possible, we will end up having to meta-analyze each intervention regimens with placebo, no intervention, graded compression stocking and IPC separately. In addition to doing meta-analysis between each pharmacological prophylaxis. To be able to do so, the number of studies to be included in each meta-analysis will be very small, which has its own limitations. We will end up with huge number of meta-analyses but with fewer studies in each analysis.

Finally, publication bias is a potential concern. A large majority of the funnel plots showed some degree of asymmetry suggestive of publications bias. However, there are other potential sources of asymmetry of the funnel plot. A well-known cause of funnel plot asymmetry is true and significant heterogeneity [39]. As we discussed earlier, most of our analysis showed a substantial heterogeneity that could also potentially explain the funnel plot asymmetry. Other possible source of asymmetry is low methodological quality leading to falsely inflated effect in smaller studies [39]. Our literature search was extensive, covered different sources of grey literature and was not restricted to English language. Thus, it is unlikely that language restriction was a significant source of publication bias.

### ***Quality of the evidence***

*GRADE* criteria and recommendations were used to assess the quality of evidence of the main outcomes (overall VTE, DVT, PE and major bleeding). There were enough reasons to downgrade the five domains in *GRADE* (risk of bias, inconsistency, indirectness, imprecision, publication bias) for all the main outcomes. In particular, two points were downgraded for

inconsistency. Therefore, overall the quality of evidence for the use of pharmacological thromboprophylaxis post major abdominal surgery was very low. With the exception of high dose LMWH in PE outcome where the quality of evidence was low due to low level of heterogeneity.

## ***Conclusion***

### ***Implications for practice***

Supported by very low quality of evidence, pharmacological thromboprophylaxis was not associated with a significant benefit in reducing the rate of overall VTE events. However, fondaparinux, high and low dose LMWH significantly appear to be associated with a lower rate of DVT events, while the rate of PE was lower in patients receiving both high or low dose LMWH. However, pharmacological thromboprophylaxis seems to also be associated with an increased risk of major bleeding events especially with high dose LMWH. When electing whether to use pharmacological thromboprophylaxis in patients post major abdominal surgery, physician needs to establish the patients' baseline risk of VTE as well as establishing their risk for major bleeding events. Physicians should also incorporate the cost and patient's preferences in making such decision.

### ***Implications for research***

Despite the large number of studies included in this review and the large number of patients included in the pooled analysis, there is still a lack of good quality evidence to recommend pharmacological thromboprophylaxis post major abdominal surgery. Researchers could use the result of this systematic review to engineer additional RCTs to settle the risk-to-benefit ratio of

pharmacological thromboprophylaxis post major abdominal surgery. The focus of these RCTs should be on clinically relevant outcomes (i.e. symptomatic proximal DVTs, PE and major bleeding), the assessment of short term (in hospital only) versus 10 days thromboprophylaxis, and include other potential agents (aspirin and DOACs).

## ***SECTION 3: Cross Sectional Survey of Thrombosis Experts and General Surgeons.***

### ***Rational for the Survey***

The main goal of the survey is to gain valuable information on current clinical practice regarding pharmacological thromboprophylaxis post major abdominal surgery. This information is to be used to help design of a RCT. In order to design a randomized clinical trial on the use of pharmacological thromboprophylaxis agent post major abdominal surgery fundamental trial components must be determined. These include the following:

- a. Review of current thromboprophylaxis practices for post major abdominal surgery among Canadian general surgeons and thrombosis experts.
- b. Extraction of acceptable comparator arms for future RCTs among Canadian general surgeons and thrombosis experts.
- c. Establishment of clinically relevant and important outcomes of therapy that would need to be shown to lead to a change in clinical practice (e.g. symptomatic vs. asymptomatic VTE, proximal DVT vs. distal DVT).
- d. Assessing interest in participating in future RCT among Canadian general surgeons and thrombosis experts.
- e. Determination of the interest and estimation of recruitment pattern for a future RCT.

## ***Cross Sectional Survey methods***

### ***Survey population***

The survey targeted two main specialty expert groups in post-surgical thromboprophylaxis. The first group, *Thrombosis Canada*, is an established group of expert Canadian clinicians dedicated to advancing education and research in the prevention and treatment of thrombo-vascular disease [40]. The second surveyed group is the *Canadian Association of General Surgeons (CAGS)*, the only national organization representing the interests of general surgeons in Canada. CAGS members include general surgeons, cancer surgeons, colorectal surgeon and other surgical specialties [41]. These two expert clinician groups have the necessary expertise and experience to provide meaningful opinions on a future RCT. They will also serve as collaborators and their centers as targets for future RCT.

### ***Survey Design and Implementation***

Survey Monkey [42] online software was used to create and distribute the survey. For the Thrombosis Canada group, each survey participant received an email with hyperlink to the survey while for the Canadian Association of General Surgeons group, the survey was sent to all members of the group in its monthly electronic newsletter. The survey started with an introduction to the survey, its goals/objectives and the reason the participant was chosen to participate. Participation in the survey was voluntary and all data were kept anonymous and confidential. Filling out the online survey was viewed as an implied consent. This was followed by series of categorical questions with 4-5 answers. The questions were formulated following the results of the aforementioned systematic review. All response answers were saved in the Survey Monkey online program, which was later was spread into Microsoft Excel program in the form

of pooled data for analysis. Aiming for a 30% response rate, a reminder email with a link to the survey was sent weekly for two weeks. The initial survey email and the follow up reminder email are depicted in *Appendix 9*.

## ***Survey Contents***

The first few questions were about the participant's current clinical practice. The following questions were related to two different clinical scenarios (See Appendix 10). We surveyed participants on their opinions on the efficacy and safety of pharmacological thromboprophylaxis and assessed if equipoise still exist around its post major abdominal surgery. Finally, we asked the participants if they would consider including their patients in a RCT, and if yes, to what intervention, dose and duration. (See *Appendix 10*).

The comprehensiveness and acceptability of the survey was reviewed by the thesis supervisors (MC, RA) each representing Thrombosis Canada and the Canadian Society of General Surgeons respectively.

## ***Survey Analysis***

Descriptive statistics were used to analyze and summarize the result of the survey. Comparisons were made between thrombosis experts and general surgeons, and between different relevant demographic subgroups.

## ***Survey results***

The initial response rate of the CAGS was 2.2% (42/1915) and the total response rate following the reminder was 2.5% (48/1915) (44% open rate and 6.4% click rate (for any link in the e-news)). Of these, 10 surgeons did not perform major abdominal surgery, leaving 38 potentially

eligible participants, of which only 30 completed the survey. The total response rate for the Thrombosis Canada group was 34.9% (30/86), of which only 26 completed the survey (30.2%).

A majority of the participating surgeons were general surgeons (61.8%), were males (55.9%) and young adults (age 25-35, 44.12%). Twenty-five percent of surgeons had been in independent practice for only one year. The majority of the responders were from Ontario (26.7%) followed by Quebec (13.3%) and Manitoba (13.3%). Half of the surgeons practiced in academic centers and the other half in non-academic centers. The majority of the thrombosis participants from Thrombosis Canada were internists (38.5%) followed by hematologists (34.6%). Similarly, most participants were males (61.5%) and young adults (age 36-45, 30.8%) but a majority were in clinical practice for more than 10 years (57.7%). Again, most responders were from Ontario (57.7%) and approximately 80% of the thrombosis experts practiced in an academic center.

All the surgeons recommend the use of thromboprophylaxis post major abdominal surgery. Interestingly, over 75% of them recommended using thromboprophylaxis during hospitalization only. The rest recommend extending thromboprophylaxis for 7-10 days or for a total of 28 days' post major abdominal surgery (7.9% and 15.8% respectively). Similarly, all the thrombosis experts recommend the use of thromboprophylaxis post major abdominal surgery. Seventy percent of them recommend the using thromboprophylaxis during hospitalization only. The rest recommend extending thromboprophylaxis for 7-10 days or for a total of 28 days' post major abdominal surgery (23.3% and 6.7% respectively).

The majority of the surgeons recommended using LMWH (60.6%) over UFH (37.9%) for post major abdominal surgery. Dalteparin 5000 units daily or UFH 5000 units every 12 hours or enoxaparin 40 mg daily were the most frequently recommended thromboprophylaxis regimens

by surgeons (30.3%, 25.8% and 24.2% respectively). Similarly, 67.7% of the thrombosis experts recommended LMWH over UFH (7.35% only). Dalteparin 5000 units daily or enoxaparin 40 mg daily were the most frequently recommended regimens by thrombosis experts (32.4% and 29.4% respectively).

Approximately a third of surgeons estimated the incidence of overall VTE (symptomatic and asymptomatic) at 7 to 10 days post-operatively in patients who do not receive thromboprophylaxis post major abdominal surgery to be between 4-6% as compared with 44.4% of the thrombosis experts who estimated the same incidence. A total of 72 % of the surgeons and 55.5 % of the thrombosis experts estimated the incidence of PE to be between 0.5-1.0 percent for the same patient population. The risk of major bleeding episode was estimated to be between 0.5 to 1% in patients receiving 7 to 10 days of pharmacological thromboprophylaxis in the post-operative period by a majority of both surgeons and thrombosis experts (36% and 70% respectively). Finally, a majority of surgeons (57.1%) and thrombosis experts (55.6%) believed that benefits of using pharmacological thromboprophylaxis for 7 to 10 days in high-risk patients outweigh the risk of bleeding in adult patients post major abdominal surgery in most cases. However, approximately 80% of surgeons and 77% of thrombosis experts believed that there is still some clinical equipoise around the use of thromboprophylaxis post discharge (up to 7 to 10 days) in high risk adult patients post major abdominal surgery. Thus, it is not surprising that they would consider allowing their patients to participate in a RCT assessing the use of thromboprophylaxis in adult patients post major abdominal surgery comparing different duration (e.g. during hospitalization only vs. 10 days) of thromboprophylaxis (82.4% and 85.2% respectively).

## ***Survey Discussion***

This survey of Canadian general surgeons and thrombosis experts showed that there is an agreement in the use of pharmacological thromboprophylaxis post major abdominal surgery. It also showed that majority of the both expert groups would use thromboprophylaxis during hospitalization only. It also confirms that there is clinical equipoise around the use of thromboprophylaxis post discharge (up to 7 to 10 days) in high-risk adult patients post major abdominal surgery.

A majority of surgeons and the clinicians selected LMWH as their preferred pharmacological thromboprophylactic agent. This is not surprising given that LMWH have a better safety profile compared to unfractionated heparin. UFH requires subcutaneous self-injections twice or three times daily making them less convenient especially for extended post discharge thromboprophylaxis. In addition, UFH is associated with 2.6% risk of HIT, a rare but potentially serious adverse reaction causing low platelets with paradoxical thrombosis and tissue necrosis [18]. LMWH is less likely to cause HIT (0.2% compared to 2.6% with UFH). Although it is also given subcutaneously, it is usually given less frequently, usually once daily making it more favorable over UFH for extended post discharge thromboprophylaxis. None of the surgeons recommended fondaparinux, while 10% of the thrombosis experts selected it a one of the options. Neither the surgeons nor the thrombosis experts recommended Aspirin or DOAC as a potential option for thromboprophylaxis post major abdominal surgery.

The majority of participants (surgeons and thrombosis experts) estimated the incidence of overall VTE (4-6%) and PE (0.5-1.0%) in patients not receiving any thromboprophylaxis closely to the pooled estimates generated in our systematic review and pooled analyses (overall VTE; 8.64%,

95% CI 4.09-14.66; and PE; 1.39%, 95% CI 0.6-2.49%). However, both groups underestimated the incidence of major bleed (0.5-1.0 %) post major abdominal surgery in those who receive pharmacological thromboprophylaxis. Our pooled analysis showed that the incidence of major bleeding event was 3.96% (95% CI: 2.7-5.45) in those receiving standard doses of LMWH and 2.52% (95% CI 1.19-4.34) in those receiving UFH at 5000 units every 12 hours.

It was not surprising that there is an agreement regarding the presence of clinical equipoise around the use of thromboprophylaxis post discharge (up to 7 to 10 days) in high-risk adult patients post major abdominal surgery. Most of clinical trials evaluated different pharmacological thromboprophylaxis either during hospitalization or for a fixed duration of 7 to 10 days. There is a lack in clinical trials that directly compared two different durations of thromboprophylaxis. Thus, the majoring of the experts would consider participating in a clinical trial comparing two different durations of thromboprophylaxis.

### ***Survey Limitation***

First, our survey had a relatively low response rate from both groups. The survey sent to the CAGS was included within a monthly e-letter. There were other materials and topics included in the e-letter which may have resulted in overlooking the survey. Unfortunately, the reminder included in the following month e-letter did not significantly improve the response rate.

Similarly, the survey sent to the Thrombosis Canada members was included within a monthly email distributed to all members.

Second, the survey was limited to Canadian experts, mostly from academic centers, and therefore may not reflect the opinion of other international experts or clinicians and surgeons in the community hospitals. Nevertheless, experts in the field and researchers in the subject would have

provided the most significant and applicable opinion in the topic. Finally, a large proportion of the surgeons who responded to the survey were in independent clinical practice for less than 10 years (61%). This might have resulted in selection bias that is probably due to low response rate resulting in low sample size that failed to represent more senior surgeons.

## ***Survey Conclusion***

There is an agreement between general surgeons performing major abdominal surgery and thrombosis experts in using LMWH for thromboprophylaxis post major abdominal surgery. There is still equipoise around the use of pharmacological thromboprophylaxis for 7-10 days post-operatively including post discharge prescription. There seems to be underestimation of major bleeding events post major surgery in patients receiving pharmacological thromboprophylaxis. There is a need for a RCT comparing the use of pharmacological thromboprophylaxis in hospital only compared to duration of 7-10 days (including post discharge prescription) post major abdominal surgery. None of the surgeons or the thrombosis experts recommended aspirin or DOACs as a thromboprophylaxis post major abdominal surgery.

## ***Thesis Conclusion***

In conclusion, while pharmacological thromboprophylaxis post major abdominal surgery is recommended for most high-risk patients, our systematic review demonstrates that these recommendations are based on low quality evidence. The incidence of overall VTE was not significantly lower in patients using pharmacological prophylaxis than in patients on observation or placebo. DVT was reduced by LMWH and fondaparinux while PE was only reduced by LMWH. However, there was an increase rate of major bleeding events associated with this benefit especially with high dose LMWH. Despite this, there is a consensus between thrombosis experts and major abdominal surgeons in the use of thromboprophylaxis post major abdominal surgery in high-risk patients. However, there was equipoise regarding the optimal duration of thromboprophylaxis and the need for post discharge prescription.

Future research and RCTs should focus on clinically relevant outcomes such as symptomatic proximal DVTs, PE and major bleeding. RCTs should also study short term (in hospital only) versus 10 days thromboprophylaxis.

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## Appendixes

### Appendix 1: The Cochrane Collaboration's tool for assessing risk of bias

#### The Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgment
<b>Sequence generation</b>	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
<b>Allocation concealment</b>	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
<b>Blinding of participants, personnel and outcome assessors</b> <i>Assessments should be made for each main outcome (or class of outcomes)</i>	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
<b>Incomplete outcome data</b> <i>Assessments should be made for each main outcome (or class of outcomes)</i>	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
<b>Selective outcome reporting</b>	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?

<b>Other sources of bias</b>	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?
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***Possible approach for summary assessments outcome (across domains) within and across studies***

<b>Risk of bias</b>	<b>Interpretation</b>	<b>Within a study</b>	<b>Across studies</b>
Low risk of bias	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias.
High risk of bias	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results.

***Criteria for judging risk of bias in the 'Risk of bias' assessment tool***

<b>SEQUENCE GENERATION</b>	
<b>Was the allocation sequence adequately generated? [Short form: Adequate sequence generation?]</b>	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	The investigators describe a random component in the sequence generation process such as: Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgment of 'NO' (i.e. high risk of bias).	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: Sequence generated by odd or even date of birth; Sequence generated by some rule based on date (or day) of admission; Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They

	<p>usually involve judgment or some method of non-random categorization of participants, for example:</p> <ul style="list-style-type: none"> <li>Allocation by judgment of the clinician;</li> <li>Allocation by preference of the participant;</li> <li>Allocation based on the results of a laboratory test or a series of tests;</li> <li>Allocation by availability of the intervention.</li> </ul>
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgment of 'Yes' or 'No'.
<p><b>ALLOCATION CONCEALMENT</b>  <b>Was allocation adequately concealed? [Short form: <i>Allocation concealment?</i>]</b></p>	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	<p>Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:</p> <ul style="list-style-type: none"> <li>Central allocation (including telephone, web-based, and pharmacy-controlled, randomization);</li> <li>Sequentially numbered drug containers of identical appearance;</li> <li>Sequentially numbered, opaque, sealed envelopes.</li> </ul>
Criteria for the judgment of 'NO' (i.e. high risk of bias).	<p>Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:</p> <ul style="list-style-type: none"> <li>Using an open random allocation schedule (e.g. a list of random numbers);</li> <li>Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);</li> <li>Alternation or rotation;</li> <li>Date of birth;</li> <li>Case record number;</li> <li>Any other explicitly unconcealed procedure.</li> </ul>
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgment of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
<p><b>BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS</b>  <b>Was knowledge of the allocated interventions adequately prevented during the study? [Short form: <i>Blinding?</i>]</b></p>	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	<p>Any one of the following:</p> <ul style="list-style-type: none"> <li>No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding;</li> </ul>

	<p>Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;</p> <p>Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non- blinding of others unlikely to introduce bias.</p>
Criteria for the judgment of ‘NO’ (i.e. high risk of bias).	<p>Any one of the following:</p> <p>No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding;</p> <p>Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;</p> <p>Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.</p>
Criteria for the judgment of ‘UNCLEAR’ (uncertain risk of bias).	<p>Any one of the following:</p> <p>Insufficient information to permit judgment of ‘Yes’ or ‘No’;</p> <p>The study did not address this outcome.</p>
<p><b>INCOMPLETE OUTCOME DATA</b></p> <p><b>Were incomplete outcome data adequately addressed? [Short form: <i>Incomplete outcome data addressed?</i>]</b></p>	
Criteria for a judgment of ‘YES’ (i.e. low risk of bias).	<p>Any one of the following:</p> <p>No missing outcome data;</p> <p>Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);</p> <p>Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;</p> <p>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;</p> <p>For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;</p> <p>Missing data have been imputed using appropriate methods.</p>
Criteria for the judgment of ‘NO’ (i.e. high risk of bias).	<p>Any one of the following:</p> <p>Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;</p> <p>For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce</p>

	<p>clinically relevant bias in intervention effect estimate;</p> <p>For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;</p> <p>‘As-treated’ analysis done with substantial departure of the intervention received from that assigned at randomization;</p> <p>Potentially inappropriate application of simple imputation.</p>
Criteria for the judgment of ‘UNCLEAR’ (uncertain risk of bias).	<p>Any one of the following:</p> <p>Insufficient reporting of attrition/exclusions to permit judgment of ‘Yes’ or ‘No’ (e.g. number randomized not stated, no reasons for missing data provided);</p> <p>The study did not address this outcome.</p>
<p><b>SELECTIVE OUTCOME REPORTING</b></p> <p><b>Are reports of the study free of suggestion of selective outcome reporting? [Short form: <i>Free of selective reporting?</i>]</b></p>	
Criteria for a judgment of ‘YES’ (i.e. low risk of bias).	<p>Any of the following:</p> <p>The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;</p> <p>The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).</p>
Criteria for the judgment of ‘NO’ (i.e. high risk of bias).	<p>Any one of the following:</p> <p>Not all of the study’s pre-specified primary outcomes have been reported;</p> <p>One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;</p> <p>One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);</p> <p>One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;</p> <p>The study report fails to include results for a key outcome that would be expected to have been reported for such a study.</p>
Criteria for the judgment of ‘UNCLEAR’ (uncertain risk of bias).	<p>Insufficient information to permit judgment of ‘Yes’ or ‘No’. It is likely that the majority of studies will fall into this category.</p>
<p><b>OTHER POTENTIAL THREATS TO VALIDITY</b></p> <p><b>Was the study apparently free of other problems that could put it at a risk of bias? [Short form: <i>Free of other bias?</i>]</b></p>	

Criteria for a judgment of 'YES' (i.e. low risk of bias).	The study appears to be free of other sources of bias.
Criteria for the judgment of 'NO' (i.e. high risk of bias).	<p>There is at least one important risk of bias. For example, the study:</p> <ul style="list-style-type: none"> <li>Had a potential source of bias related to the specific study design used; or</li> <li>Stopped early due to some data-dependent process (including a formal-stopping rule); or</li> <li>Had extreme baseline imbalance; or</li> <li>Has been claimed to have been fraudulent; or</li> <li>Had some other problem.</li> </ul>
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	<p>There may be a risk of bias, but there is either:</p> <ul style="list-style-type: none"> <li>Insufficient information to assess whether an important risk of bias exists; or</li> <li>Insufficient rationale or evidence that an identified problem will introduce bias.</li> </ul>

## ***Appendix 2: Newcastle - Ottawa Quality Assessment Scale for Cohort Studies***

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

### **Selection**

#### 1) Representativeness of the exposed cohort

- a) Truly representative of the average \_\_\_\_\_ (describe) in the community ✱
- b) Somewhat representative of the average \_\_\_\_\_ in the community ✱
- c) Selected group of users eg nurses, volunteers
- d) No description of the derivation of the cohort

#### 2) Selection of the non-exposed cohort

- a) Drawn from the same community as the exposed cohort ✱
- b) Drawn from a different source
- c) No description of the derivation of the non-exposed cohort

#### 3) Ascertainment of exposure

- a) Secure record (eg surgical records) ✱
- b) Structured interview ✱

c) Written self-report

d) No description

4) Demonstration that outcome of interest was not present at start of study

a) Yes ✱

b) No

### **Comparability**

1) Comparability of cohorts on the basis of the design or analysis

a) Study controls for \_\_\_\_\_ (select the most important factor) ✱

b) Study controls for any additional factor ✱ (This criteria could be modified to indicate specific control for a second important factor.)

### **Outcome**

1) Assessment of outcome

a) Independent blind assessment ✱

b) Record linkage ✱

c) Self-report

d) No description

2) Was follow-up long enough for outcomes to occur

a) Yes (select an adequate follow up period for outcome of interest) ✱

b) No

3) Adequacy of follow up of cohorts

a) Complete follow up - all subjects accounted for ✱

b) Subjects lost to follow up unlikely to introduce bias - small number lost - > \_\_\_\_ % (select an adequate %) follow up, or description provided of those lost) ✱

c) Follow up rate < \_\_\_\_ % (select an adequate %) and no description of those lost

d) No statement

## ***Appendix 3: Grey literature search***

ISTH:

- Manual search of ISTH annual congress meeting abstracts for the past years from 2010 to 2015 revealed no new studies.

ASH:

- Manual search of ASH annual congress meeting abstract for the last 5 years from 2010 to 2014 revealed no new studies.

ClinicalTrials.gov:

- Incidence of Venous Thromboembolism Following Surgery in Korean Patients with Colorectal Cancer; a Prospective Study.
  - o Prospective cohort study by Keun-Wook Lee.
  - o Email was sent to get some info.
  - o Study is for submission. Could not unveil result.
- Incidence of Venous Thromboembolism Following Surgery in Patients with Gastric Cancer; a Prospective Study.
  - o Prospective cohort study by Keun-Wook Lee.
  - o Email was sent to get some info.
  - o Study is for submission. Could not unveil result.

- Total of 37 trials met the search for thrombosis and abdominal surgery. Only the above two trials were missing. Others either included previously, terminated or still recruiting or did not meet inclusion criteria.

#### PROSPERO:

- No other systematic review register in the topic.

#### Health technology:

- CADTH:
  - 3 Reviews (June 2011, August 2011, 2014) on the use of aspirin post total knee and total hip arthroplasty.
  - 1 review (2008) comparing fondaparinux to enoxaparin post major orthopedic surgery.
  - 1 review (2011) looked into heparin in hospitalized patient. This was mainly for medically ill patients. No summary of the data presented. One systematic review and one RCT were included in the appendix. Both were available in priori.
  - 1 review (2013) compared the cost-effectiveness and safety of UFH to LMWH. The review only included economic studies, HTA and systematic review-meta-analysis. I added on Cochrane review that looked into perioperative thromboprophylaxis in cancer patients.
  - 1 review (2009) only looked into cost-effectiveness of UFH compared to LMWH.
  - 1 review (2011) looked into post discharge thromboprophylaxis post major general surgery using any kind of thromboprophylaxis. One systematic review

added from this review. One other systematic review and one RCT were included in priori.

- 1 review (2011) looked into thromboprophylaxis for patient in hospital and emergency room setting. Three systematic reviews were added to be reviewed.
- Total of 5 systematic reviews added from CADTH.

Systematic reviews:

- 12 systematic reviews were reviewed manually for included articles.
  - 6 systematic reviews from original literature search.
  - 5 from CADTH.
  - 1 recommended by colleague.

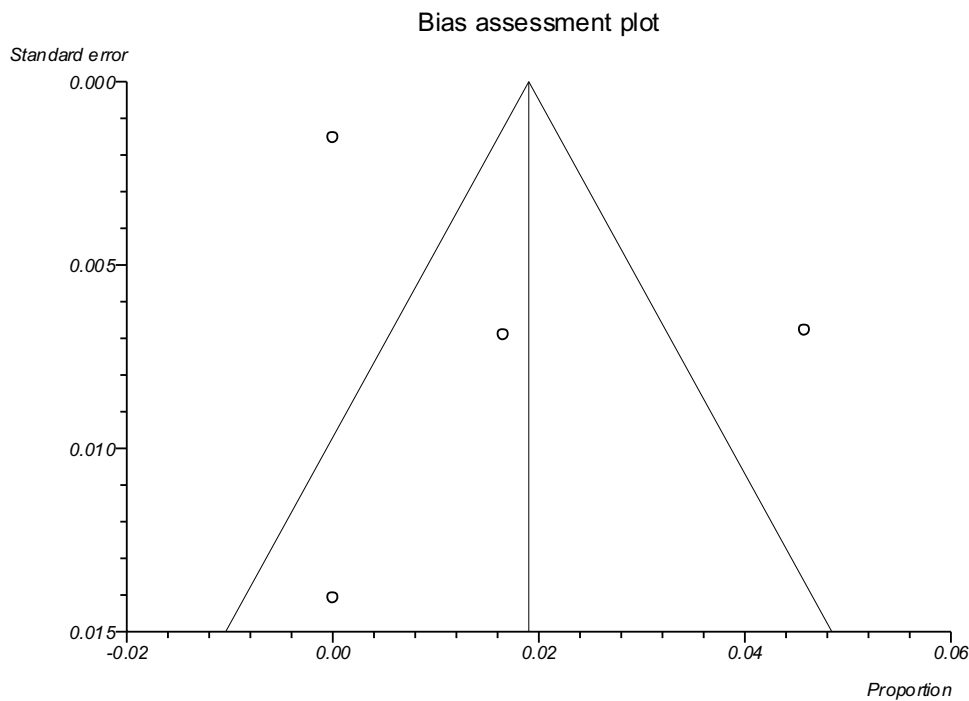
## ***Appendix 4: Reporting and Publication Bias Assessment***

### ***Venous Thromboembolic Events***

#### ***Fondaparinux (2.5mg s/c daily)***

Figure 82 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

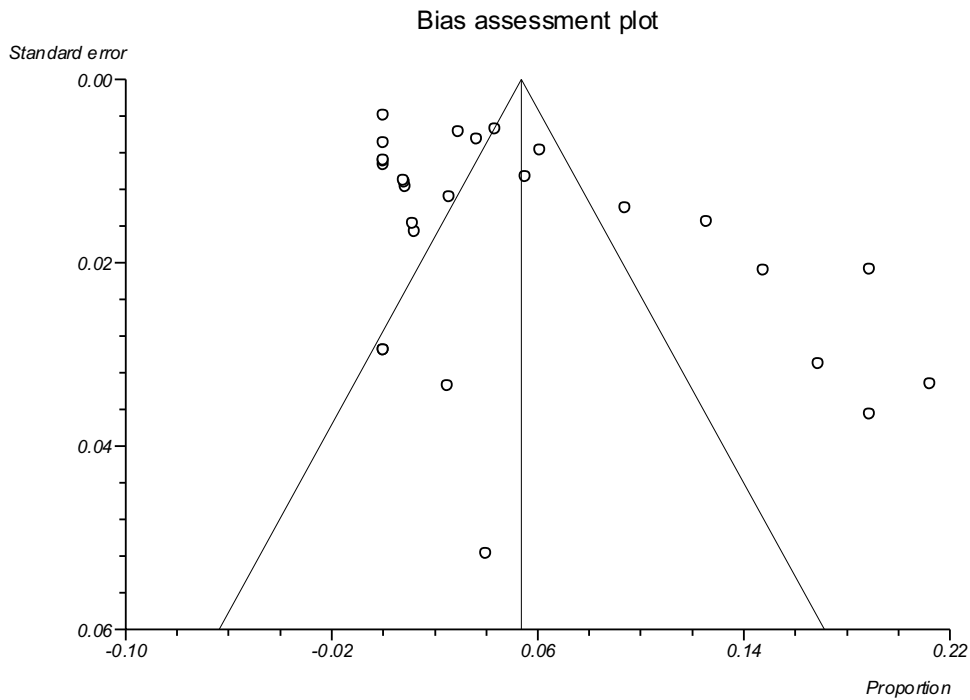
***Figure 82 Funnel plot for assessment of publication bias for the VTE pooled proportion for fondaparinux used thromboprophylaxis post major abdominal surgery***



**High thromboprophylactic dose of low molecular weight heparin**  
**( $\geq 4000$  IU)**

Figure 83 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

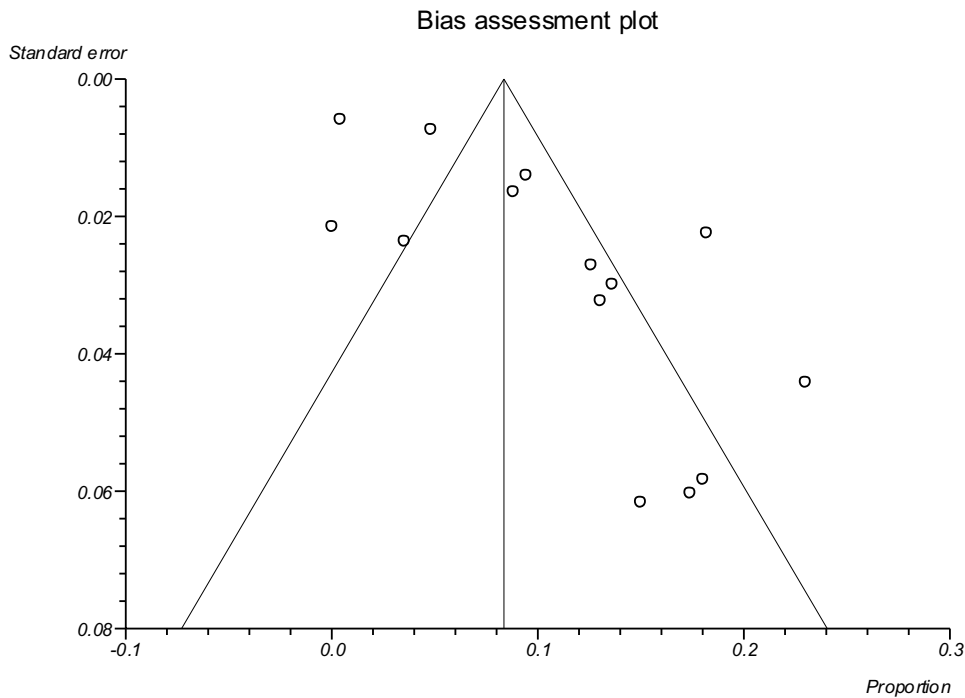
***Figure 83 Funnel plot for assessment of publication bias for the VTE pooled proportion for high dose LMWH used thromboprophylaxis post major abdominal surgery***



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

Figure 84 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

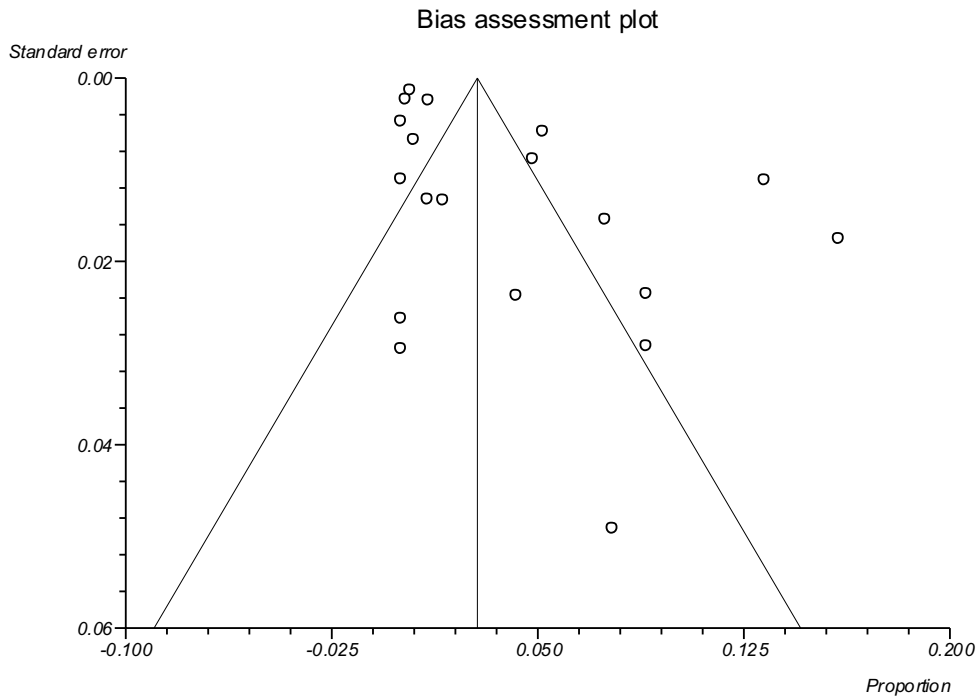
***Figure 84 Funnel plot for assessment of publication bias for the VTE pooled proportion for high dose UFH used thromboprophylaxis post major abdominal surgery***



**Low prophylactic dose of low molecular weight heparin (<4000 IU)**

Figure 85 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

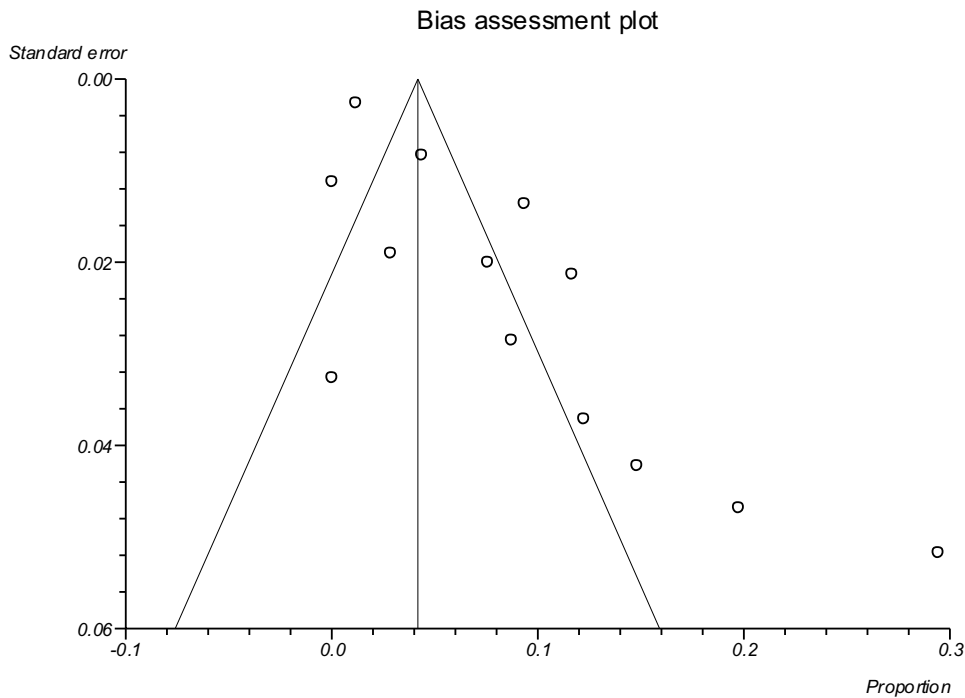
***Figure 85 Funnel plot for assessment of publication bias for the VTE pooled proportion for low dose LMWH used thromboprophylaxis post major abdominal surgery***



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

Figure 86 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

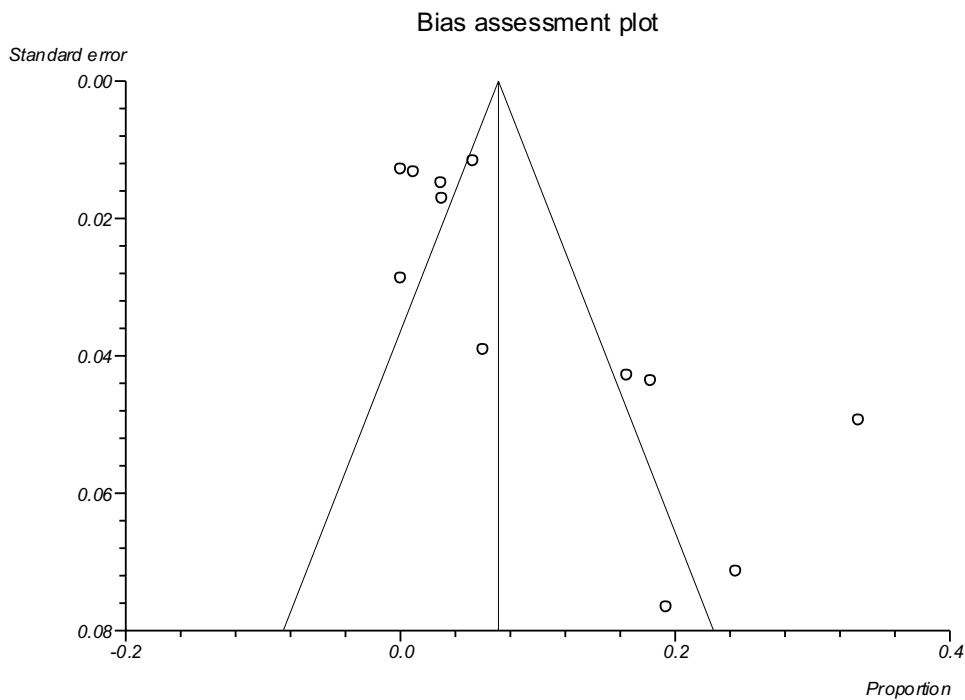
***Figure 86 Funnel plot for assessment of publication bias for the VTE pooled proportion for low dose UFH used thromboprophylaxis post major abdominal surgery***



**Placebo, non-pharmacological thromboprophylaxis or no treatment**

Figure 87 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

***Figure 87 Funnel plot for assessment of publication bias for the VTE pooled proportion for placebo, non-pharmacological thromboprophylaxis or no treatment post major abdominal surgery.***



## **Deep vein thrombosis Events**

### **Fondaparinux (2.5mg s/c daily)**

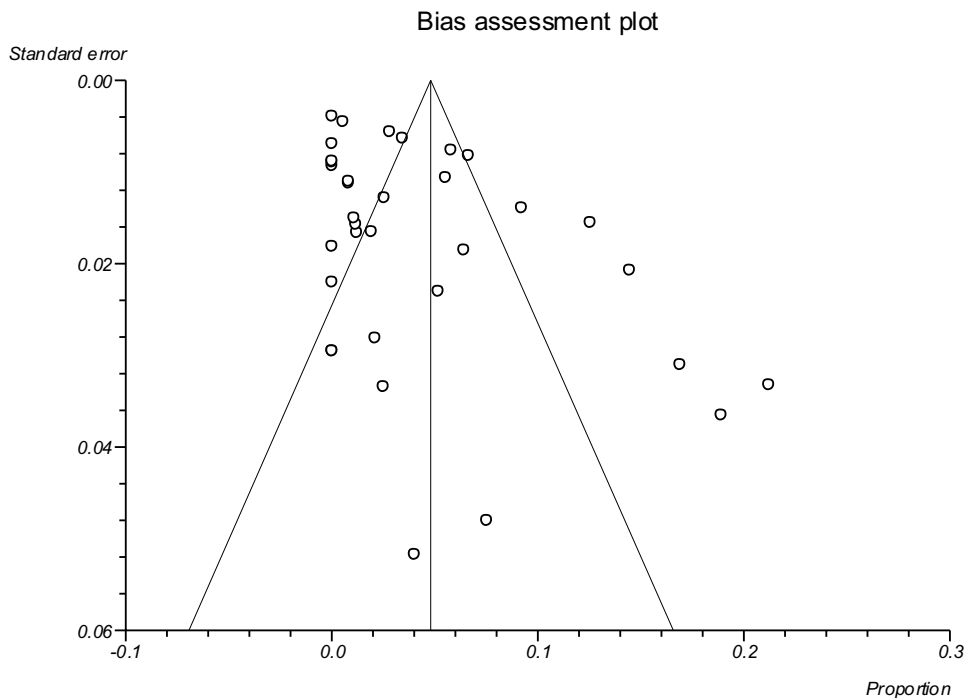
Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

### **High thromboprophylactic dose of low molecular weight heparin**

#### **(≥4000 IU)**

Figure 88 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

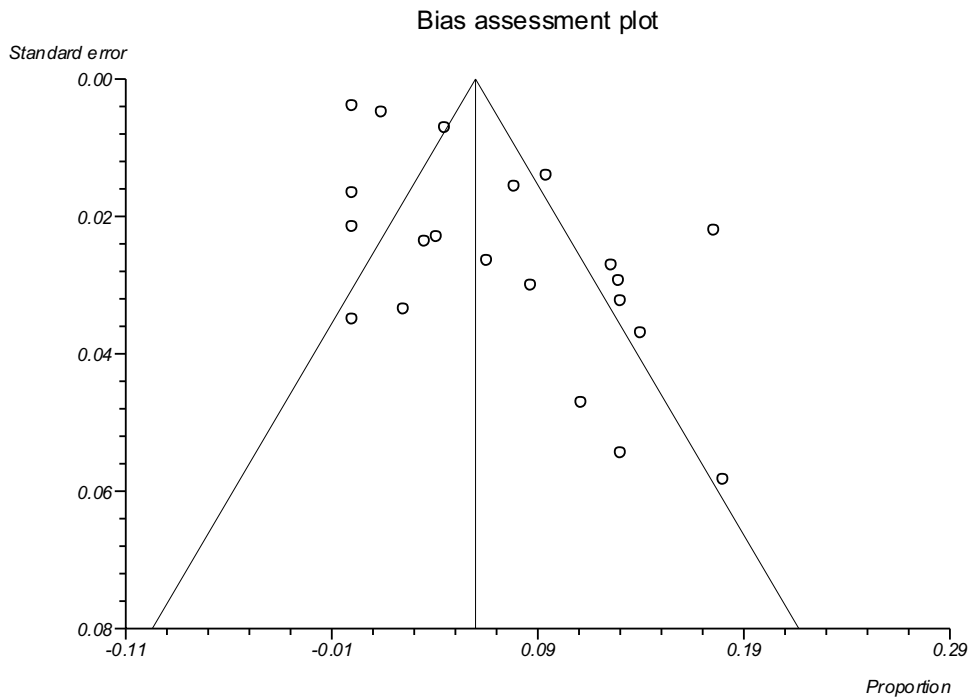
**Figure 88 Funnel plot for assessment of publication bias for the DVT pooled proportion for high dose LMWH post major abdominal surgery.**



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

Figure 89 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

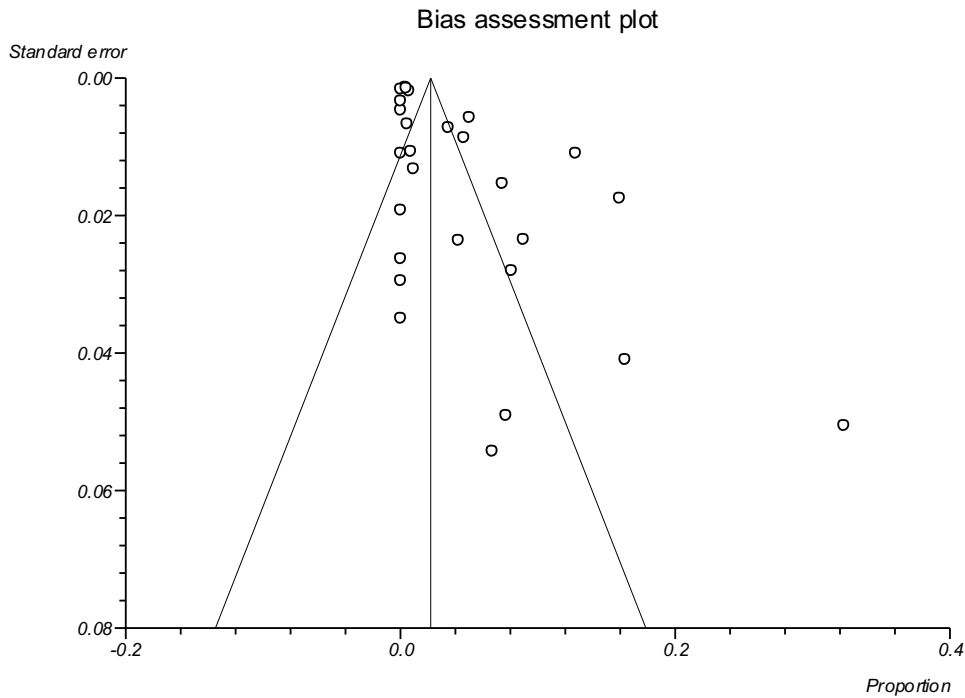
**Figure 89 Funnel plot for assessment of publication bias for the DVT pooled proportion for high dose UFH post major abdominal surgery.**



**Low prophylactic dose of low molecular weight heparin (<4000 IU)**

Figure 90 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

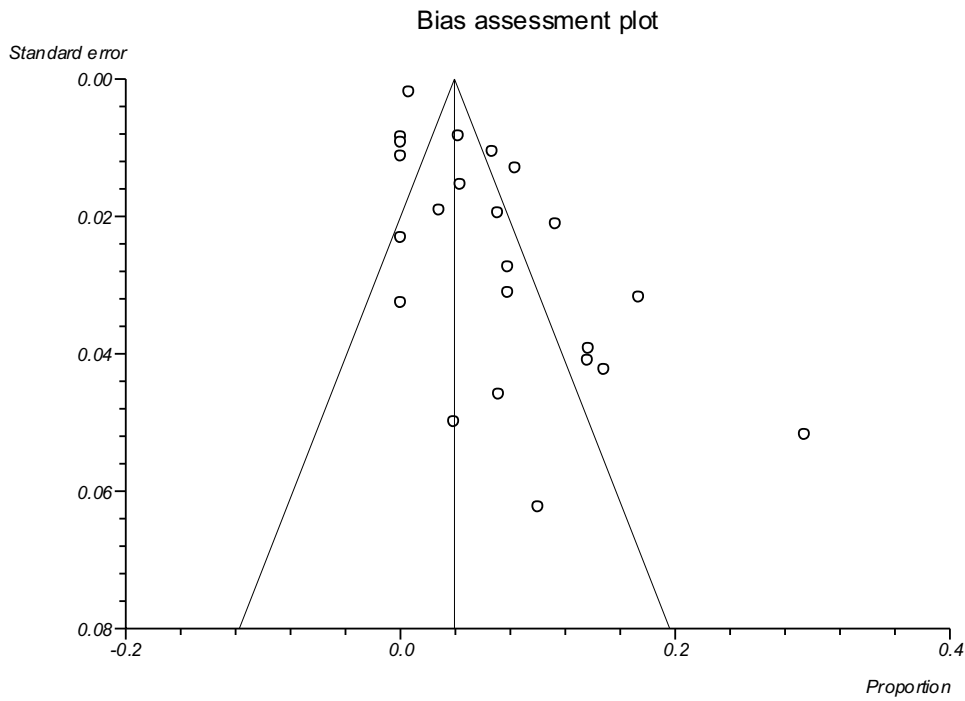
***Figure 90 Funnel plot for assessment of publication bias for the DVT pooled proportion for low dose LMWH post major abdominal surgery.***



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

Figure 91 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

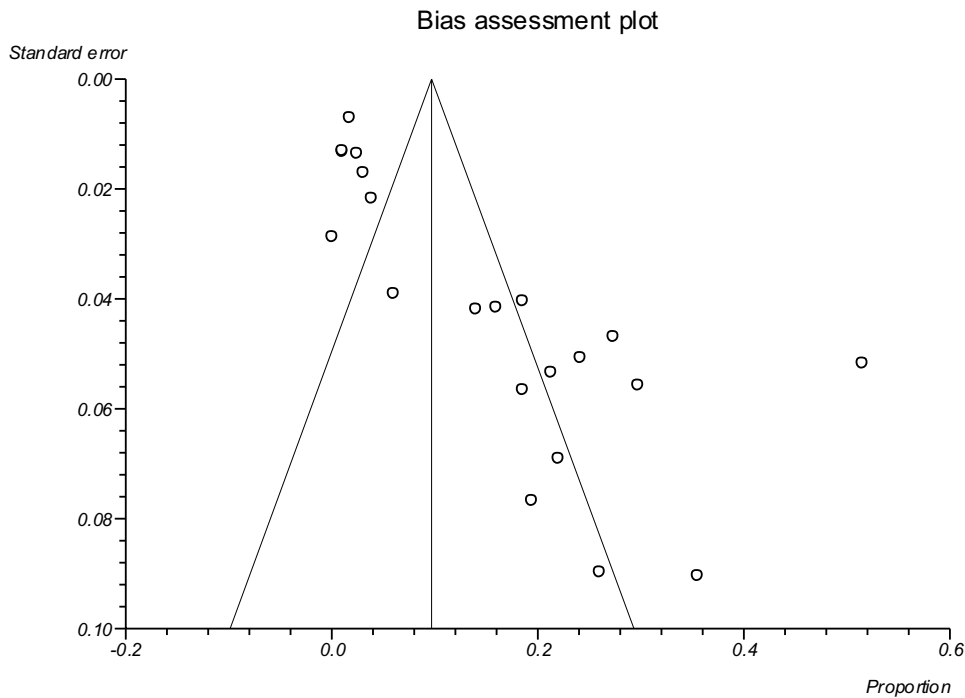
***Figure 91 Funnel plot for assessment of publication bias for the DVT pooled proportion for low dose UFH post major abdominal surgery.***



**Placebo, non-pharmacological thromboprophylaxis or no treatment**

Figure 92 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

***Figure 92 Funnel plot for assessment of publication bias for the DVT pooled proportion for placebo, non-pharmacological thromboprophylaxis or no treatment post major abdominal surgery.***



## **Pulmonary Embolism Events**

### **Fondaparinux (2.5mg s/c daily)**

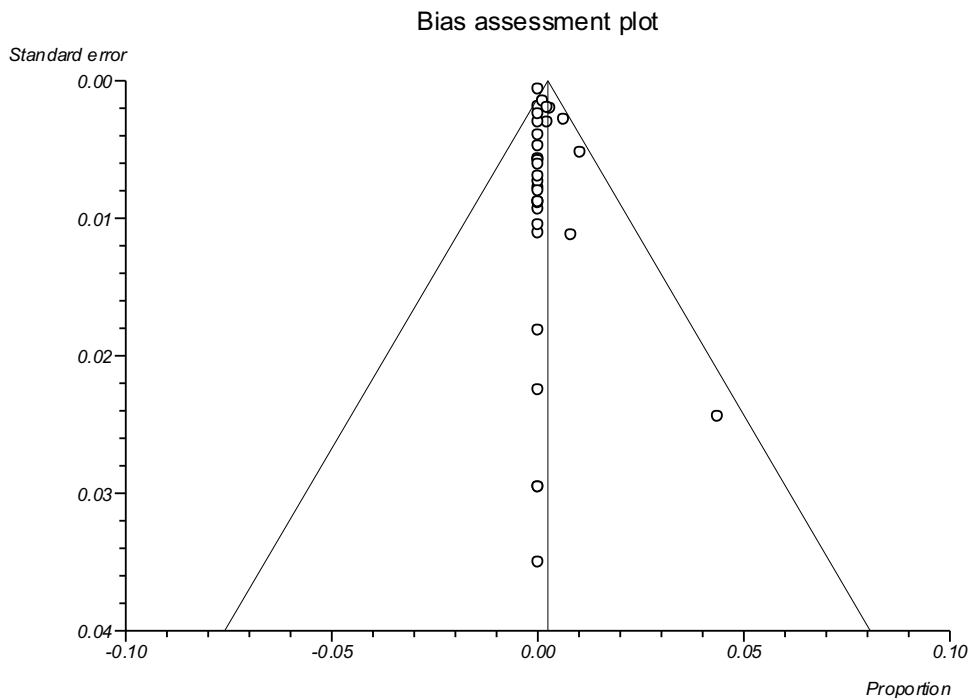
Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

### **High thromboprophylactic dose of low molecular weight heparin**

#### **(≥4000 IU)**

Figure 93 shows the funnel plot for assessment of reporting bias. Apart from one outlier, the funnel plot shows symmetry with no evidence for publication bias.

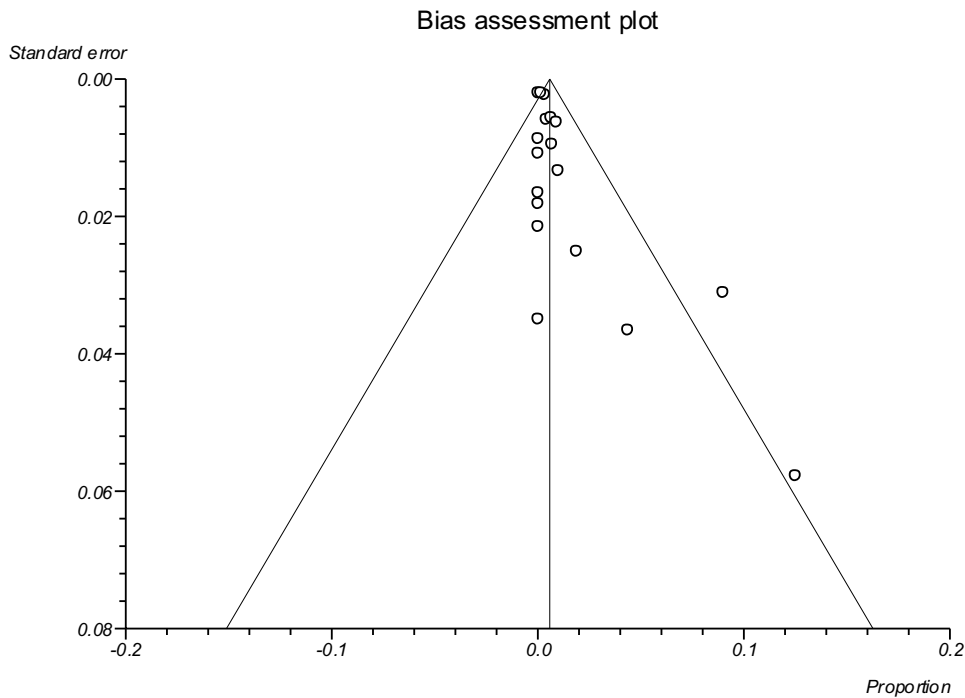
***Figure 93 Funnel plot for assessment of publication bias for the PE pooled proportion for high dose LMWH post major abdominal surgery.***



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

Figure 94 shows the funnel plot for assessment of reporting bias. The graph shows some asymmetry suggestive of reporting bias. However, the substantial heterogeneity may also explain the asymmetry in the funnel plot.

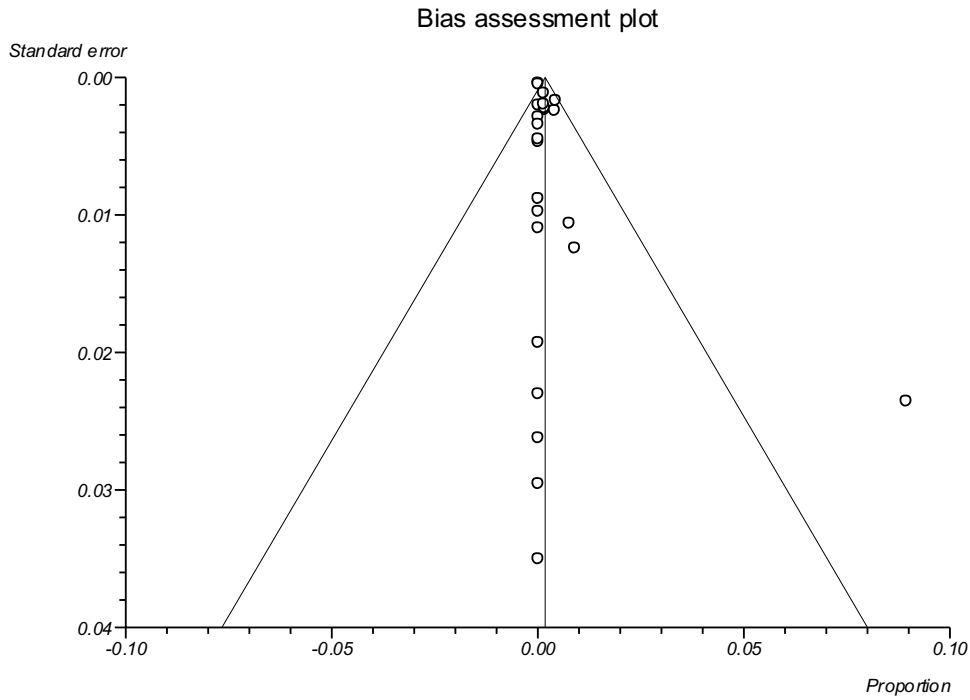
***Figure 94 Funnel plot for assessment of publication bias for the PE pooled proportion for high dose UFH post major abdominal surgery.***



**Low prophylactic dose of low molecular weight heparin (<4000 IU)**

Figure 95 shows the funnel plot for assessment of reporting bias. Apart from one outlier, the funnel plot shows symmetry with no evidence for publication bias.

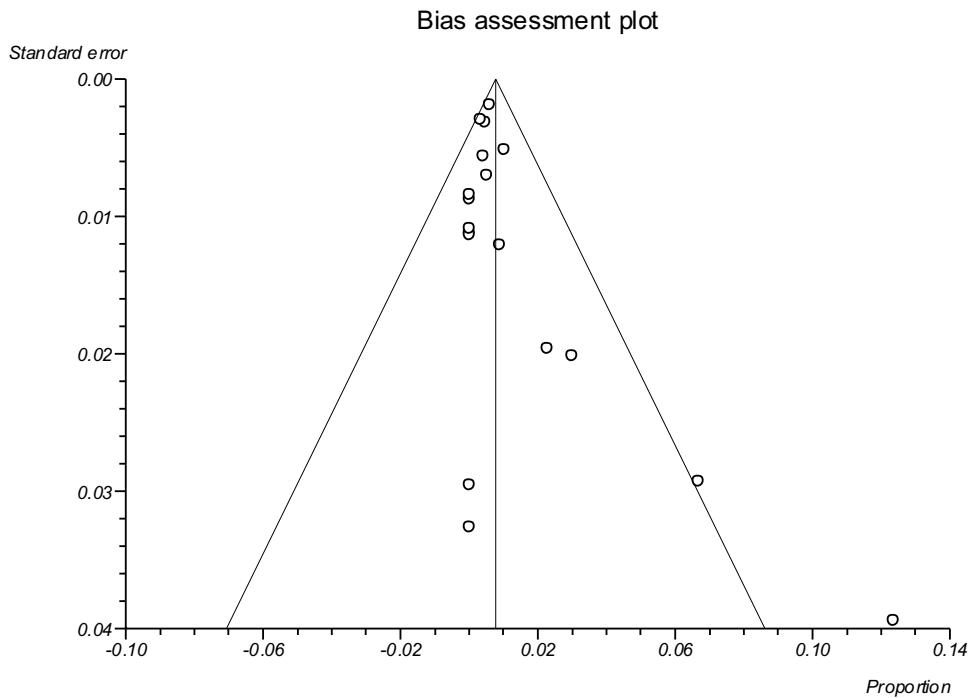
***Figure 95 Funnel plot for assessment of publication bias for the PE pooled proportion for low dose LMWH post major abdominal surgery.***



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

Figure 96 shows the funnel plot for assessment of reporting bias. There is some degree of asymmetry suggestive publication bias. Again, the substantial heterogeneity could explain to some extent the asymmetry in the funnel plot.

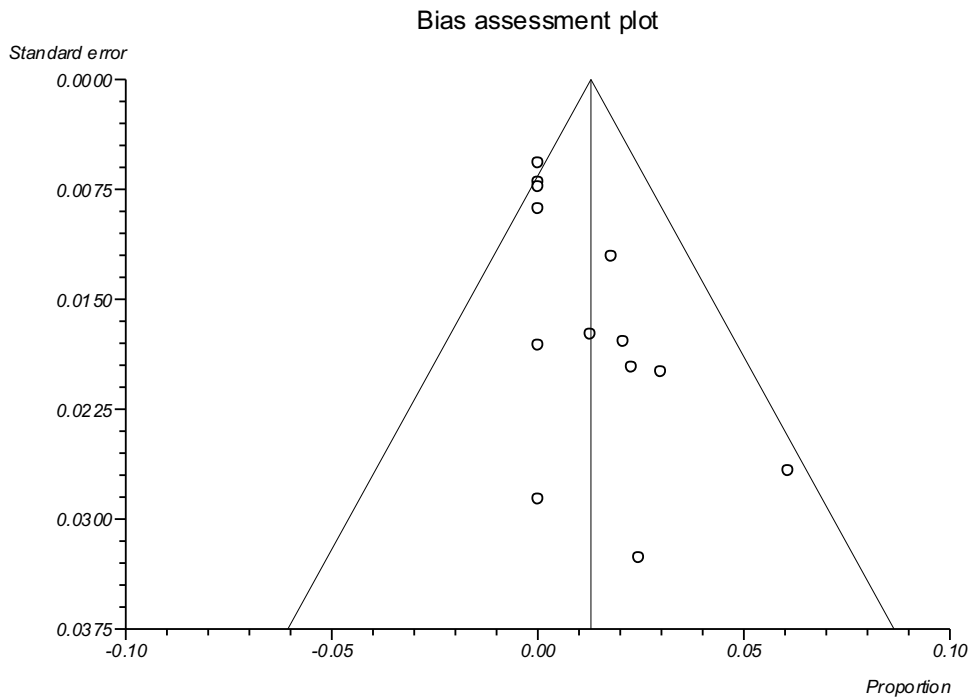
**Figure 96 Funnel plot for assessment of publication bias for the PE pooled proportion for low dose UFH post major abdominal surgery.**



**Placebo, non-pharmacological thromboprophylaxis or no treatment**

Figure 97 shows the funnel plot for assessment of reporting bias. There is some degree of asymmetry suggestive of publication bias.

***Figure 97 Funnel plot for assessment of publication bias for the PE pooled proportion for placebo, non-pharmacological thromboprophylaxis or no treatment post major abdominal surgery.***

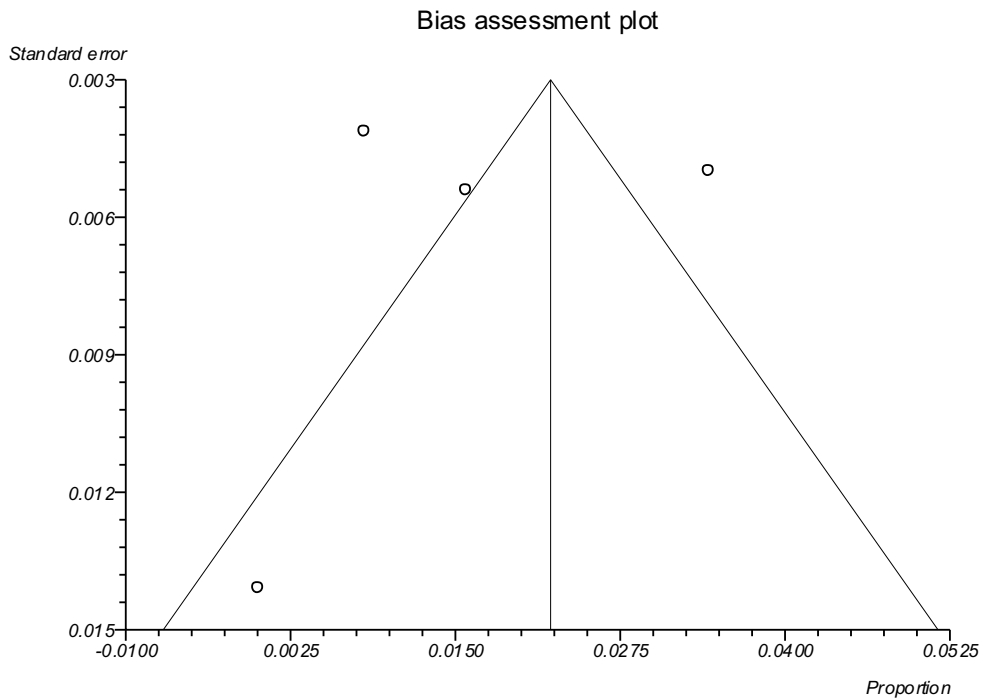


## Major Bleeding Events

### Fondaparinux (2.5mg s/c daily)

Figure 98 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the substantial heterogeneity may also explain the asymmetry in the funnel plot.

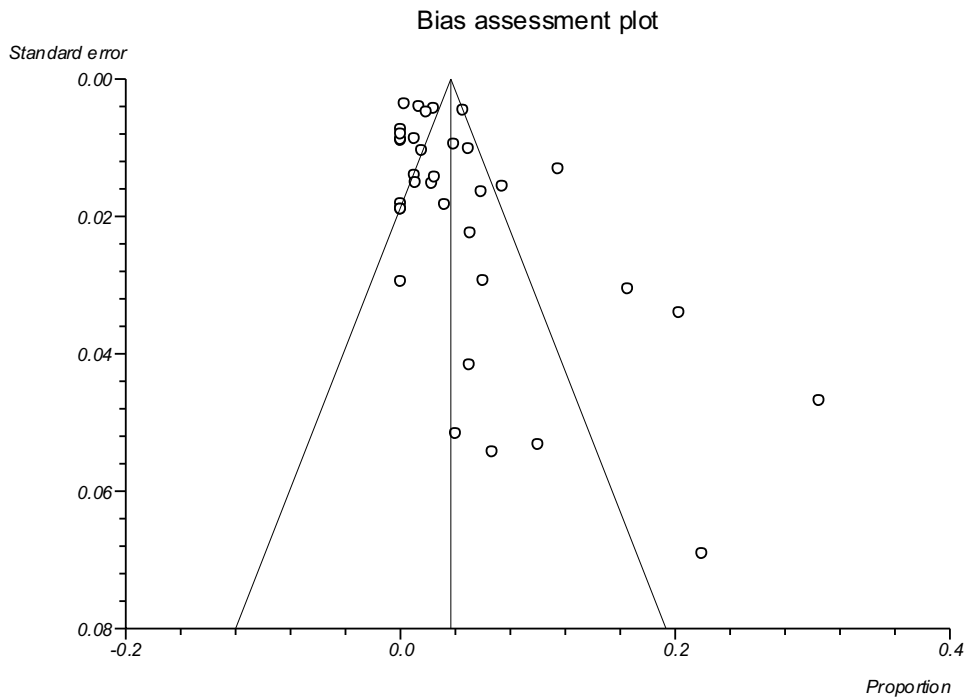
**Figure 98 Funnel plot for assessment of publication bias for major bleeding pooled proportion for fondaparinux thromboprophylaxis used post major abdominal surgery**



**High thromboprophylactic dose of low molecular weight heparin**  
**( $\geq 4000$  IU)**

Figure 99 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

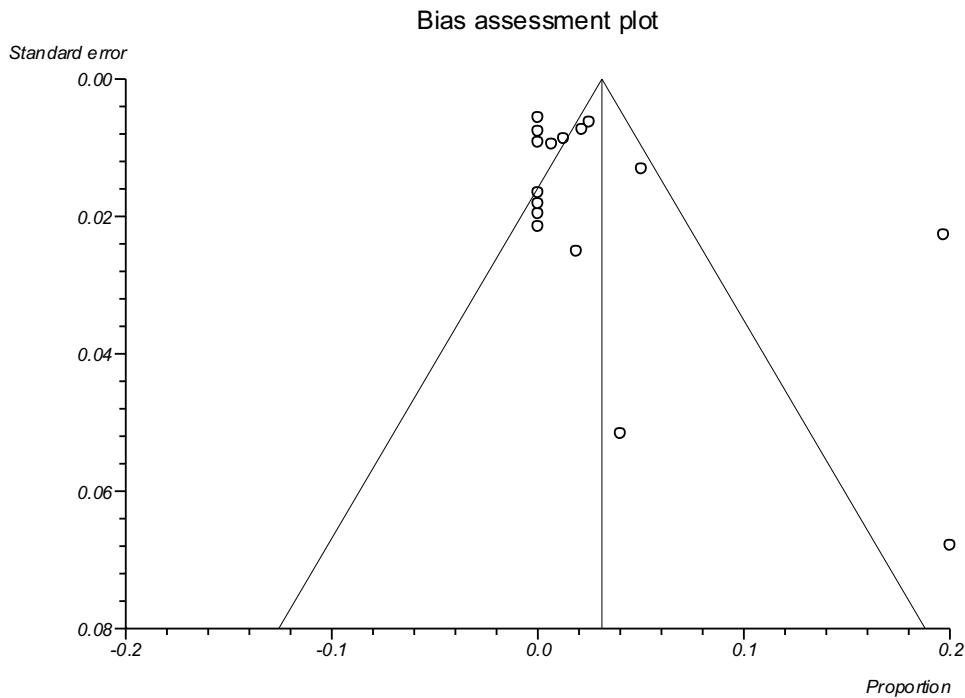
***Figure 99 Funnel plot for assessment of publication bias for major bleeding pooled proportion for high dose LMWH thromboprophylaxis used post major abdominal surgery***



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

Figure 100 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

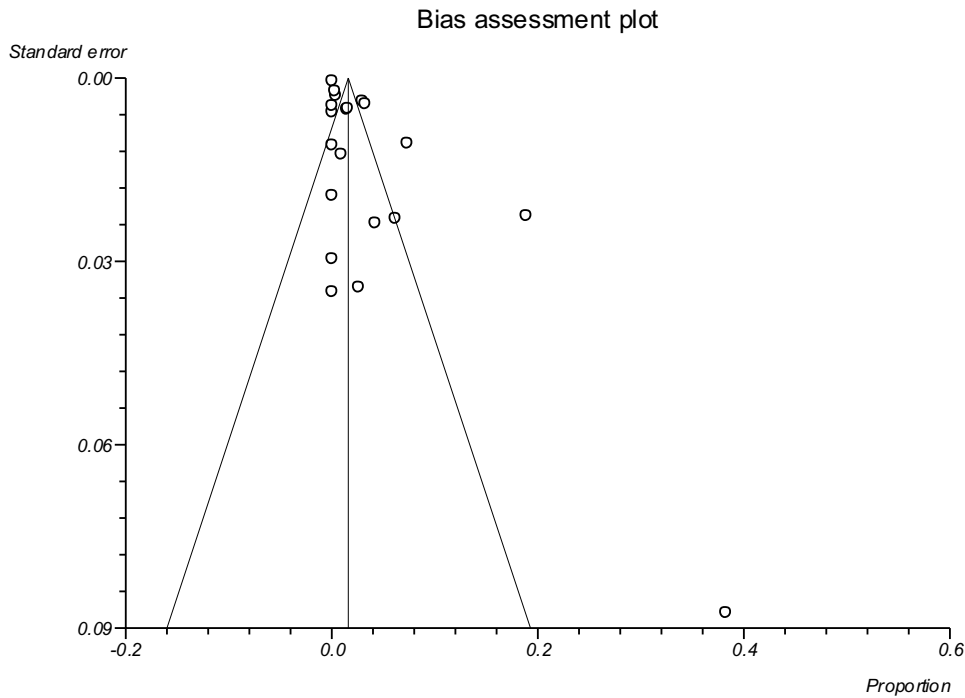
***Figure 100 Funnel plot for assessment of publication bias for major bleeding pooled proportion for high dose UFH thromboprophylaxis used post major abdominal surgery***



**Low prophylactic dose of low molecular weight heparin (<4000 IU)**

Figure 101 shows the funnel plot for assessment of reporting bias. The graph shows symmetry, apart from few outliers, suggestive of low risk for publication bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

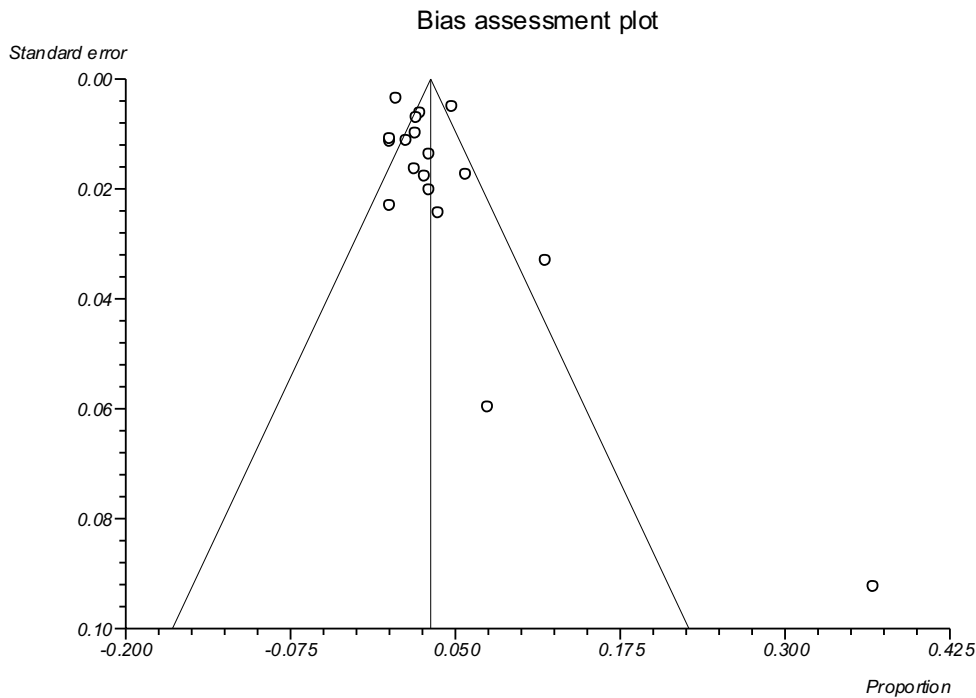
***Figure 101 Funnel plot for assessment of publication bias for major bleeding pooled proportion for low dose LMWH thromboprophylaxis used post major abdominal surgery***



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

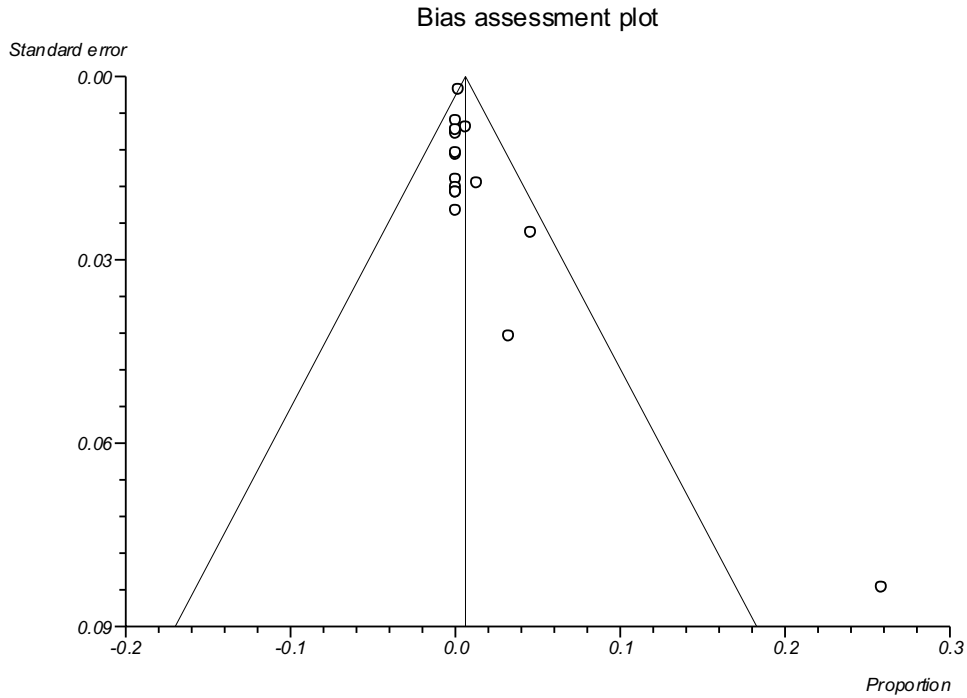
Figure 102 shows the funnel plot for assessment of reporting bias. The graph shows symmetry, apart from few outliers, suggestive of low risk for publication bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

***Figure 102 Funnel plot for assessment of publication bias for major bleeding pooled proportion for low dose UFH thromboprophylaxis used post major abdominal surgery***



**Placebo, non-pharmacological thromboprophylaxis or no treatment**

***Figure 103 Funnel plot for assessment of publication bias for major bleeding pooled proportion for patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment post major abdominal surgery***



## **30 days Mortality**

### **Fondaparinux (2.5mg s/c daily)**

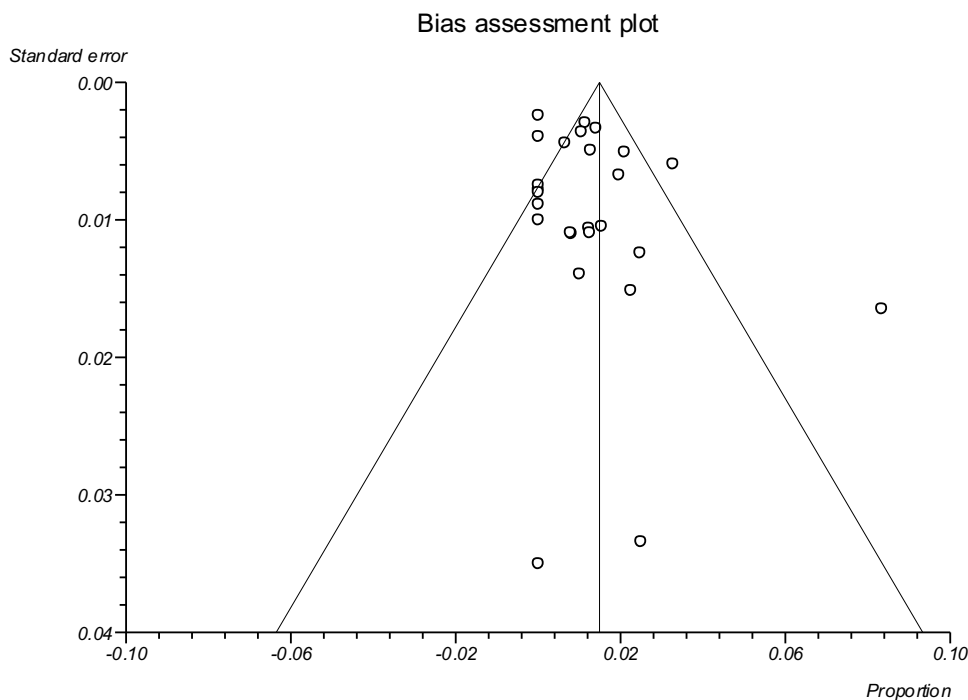
Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

### **High thromboprophylactic dose of low molecular weight heparin**

#### **( $\geq 4000$ IU)**

Figure 104 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the substantial heterogeneity may also explain the asymmetry in the funnel plot.

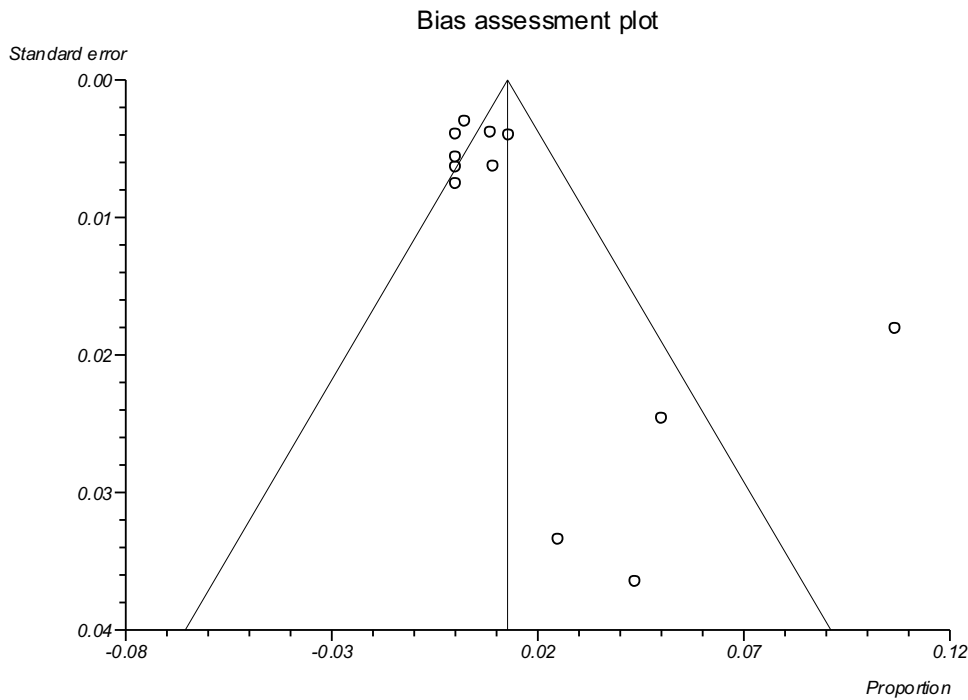
***Figure 104 Funnel plot for assessment of publication bias for 30 days mortality pooled proportion for high dose LMWH thromboprophylaxis used post major abdominal surgery***



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

Figure 105 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

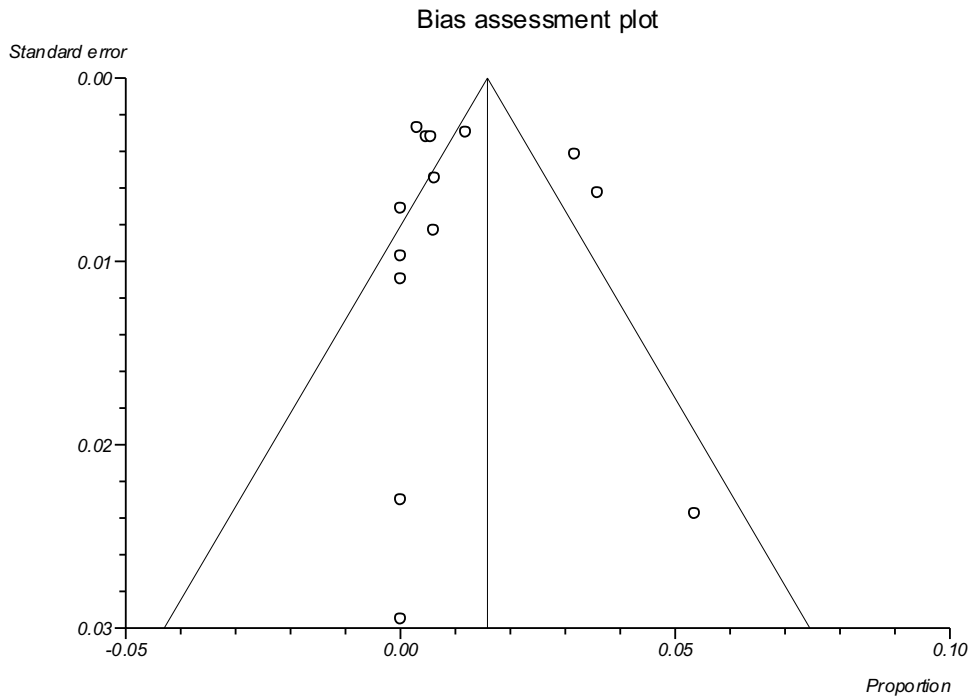
***Figure 105 Funnel plot for assessment of publication bias for 30 days mortality pooled proportion for high dose UFH thromboprophylaxis used post major abdominal surgery***



**Low prophylactic dose of low molecular weight heparin (<4000 IU)**

Figure 106 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

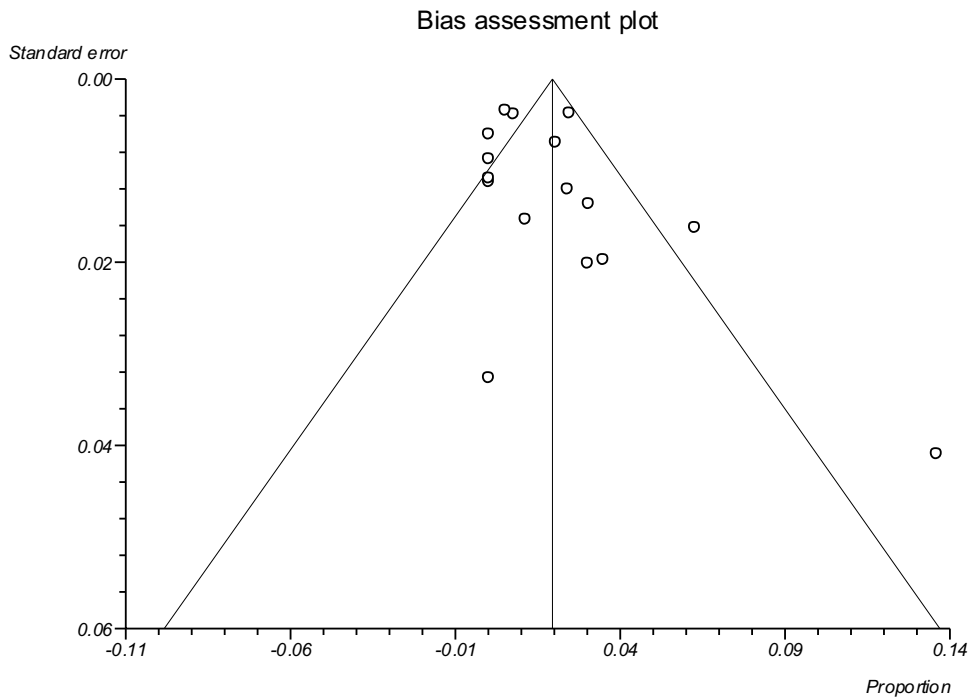
***Figure 106 Funnel plot for assessment of publication bias for 30 days mortality pooled proportion for low dose LMWH thromboprophylaxis used post major abdominal surgery***



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

Figure 107 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity may also explain the asymmetry in the funnel plot.

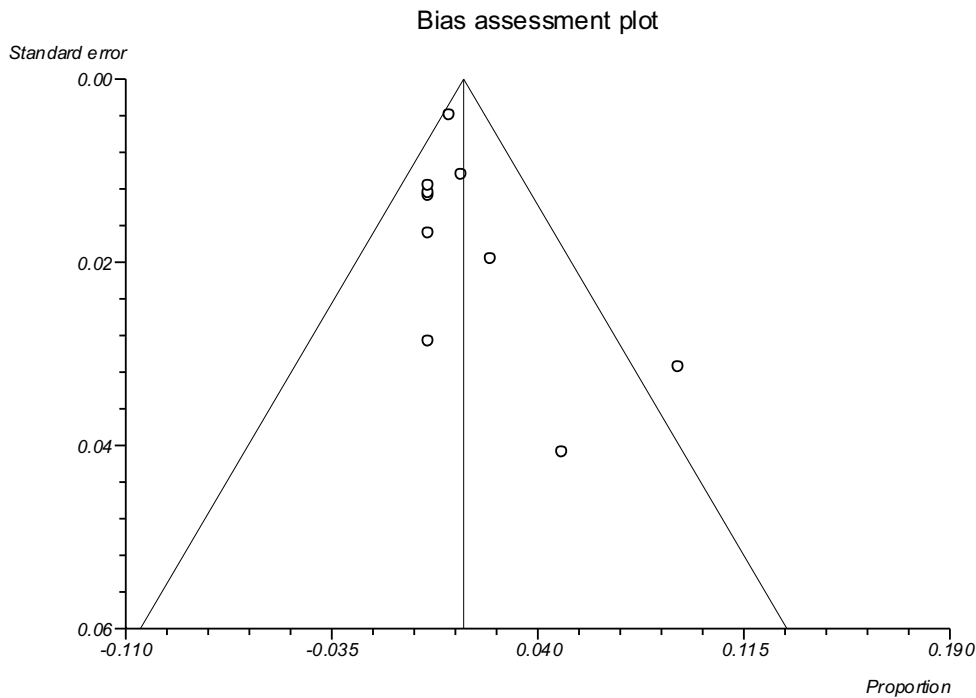
***Figure 107 Funnel plot for assessment of publication bias for 30 days mortality pooled proportion for low dose UFH thromboprophylaxis used post major abdominal surgery***



**Placebo, non-pharmacological thromboprophylaxis or no treatment**

Figure 108 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the substantial heterogeneity may also explain the asymmetry in the funnel plot.

***Figure 108 Funnel plot for assessment of publication bias for 30 days mortality pooled proportion for patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment post major abdominal surgery***



## **30 Days Re-Operation Rate**

### **Fondaparinux (2.5mg s/c daily)**

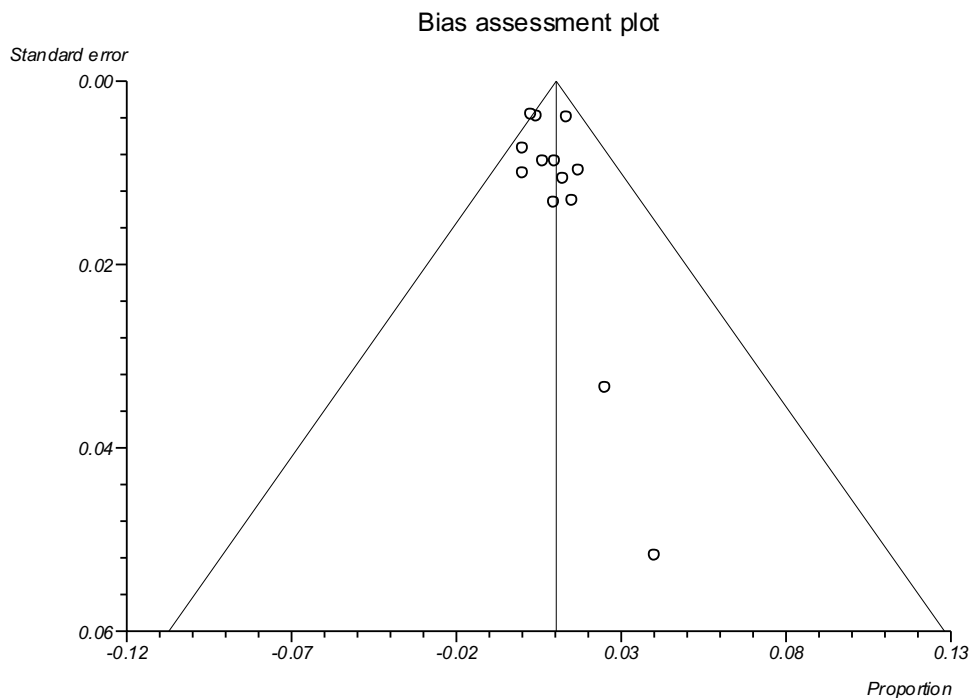
None of the fondaparinux studies reported on 30 days re-operation rate.

### **High thromboprophylactic dose of low molecular weight heparin**

#### **( $\geq 4000$ IU)**

Figure 109 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias.

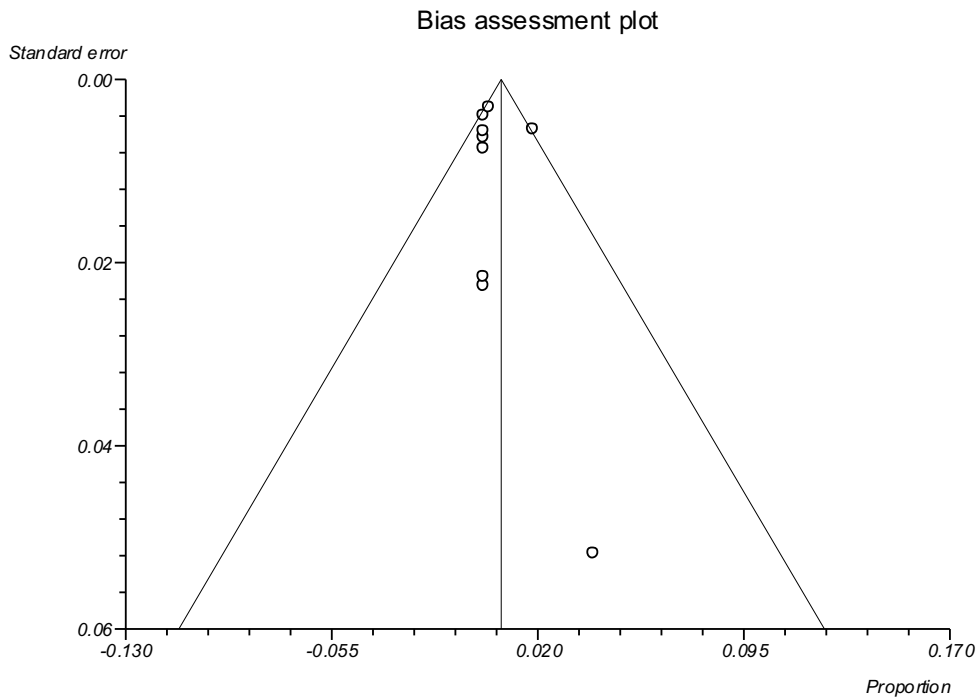
***Figure 109 Funnel plot for assessment of publication bias for 30 days re-operation rate pooled proportion for high dose LMWH thromboprophylaxis used post major abdominal surgery***



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

Figure 110 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias.

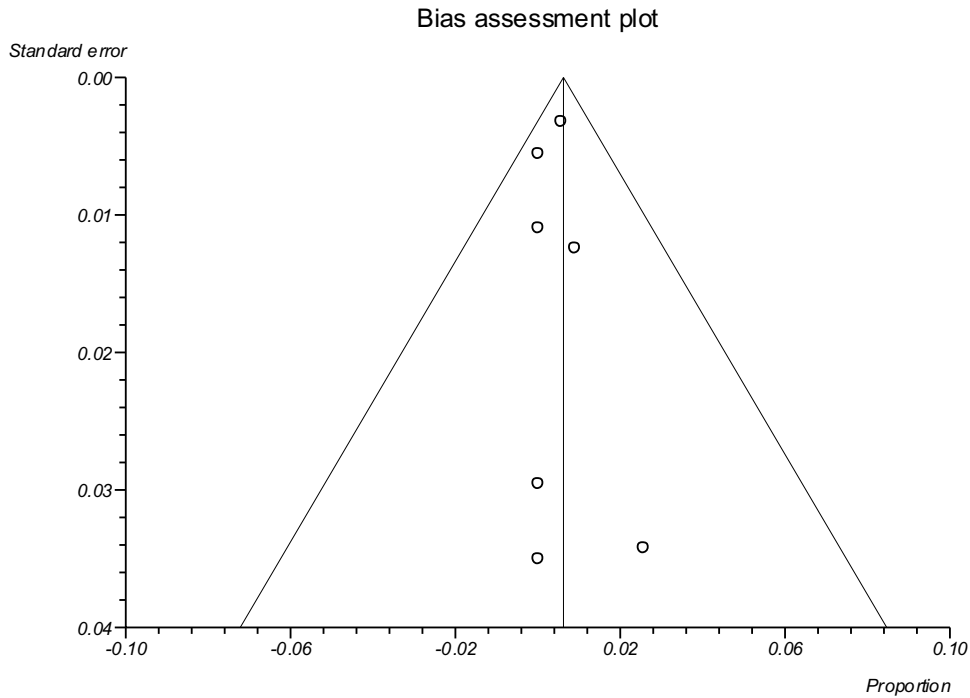
***Figure 110 Funnel plot for assessment of publication bias for 30 days re-operation rate pooled proportion for high dose UFH thromboprophylaxis used post major abdominal surgery***



**Low prophylactic dose of low molecular weight heparin (<4000 IU)**

Figure 111 shows the funnel plot for assessment of reporting bias. The graph did not show a significant asymmetry to suggest reporting bias.

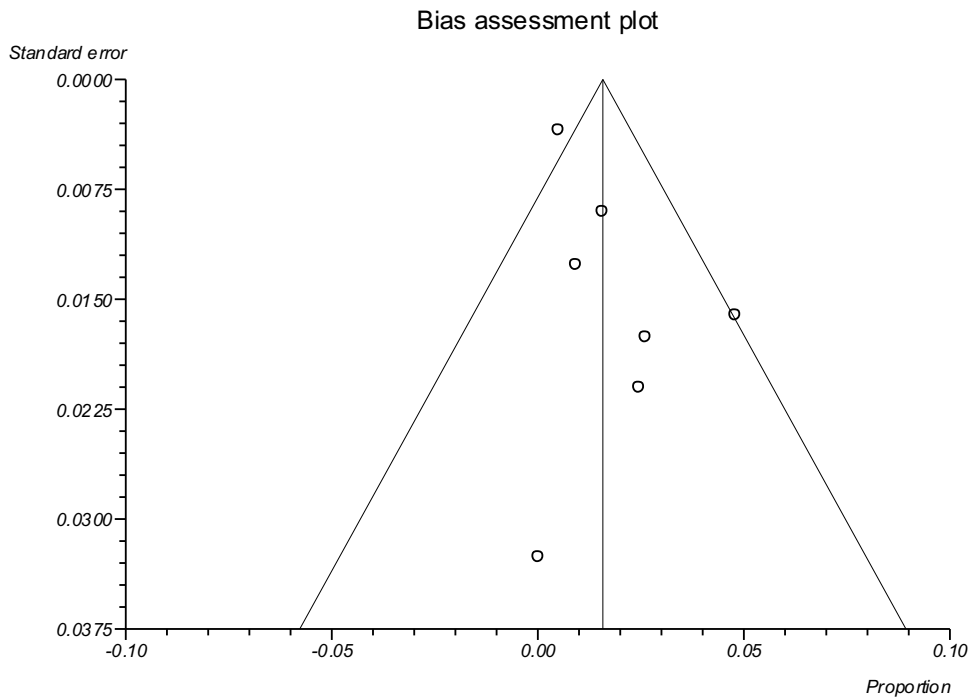
***Figure 111 Funnel plot for assessment of publication bias for 30 days re-operation rate pooled proportion for low dose LMWH thromboprophylaxis used post major abdominal surgery***



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

Figure 112 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of publication bias.

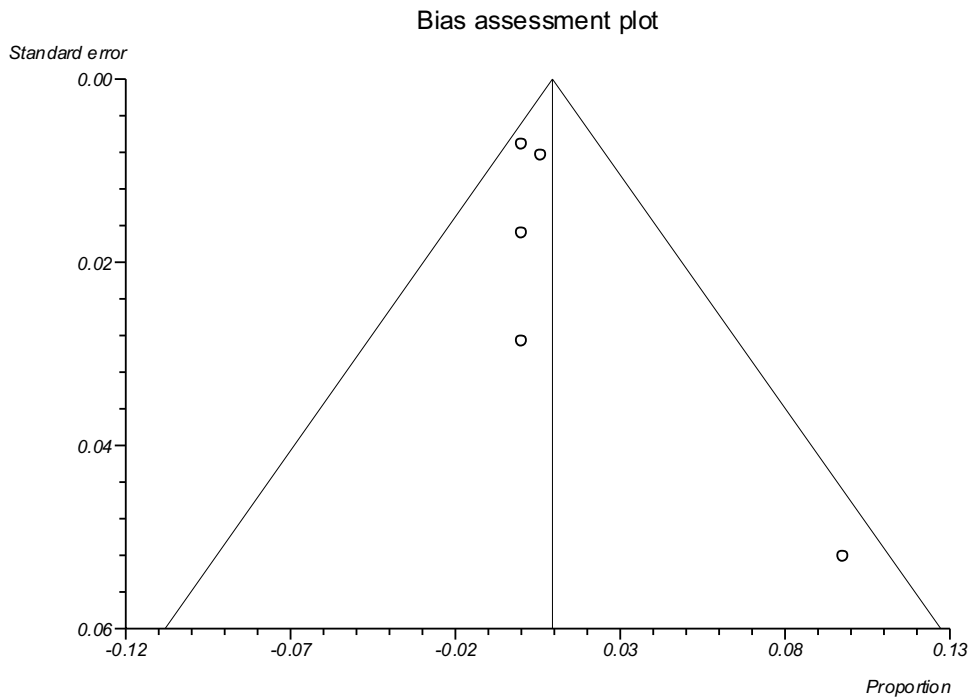
***Figure 112 Funnel plot for assessment of publication bias for 30 days re-operation rate pooled proportion for low dose UFH thromboprophylaxis used post major abdominal surgery***



**Placebo, non-pharmacological thromboprophylaxis or no treatment**

Figure 113 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the substantial heterogeneity may also explain the asymmetry in the funnel plot.

***Figure 113 Funnel plot for assessment of publication bias for 30 days re-operation rate pooled proportion for patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment post major abdominal surgery***



## **Pooled Proportions of wound infection**

### **Fondaparinux (2.5mg s/c daily)**

None of the fondaparinux studies reported on wound infection.

### **High thromboprophylactic dose of low molecular weight heparin**

#### **( $\geq 4000$ IU)**

#### ***Reporting and Publication Bias Assessment***

Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

### **High thromboprophylactic dose of unfractionated heparin (UFH 5000**

#### **units every 8 hours)**

Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

### **Low prophylactic dose of low molecular weight heparin (<4000 IU)**

Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

**Placebo, non-pharmacological thromboprophylaxis or no treatment**

Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

**Wound oozing**

**Fondaparinux (2.5mg s/c daily)**

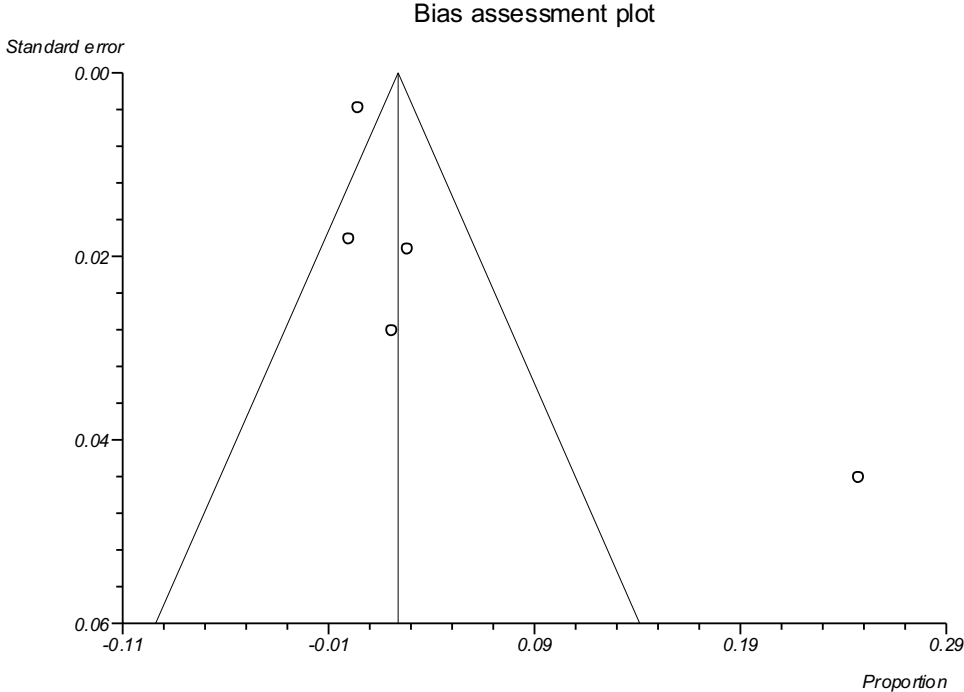
None of the fondaparinux studies reported on wound oozing.

**High thromboprophylactic dose of low molecular weight heparin**

**(≥4000 IU)**

Figure 114 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. Funnel plot asymmetry can be also explained by the considerable degree of heterogeneity.

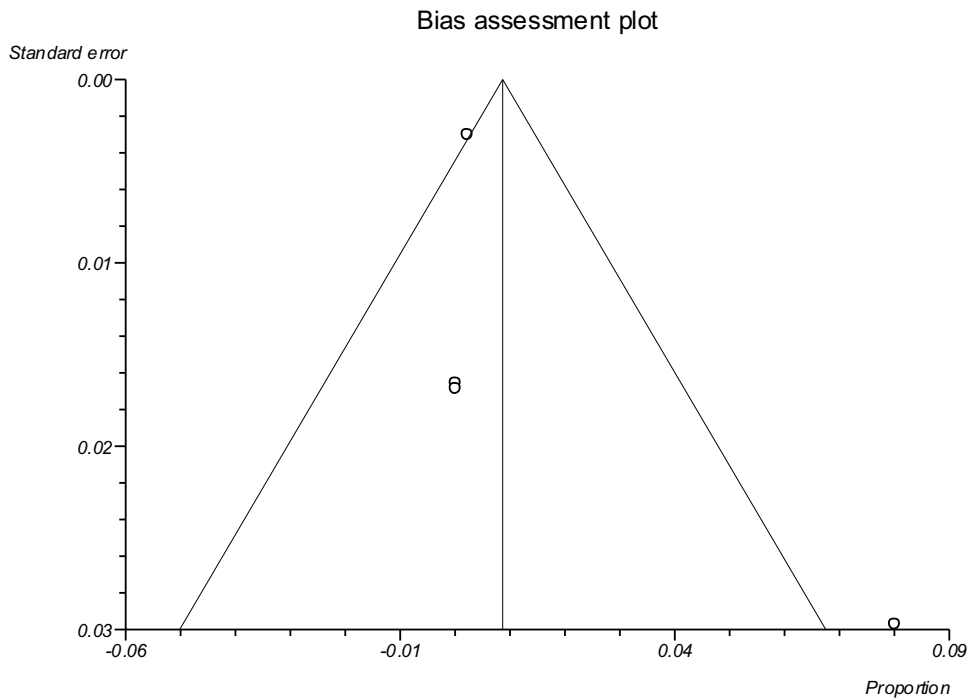
***Figure 114 Funnel plot for assessment of publication bias for wound oozing pooled proportion for high dose LMWH thromboprophylaxis used post major abdominal surgery***



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

Figure 115 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias.

***Figure 115 Funnel plot for assessment of publication bias for wound oozing pooled proportion for high dose UFH thromboprophylaxis used post major abdominal surgery***



**Low prophylactic dose of low molecular weight heparin (<4000 IU)**

Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

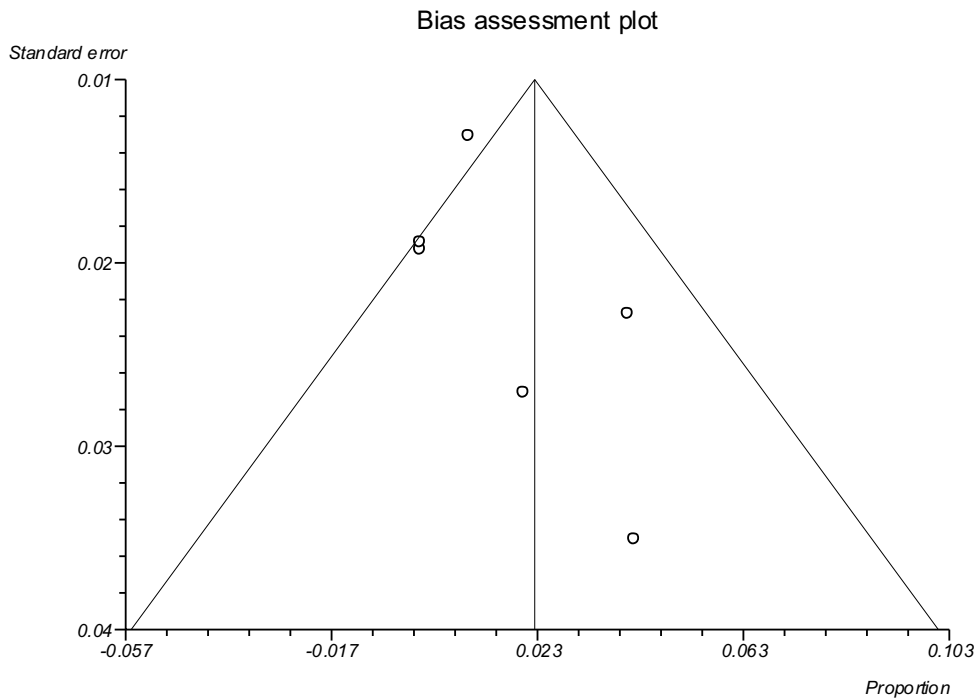
**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

**Placebo, non-pharmacological thromboprophylaxis or no treatment**

Figure 116 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias.

***Figure 116 Funnel plot for assessment of publication bias for wound oozing events pooled proportion for patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment post major abdominal surgery***



## Subgroup Analysis

### Laparoscopic Surgery

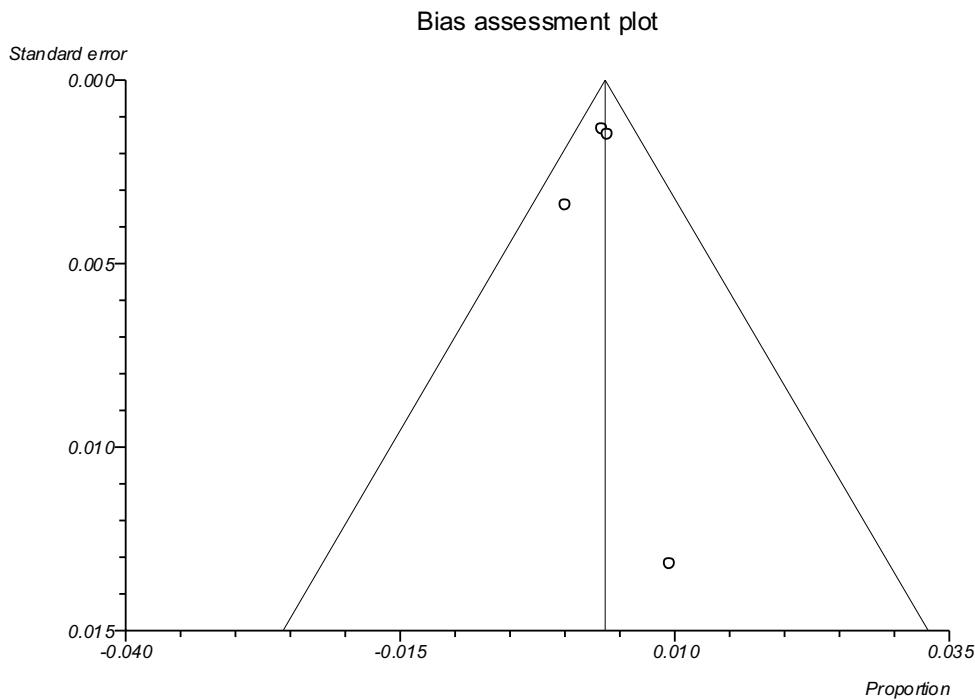
Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

### ***Low prophylactic dose of low molecular weight heparin (<4000 IU)***

#### ***Pooled proportion of VTE and DVT***

Figure 117 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias.

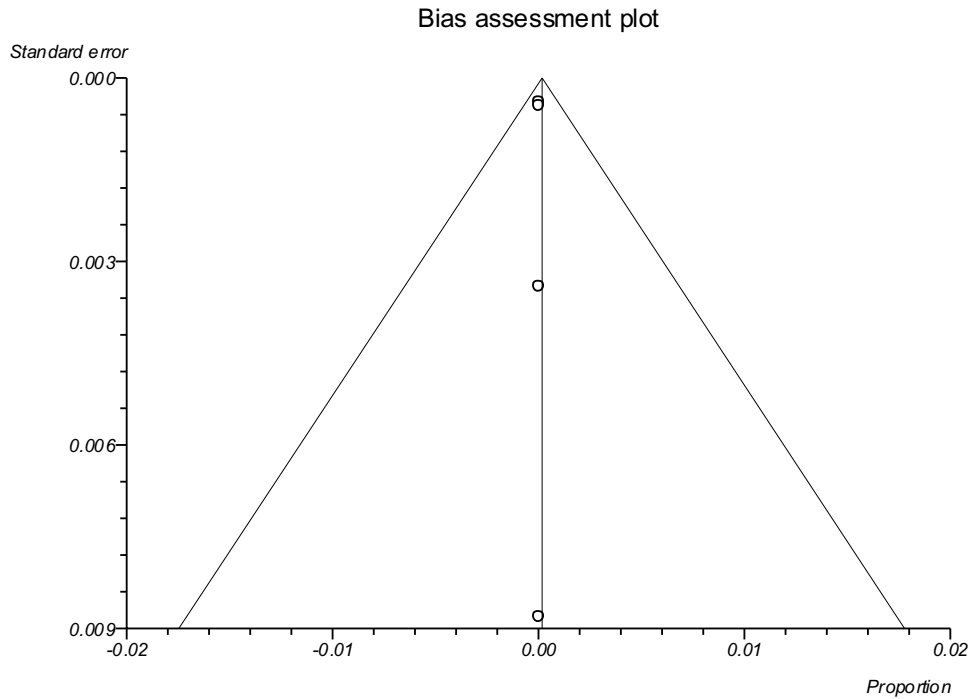
***Figure 117 Funnel plot for assessment of publication bias for VTE pooled proportion for high dose LMWH thromboprophylaxis used post major laparoscopic abdominal surgery***



### ***Pooled proportion of PE***

Figure 118 shows the funnel plot for assessment of reporting bias. The graph shows does not show asymmetry suggestive of reporting bias.

***Figure 118 Funnel plot for assessment of publication bias for PE pooled proportion for high dose LMWH thromboprophylaxis used post major laparoscopic abdominal surgery***



### ***Pooled proportion of major bleeding***

Funnel plot is not available to assess publication bias. The numbers of studies were not enough for the funnel plot.

## **Bariatric Surgery**

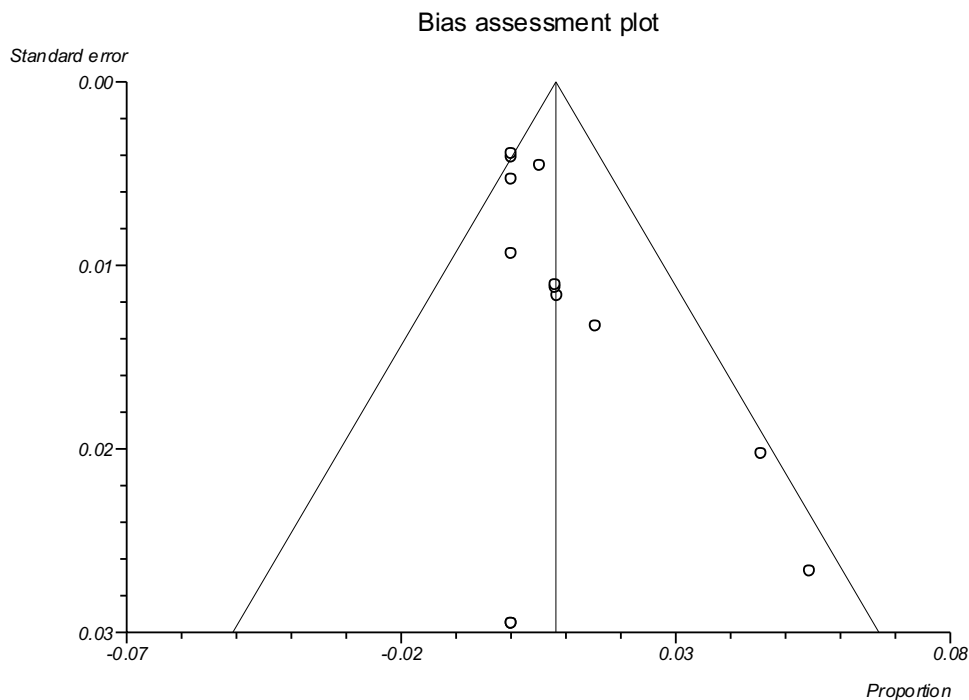
### ***High thromboprophylactic dose of low molecular weight heparin ( $\geq 4000$***

***IU)***

#### ***Pooled proportion of VTE***

Figure 119 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias.

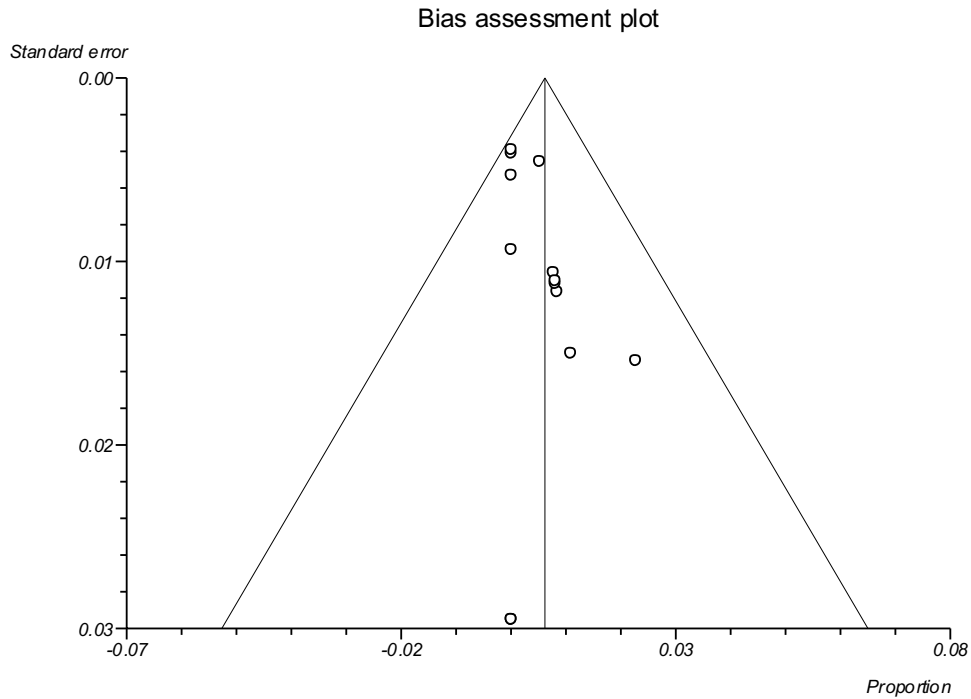
***Figure 119 Funnel plot for assessment of publication bias for VTE pooled proportion for high dose LMWH thromboprophylaxis used post major bariatric abdominal surgery***



***Pooled proportion of DVT***

Figure 120 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias.

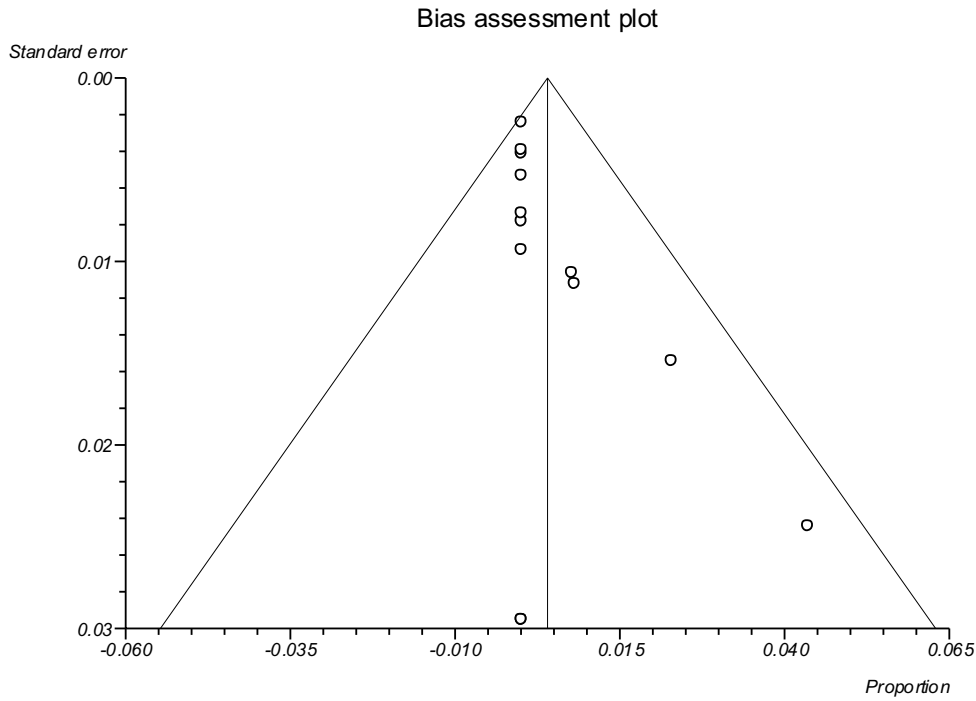
***Figure 120 Funnel plot for assessment of publication bias for DVT pooled proportion for high dose LMWH thromboprophylaxis used post major bariatric abdominal surgery***



**Pooled proportion of PE**

Figure 121 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias.

**Figure 121 Funnel plot for assessment of publication bias for PE pooled proportion for high dose LMWH thromboprophylaxis used post major bariatric abdominal surgery**



## Cancer Surgery

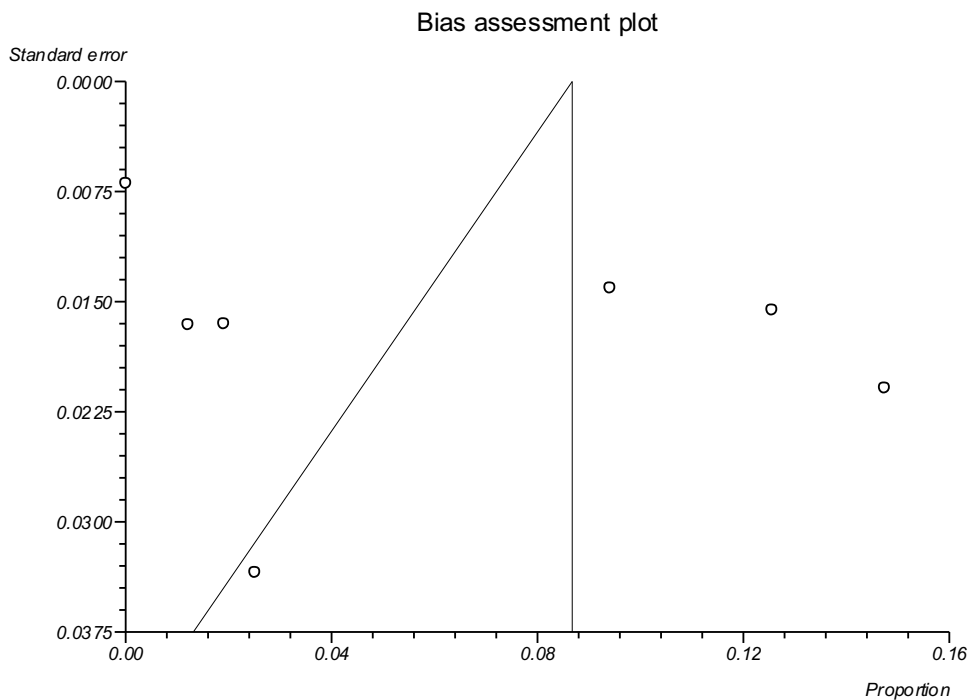
### **High thromboprophylactic dose of low molecular weight heparin ( $\geq 4000$**

**IU)**

#### ***Pooled proportion of VTE***

Figure 122 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity could also explain the asymmetry of the funnel plot.

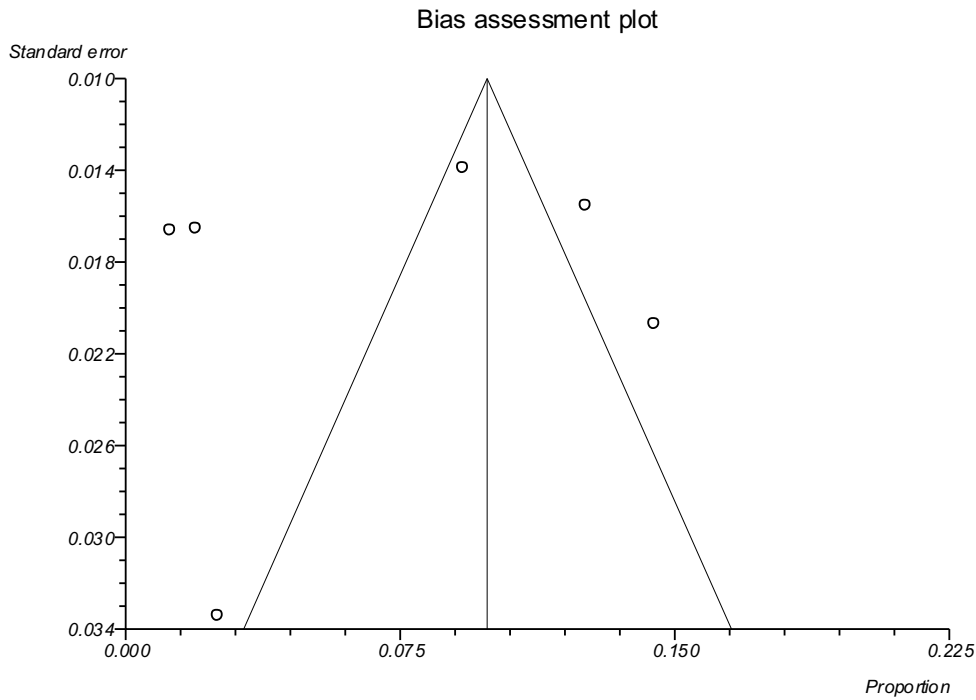
**Figure 122 Funnel plot for assessment of publication bias for VTE pooled proportion for high dose LMWH thromboprophylaxis used post major abdominal cancer surgery**



**Pooled proportion of DVT**

Figure 123 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity could also explain the asymmetry of the funnel plot.

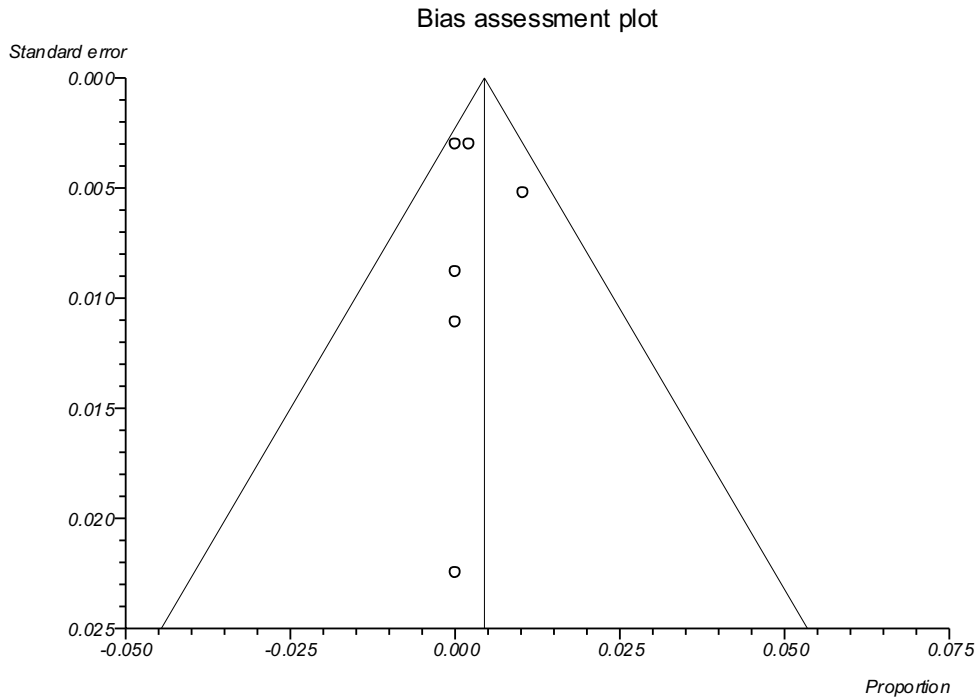
**Figure 123 Funnel plot for assessment of publication bias for DVT pooled proportion for high dose LMWH thromboprophylaxis used post major abdominal cancer surgery**



**Pooled proportion of PE**

Figure 124 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias.

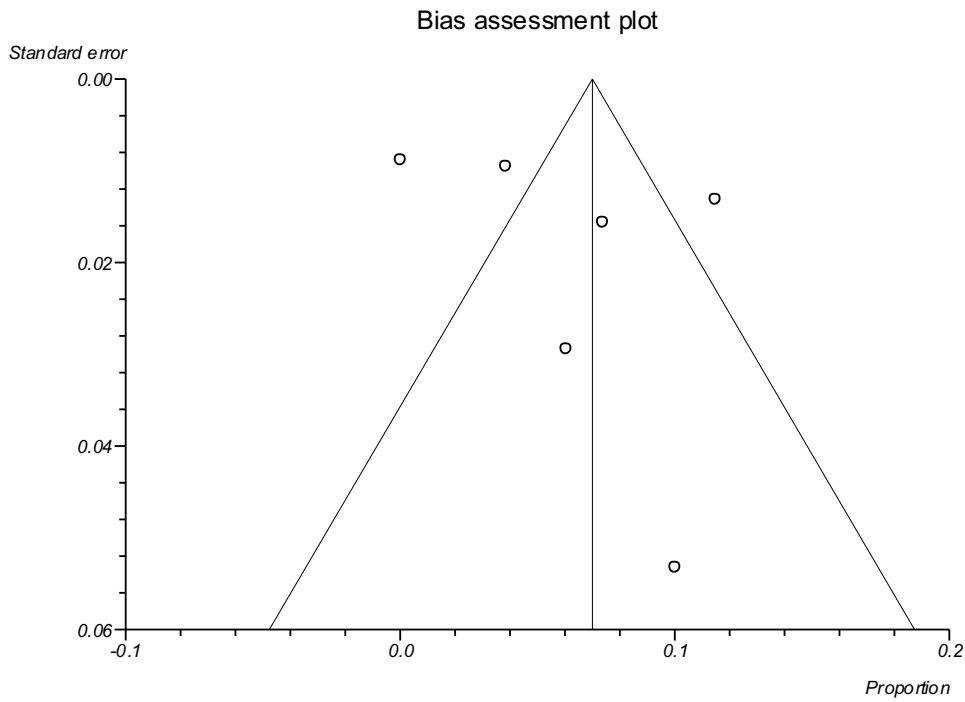
**Figure 124 Funnel plot for assessment of publication bias for PE pooled proportion for high dose LMWH thromboprophylaxis used post major abdominal cancer surgery**



***Pooled proportion of major bleeding events***

Figure 125 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity could also explain the asymmetry of the funnel plot

***Figure 125 Funnel plot for assessment of publication bias for major bleeding pooled proportion for high dose LMWH thromboprophylaxis used post major abdominal cancer surgery***

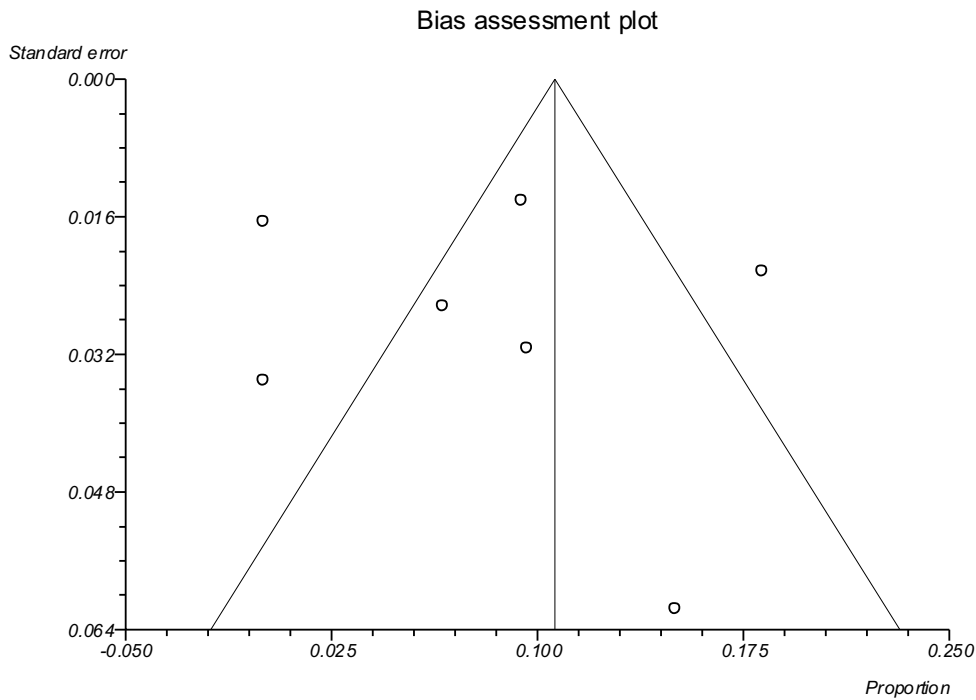


**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

**Pooled proportion of VTE**

Figure 126 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity could also explain the asymmetry of the funnel plot.

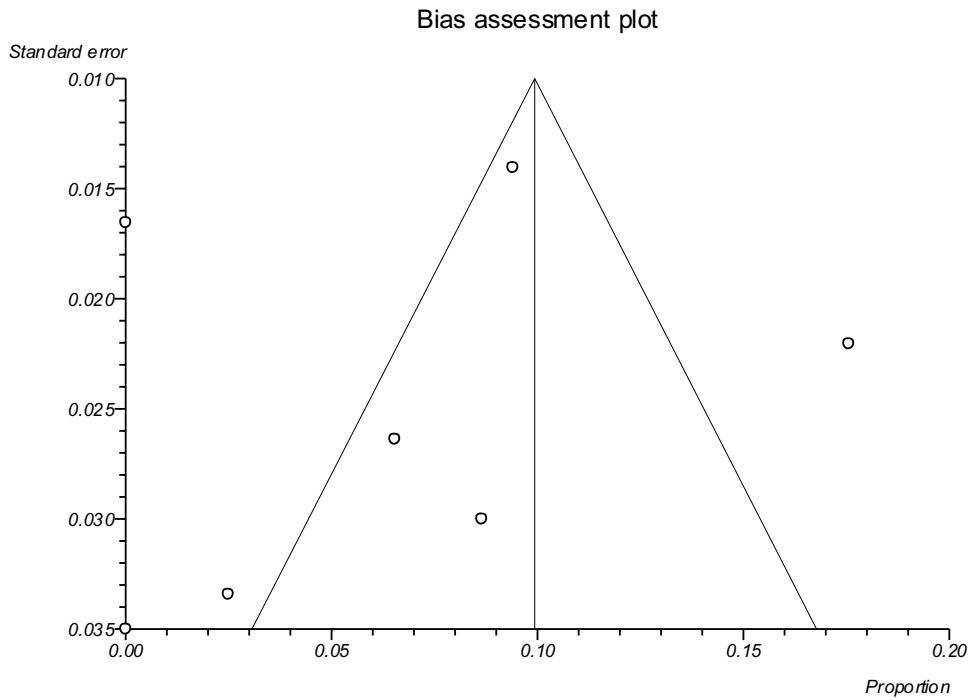
**Figure 126 Funnel plot for assessment of publication bias for VTE pooled proportion for high dose UFH thromboprophylaxis used post major abdominal cancer surgery**



***Pooled proportion of DVT***

Figure 127 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity could also explain the asymmetry of the funnel plot.

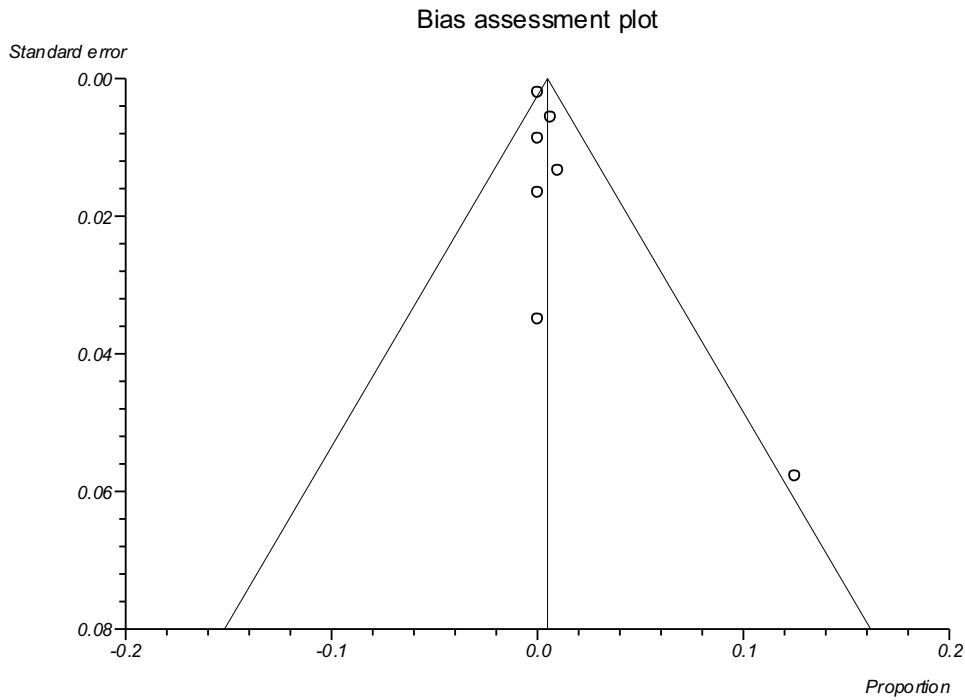
***Figure 127 Funnel plot for assessment of publication bias for DVT pooled proportion for high dose UFH thromboprophylaxis used post major abdominal cancer surgery***



***Pooled proportion of PE***

Figure 128 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity could also explain the asymmetry of the funnel plot.

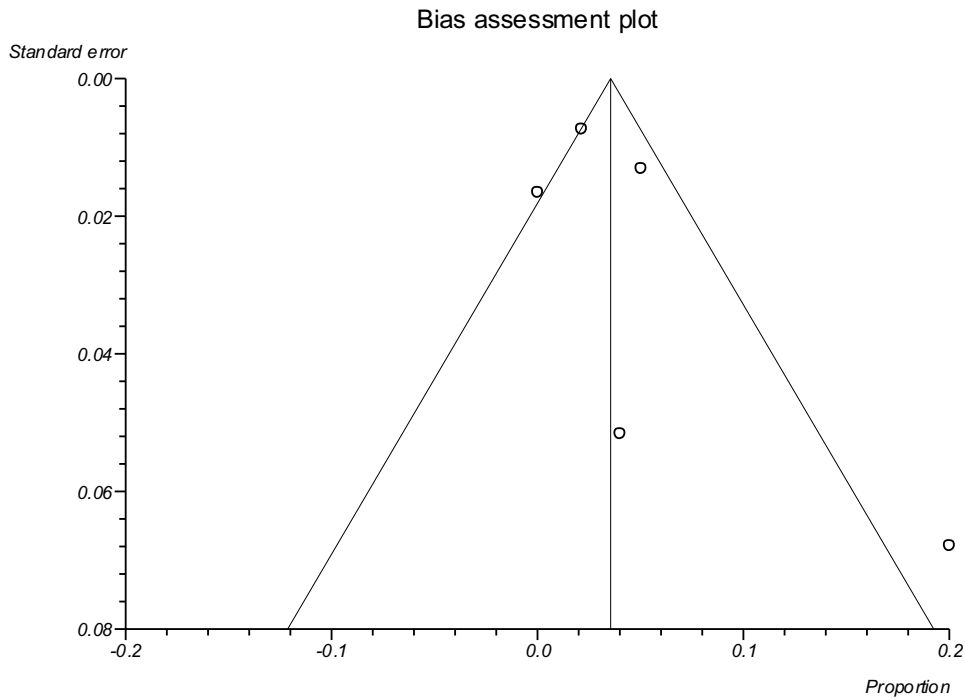
***Figure 128 Funnel plot for assessment of publication bias for PE pooled proportion for high dose UFH thromboprophylaxis used post major abdominal cancer surgery***



***Pooled proportion of major bleeding***

Figure 129 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity could also explain the asymmetry of the funnel plot.

***Figure 129 Funnel plot for assessment of publication bias for major bleeding pooled proportion for high dose UFH thromboprophylaxis used post major abdominal cancer surgery***

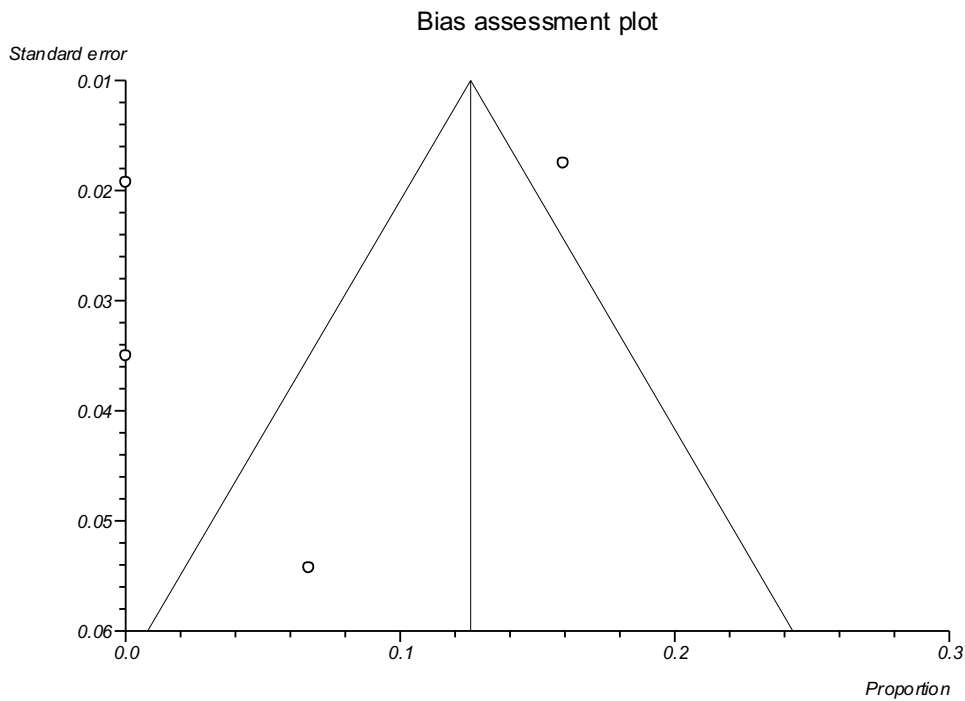


## ***Low prophylactic dose of low molecular weight heparin (<4000 IU)***

### ***Pooled proportion of DVT***

Figure 130 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity could also explain the asymmetry of the funnel plot.

***Figure 130 Funnel plot for assessment of publication bias for DVT pooled proportion for low dose LMWH thromboprophylaxis used post major abdominal cancer surgery***

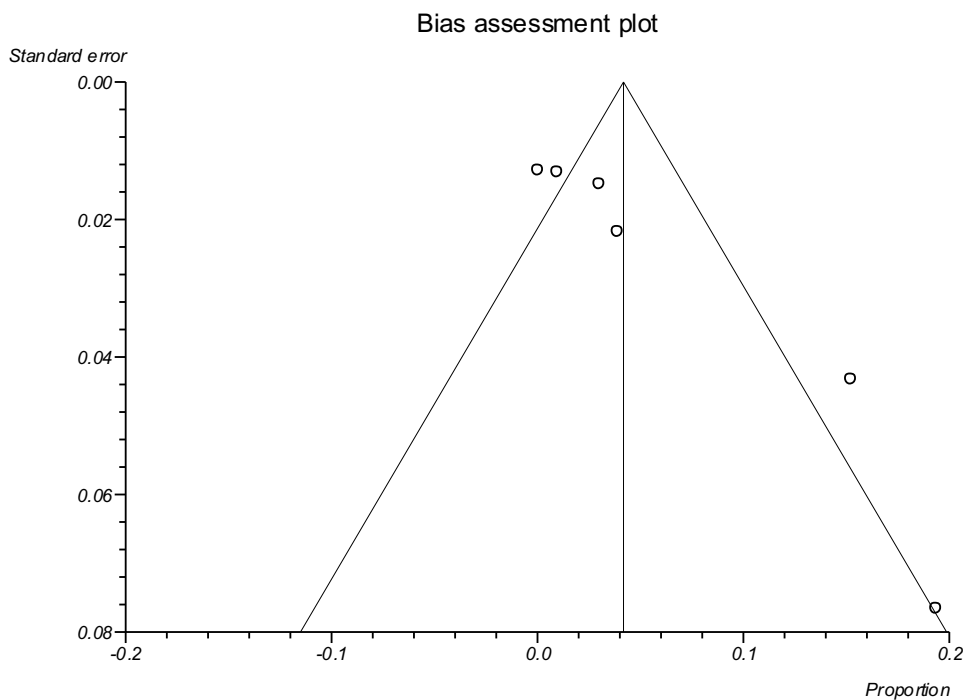


## ***Placebo, non-pharmacological thromboprophylaxis or no treatment***

### ***Pooled proportion of VTE***

Figure 131 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity could also explain the asymmetry of the funnel plot.

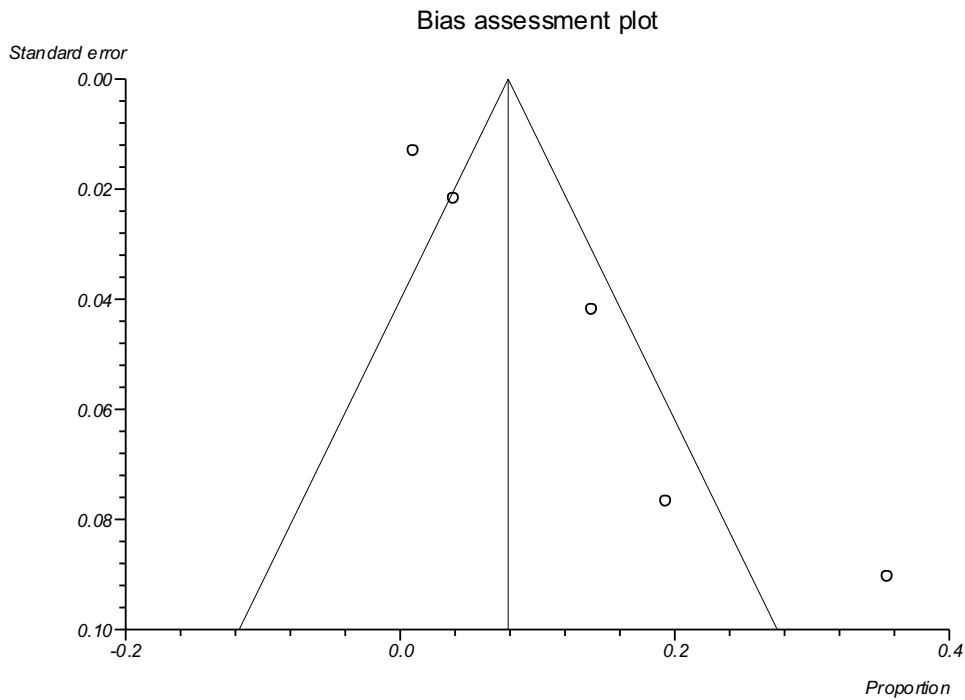
***Figure 131 Funnel plot for assessment of publication bias for VTE pooled proportion for placebo, non-pharmacological thromboprophylaxis or no treatment used post major abdominal cancer surgery***



### ***Pooled proportion of DVT***

Figure 132 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias. However, the considerable heterogeneity could also explain the asymmetry of the funnel plot.

***Figure 132 Funnel plot for assessment of publication bias for DVT pooled proportion for placebo, non-pharmacological thromboprophylaxis or no treatment used post major abdominal cancer surgery***

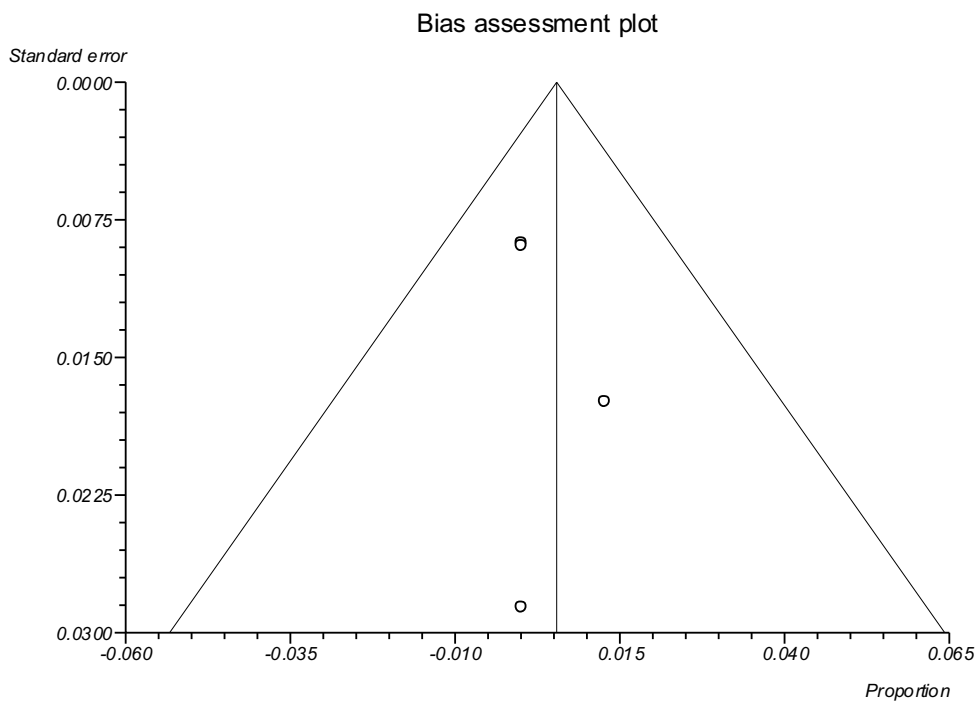


## ***Pooled proportion of PE***

### ***Reporting and Publication Bias Assessment***

Figure 133 shows the funnel plot for assessment of reporting bias. The graph shows a clear asymmetry suggestive of reporting bias.

***Figure 133 Funnel plot for assessment of publication bias for PE pooled proportion for placebo, non-pharmacological thromboprophylaxis or no treatment used post major abdominal cancer surgery***



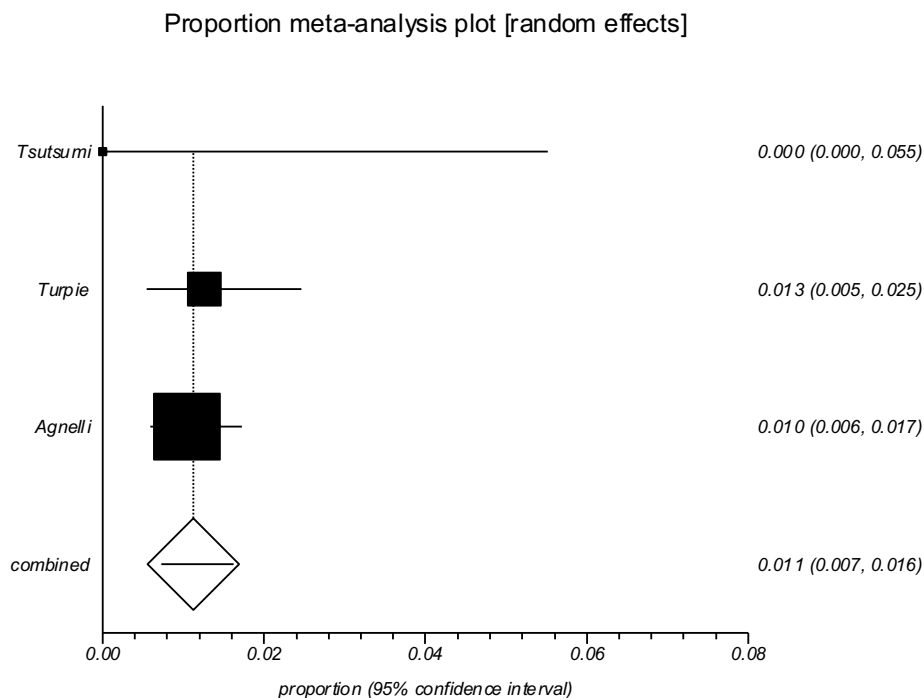
## ***Appendix 5: Pooled Proportions for Secondary Outcomes***

### **Pooled Proportions of 30 days Mortality**

#### **Fondaparinux (2.5mg s/c daily)**

A total of 2133 patients from 3 RCTs were included this analysis. There were a total of 23 deaths at 30 days post-surgery corresponding to pooled proportion of 1.13% (95% CI = 0.72 to 1.62) with no heterogeneity ( $I^2 = 0\%$ ). Figure 26 shows the forest plot of the analysis.

***Figure 26 Forest plot of the pooled proportion of 30 days mortality post major abdominal surgery in patient receiving Fondaparinux for 7-10 days post-surgery***

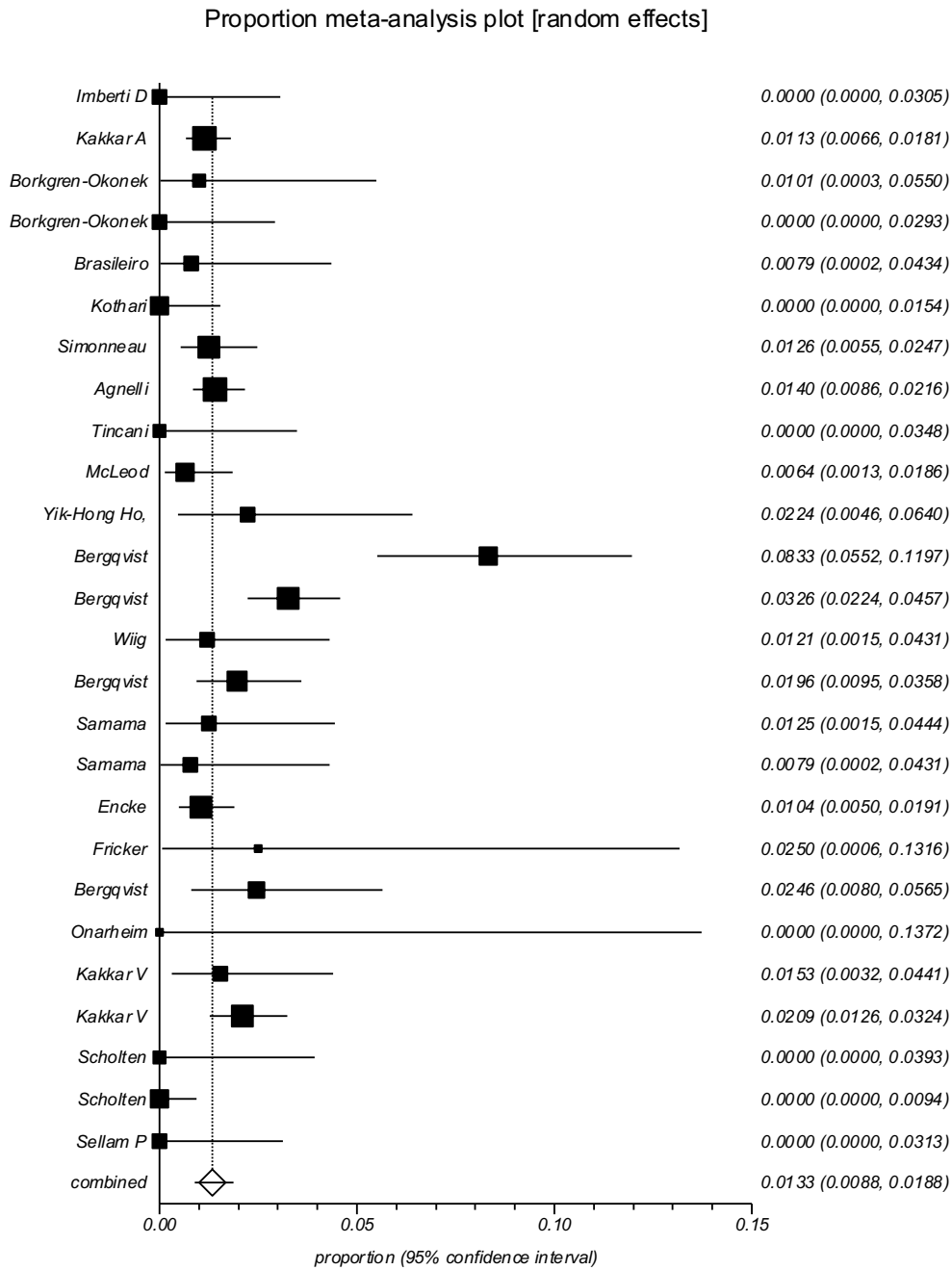


## **High thromboprophylactic dose of low molecular weight heparin**

### **( $\geq 4000$ IU)**

A total of 10156 patients from 20 RCTs and 6 prospective cohort studies were used for this analysis. There were a total of 164 deaths at 30 days post-surgery corresponding to pooled proportion of 1.33% (95% CI = 0.88 to 1.88) with substantial heterogeneity ( $I^2 = 74.6\%$ ). Figure 27 shows the forest plot of the analysis.

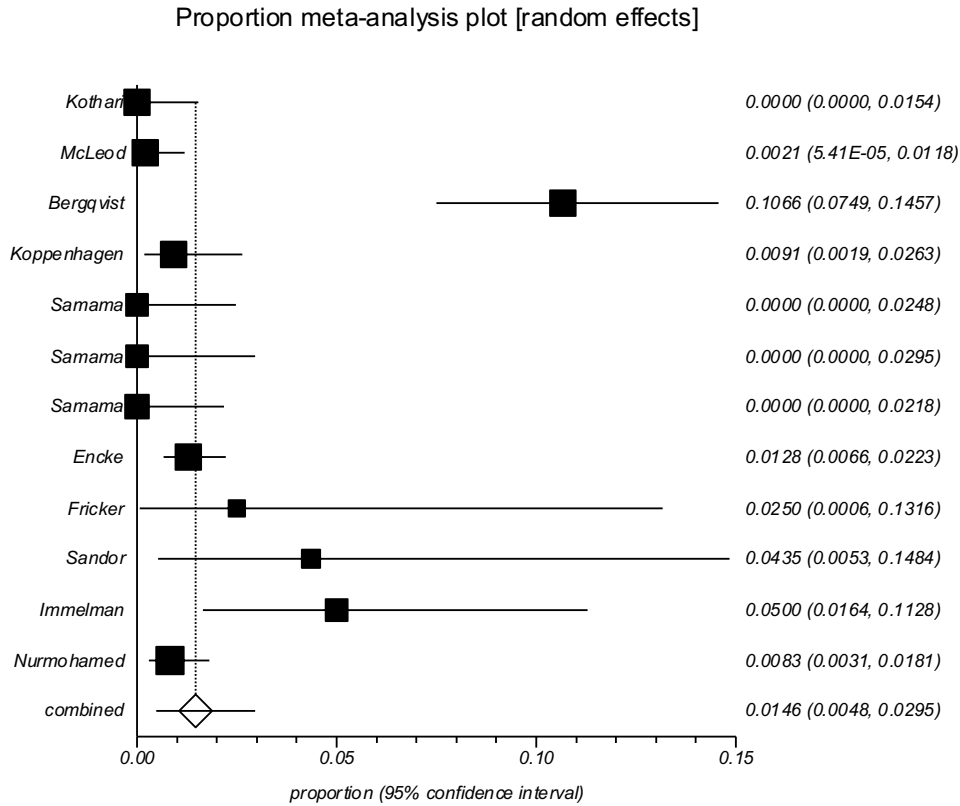
**Figure 27 Forest plot of the pooled proportion 30 days mortality post major abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery**



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

A total of 3633 patients from 11 RCTs and one prospective cohort study were included in this analysis. There were a total of 64 deaths at 30 days post-surgery corresponding to pooled proportion of 1.46 (95% CI = 0.48 to 2.95) with considerable heterogeneity ( $I^2 = 88.4\%$ ). Figure 28 shows the forest plot of the analysis.

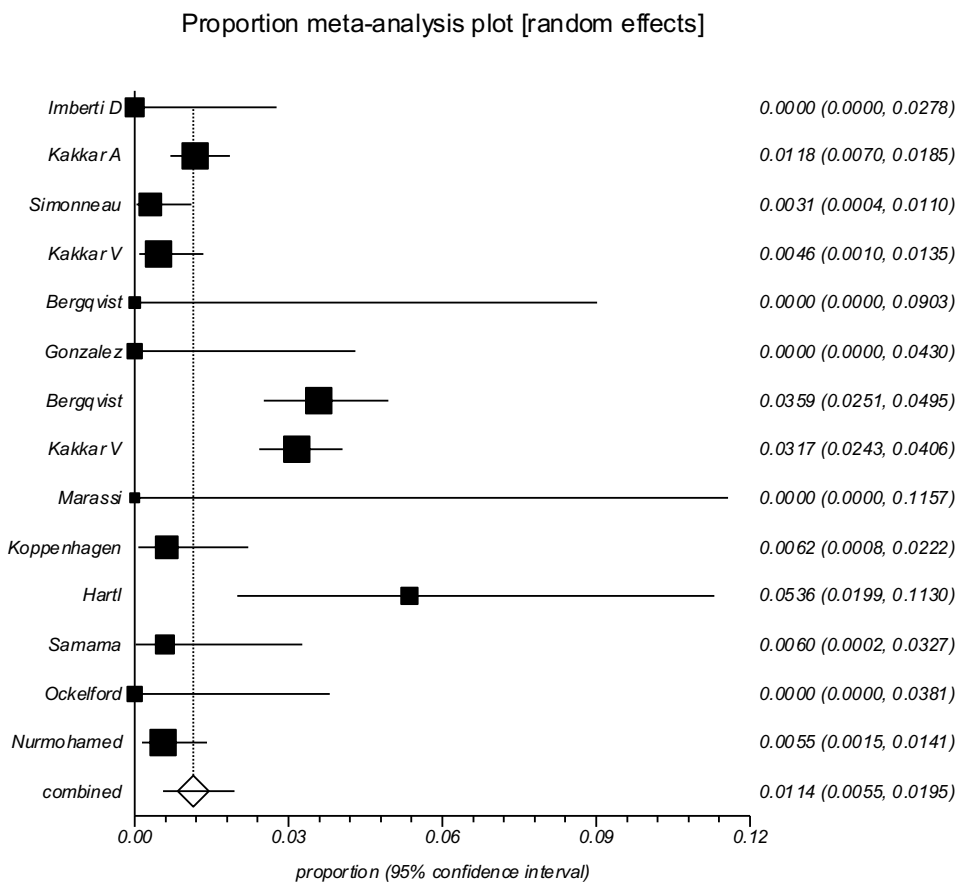
**Figure 28 Forest plot of the pooled proportion of 30 days mortality post major abdominal surgery in patients receiving high dose UFH for 7-10 days post-surgery.**



## Low prophylactic dose of low molecular weight heparin (<4000 IU)

A total of 7409 patients from 14 RCTs were used for this analysis. There were a total of 131 deaths at 30 days post-surgery corresponding to pooled proportion of 1.14% (95% CI = 0.55 to 1.95) with considerable heterogeneity ( $I^2 = 84.1\%$ ). Figure 29 shows the forest plot of the analysis.

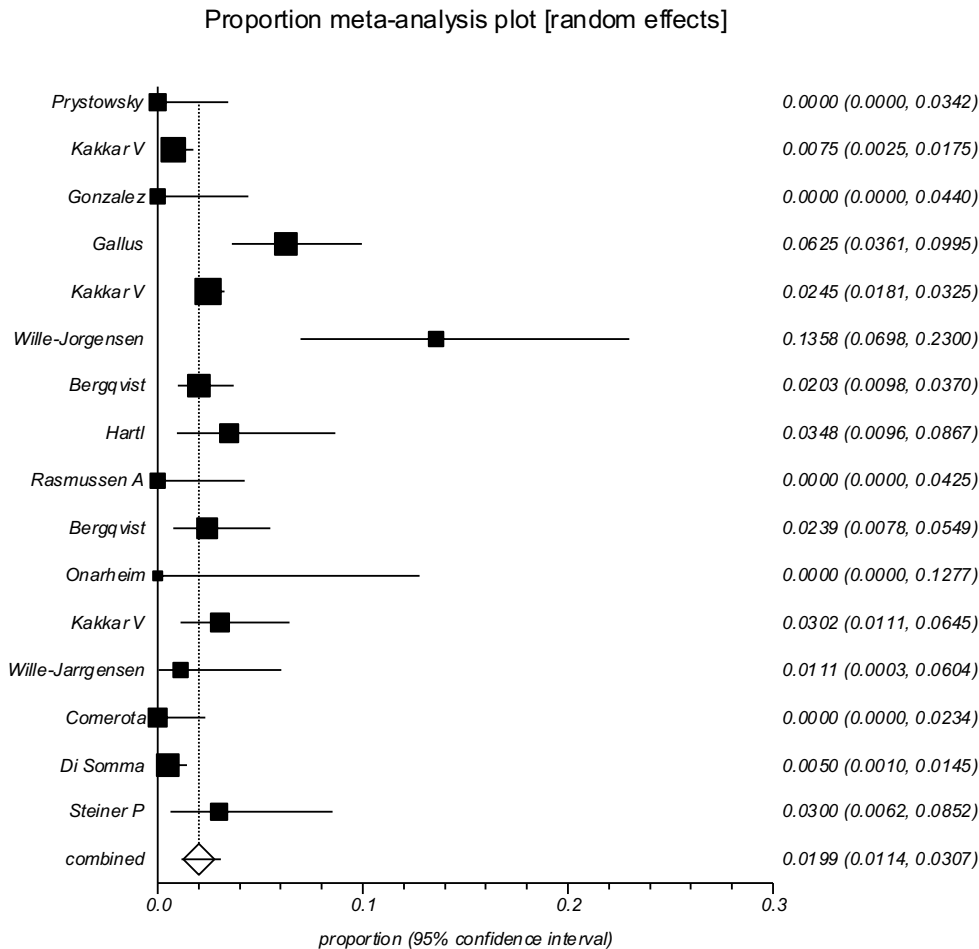
**Figure 29 Forest plot of the pooled proportion for 30 days mortality post major abdominal surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

A total of 5179 patients from 14 RCTs and 2 prospective cohorts studies used were included this analysis. There were a total of 111 deaths 30 days post-surgery corresponding to pooled proportion of 1.99% (95% CI = 1.14 to 3.07) with substantial heterogeneity ( $I^2 = 79\%$ ). Figure 30 shows the forest plot of the analysis.

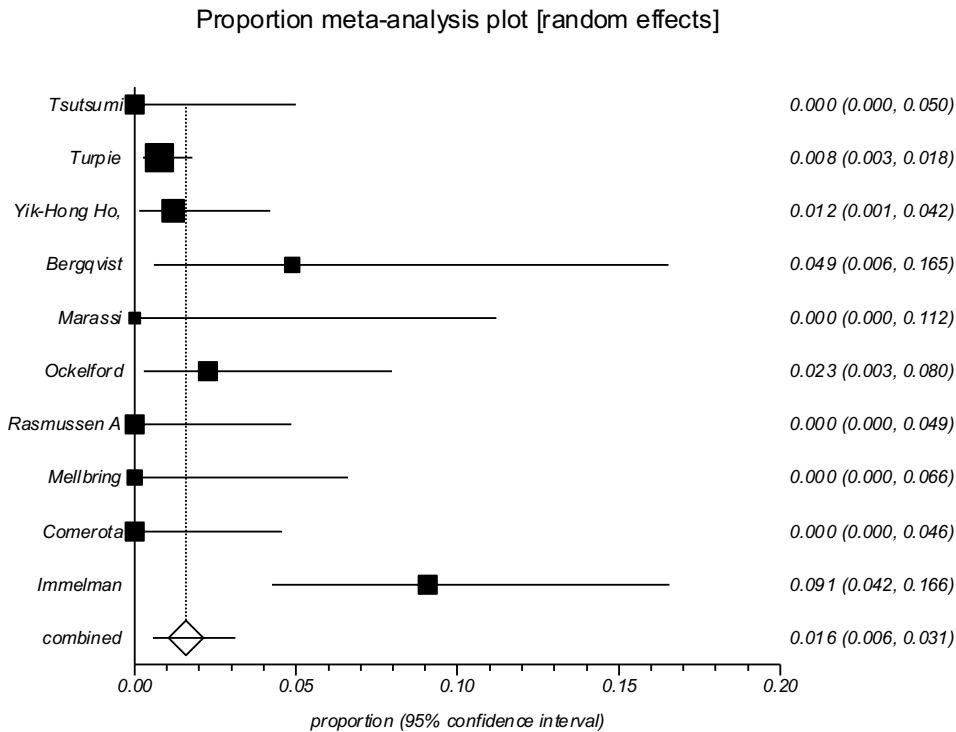
**Figure 30 Forest plot of the pooled proportion for 30 days mortality post major abdominal surgery in patient receiving low dose UFH for 7-10 days post-surgery.**



## **Placebo, non-pharmacological thromboprophylaxis or no treatment**

A total of 1357 patients from 10 RCTs were used for this analysis. There were a total of deaths at 30 days post-surgery corresponding to pooled proportion of 1.58% (95% CI = 0.56 to 3.11) with substantial heterogeneity ( $I^2 = 63.4\%$ ). Figure 31 shows the forest plot of the analysis.

**Figure 31 Forest plot of the pooled proportion 30 days mortality post major abdominal surgery in patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment.**



## **Pooled Proportions of 30 Days Re-Operation Rate**

### **Fondaparinux (2.5mg s/c daily)**

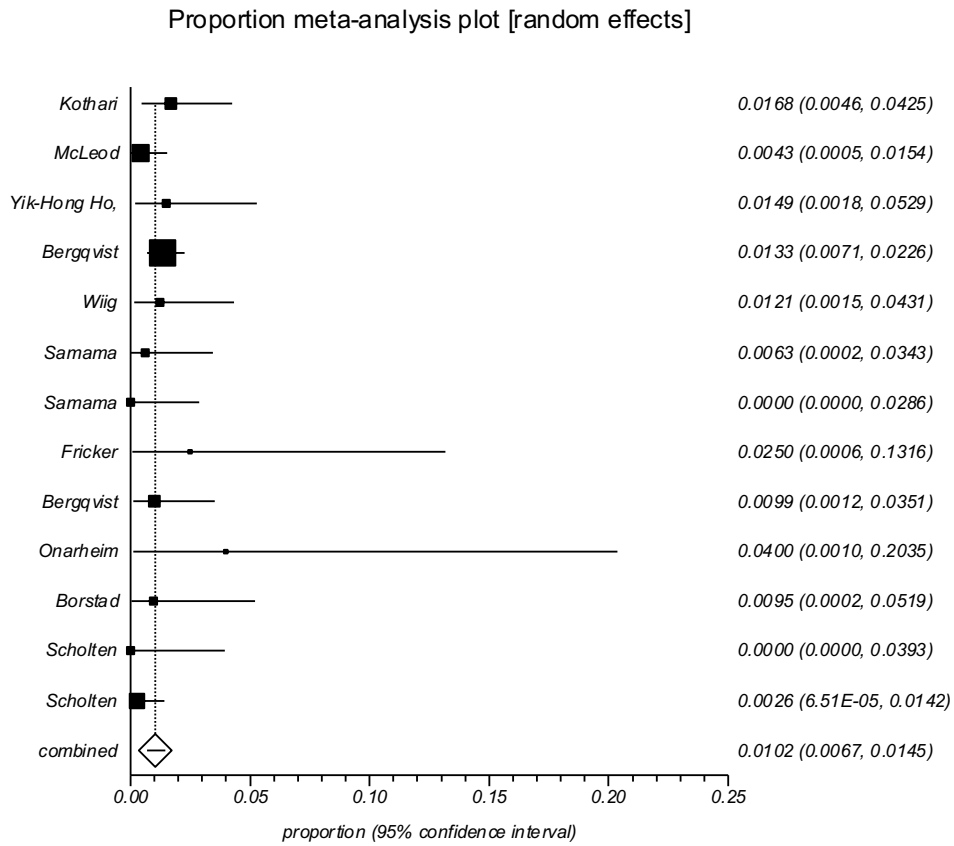
None of the fondaparinux studies reported on 30 days re-operation rate.

### **High thromboprophylactic dose of low molecular weight heparin**

#### **( $\geq 4000$ IU)**

A total of 3127 patients from 10 RCTs and 3 prospective cohort studies were included in this analysis. There were a total of 30 re-operation at 30 days post-surgery corresponding to pooled proportion of 1.03% (95% CI = 0.67 to 1.45) with low heterogeneity ( $I^2 = 9.8\%$ ). Figure 32 shows the forest plot of the analysis.

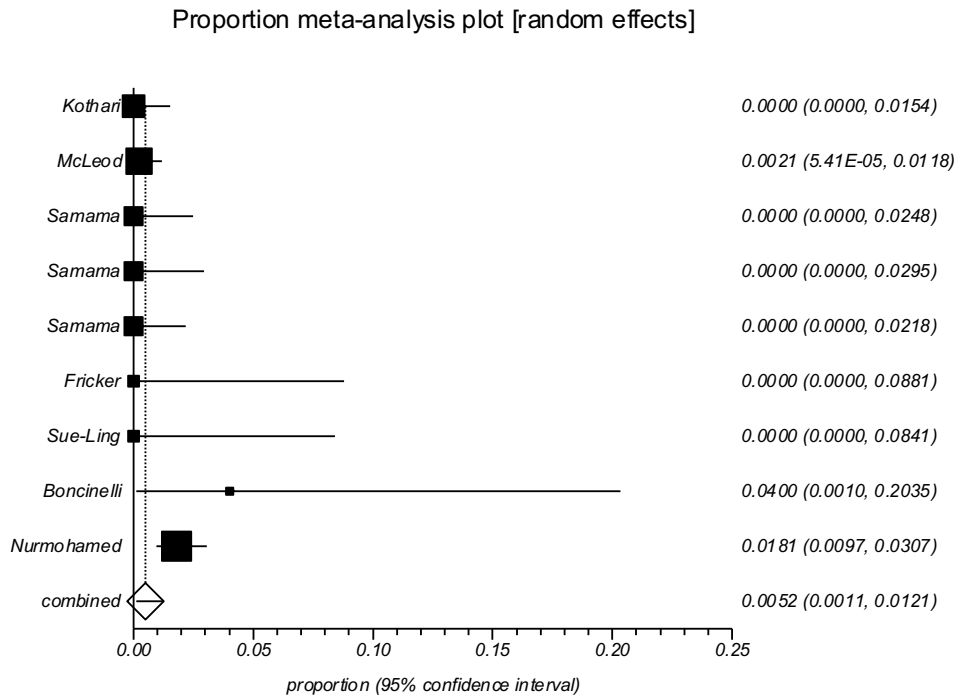
**Figure 32 Forest plot of the pooled proportion 30 days re-operation rate post major abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery**



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

A total of 1969 patients from 8 RCTs and one prospective cohort study were used for this analysis. There were a total of 15 re-operations at 30 days post-surgery corresponding to pooled proportion of = 0.52% (95% CI = 0.11 to 1.21) with moderate heterogeneity ( $I^2 = 55.5\%$ ). Figure 33 shows the forest plot of the analysis.

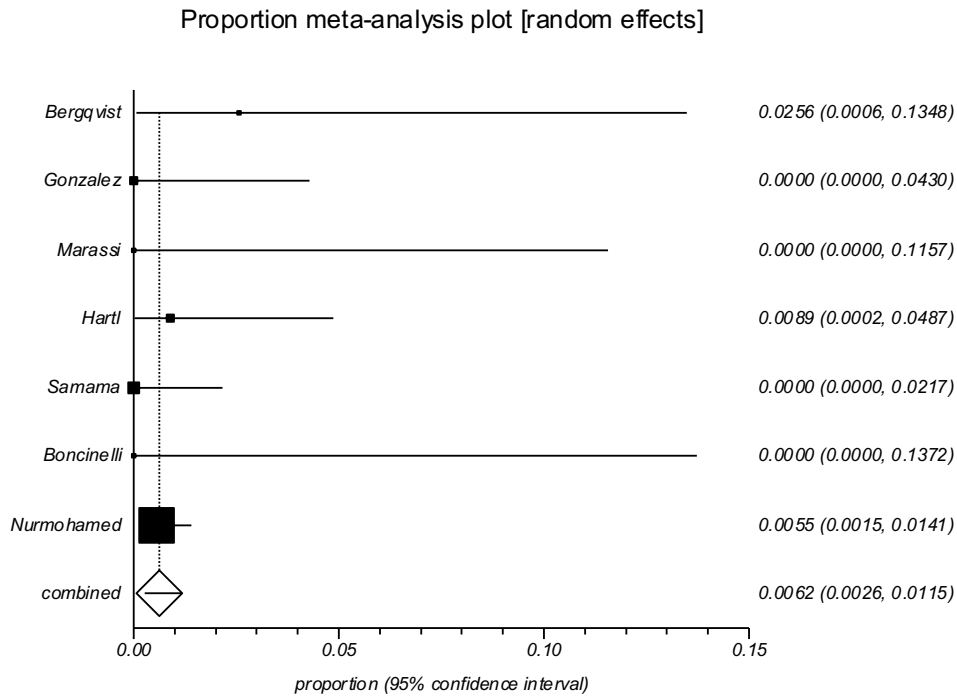
**Figure 33 Forest plot of the pooled proportion of 30 days re-operation rate post major abdominal surgery in patients receiving high dose UFH for 7-10 days post-surgery.**



## Low prophylactic dose of low molecular weight heparin (<4000 IU)

A total of 1183 patients from 7 RCTs were used for this analysis. There were a total of 6 re-operations at 30 days post-surgery corresponding to pooled proportion of 0.62% (95% CI = 0.2571 to 1.15) with no heterogeneity ( $I^2 = 0\%$ ). Figure 34 shows the forest plot of the analysis.

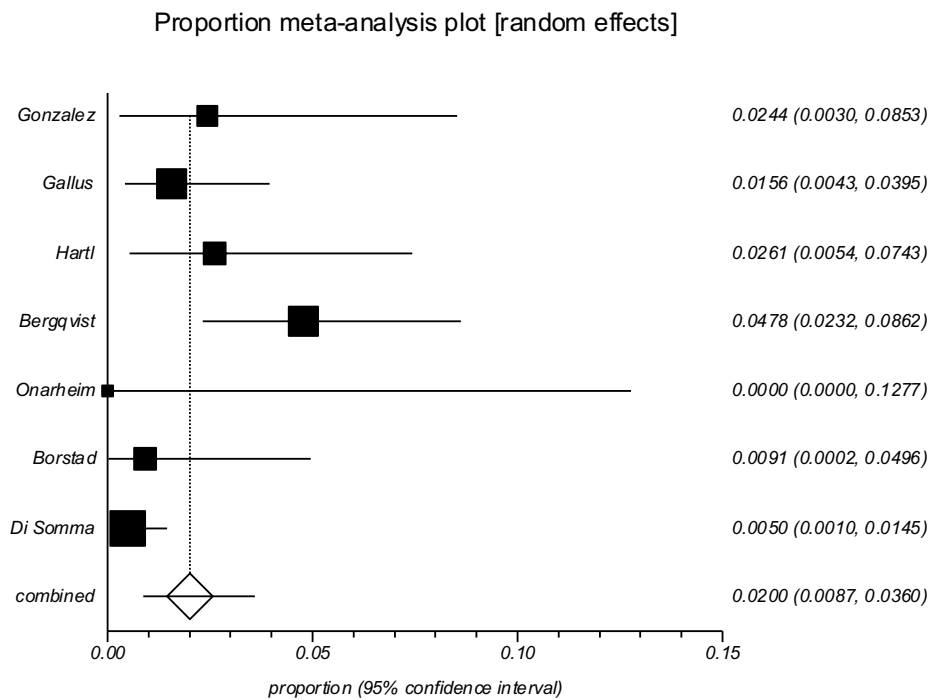
**Figure 34 Forest plot of the pooled proportion for 30 days reoperation rate post major abdominal surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

A total of 1401 patients from 7 RCTs were included in this analysis. There were a total of 23 re-operations at 30 days post-surgery corresponding to pooled proportion of 2.00 (95% CI = 0.87 to 3.60) with moderate heterogeneity ( $I^2 = 63.3\%$ ). Figure 35 shows the forest plot of the analysis.

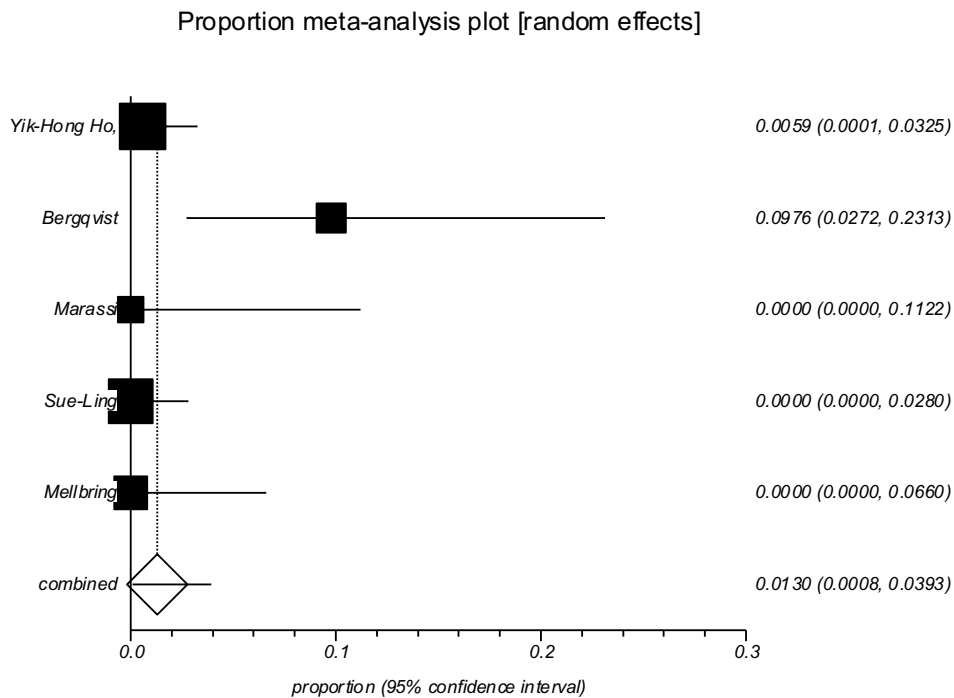
**Figure 35 Forest plot of the pooled proportion for 30 days re-operation rate post major abdominal surgery in patient receiving low dose UFH for 7-10 days post-surgery.**



## **Placebo, non-pharmacological thromboprophylaxis or no treatment**

A total of 425 patients from 5 RCTs were used for this analysis. There were a total of 5 reoperations at 30 days post-surgery corresponding to pooled proportion of 1.30% (95% CI = 0.08 to 3.93) with substantial heterogeneity ( $I^2 = 63.8\%$ ). Figure 36 shows the forest plot of the analysis.

**Figure 36 Forest plot of the pooled proportion 30 days re-operation rate post major abdominal surgery in patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment.**



## **Pooled Proportions of wound infection**

### **Fondaparinux (2.5mg s/c daily)**

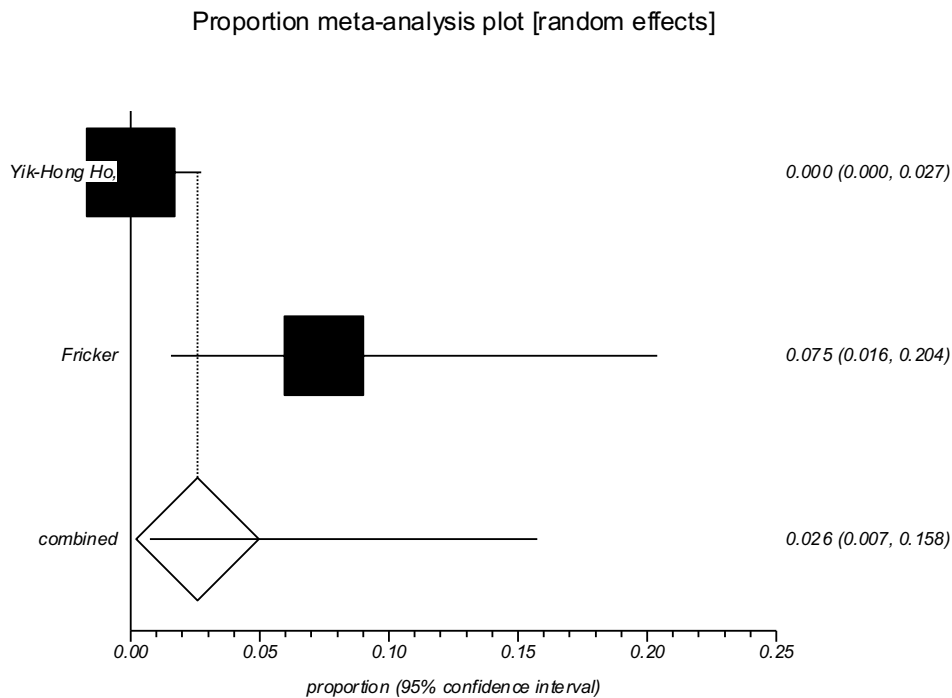
None of the fondaparinux studies reported on wound infection.

### **High thromboprophylactic dose of low molecular weight heparin**

#### **(≥4000 IU)**

A total of 174 patients from 2 RCTs were included in this analysis. There were a total of 3 reported wound infections post-surgery corresponding to pooled proportion of 2.57% (95% CI = 0.74 to 15.75). Figure 37 shows the forest plot of the analysis.

**Figure 37 Forest plot of the pooled proportion for wound infection post major abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery**



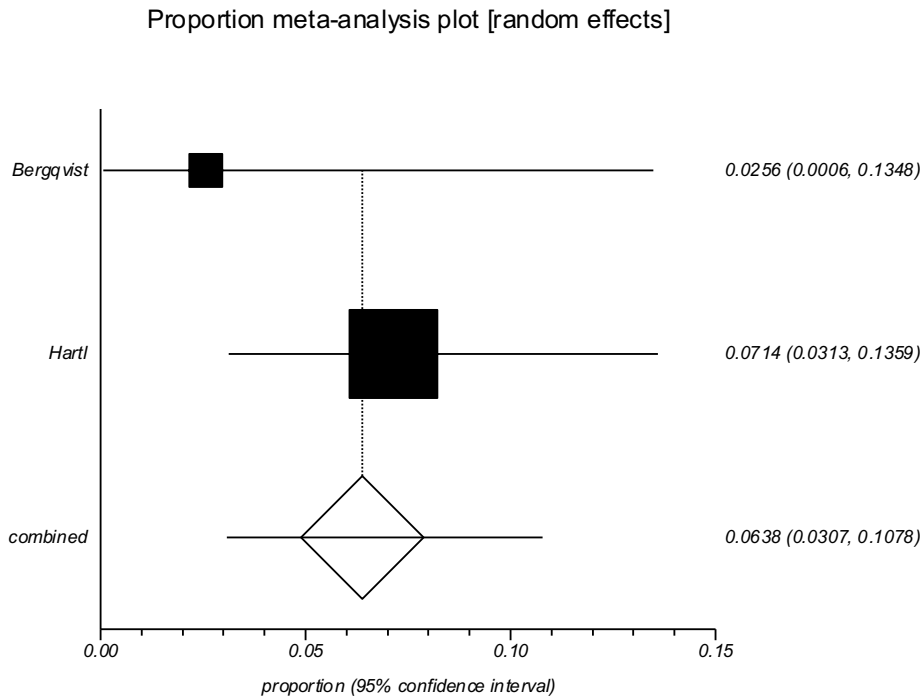
**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

A total of 40 patients from one RCT were used for this analysis. This study reported no wound infection in any of the 40 patients received high dose UFH.

**Low prophylactic dose of low molecular weight heparin (<4000 IU)**

A total of 151 patients from 2 RCTs were used for this analysis. There were a total of 9 wound infections corresponding to pooled proportion 6.38% (95% CI = 3.07 to 10.78). Figure 38 shows the forest plot of the analysis.

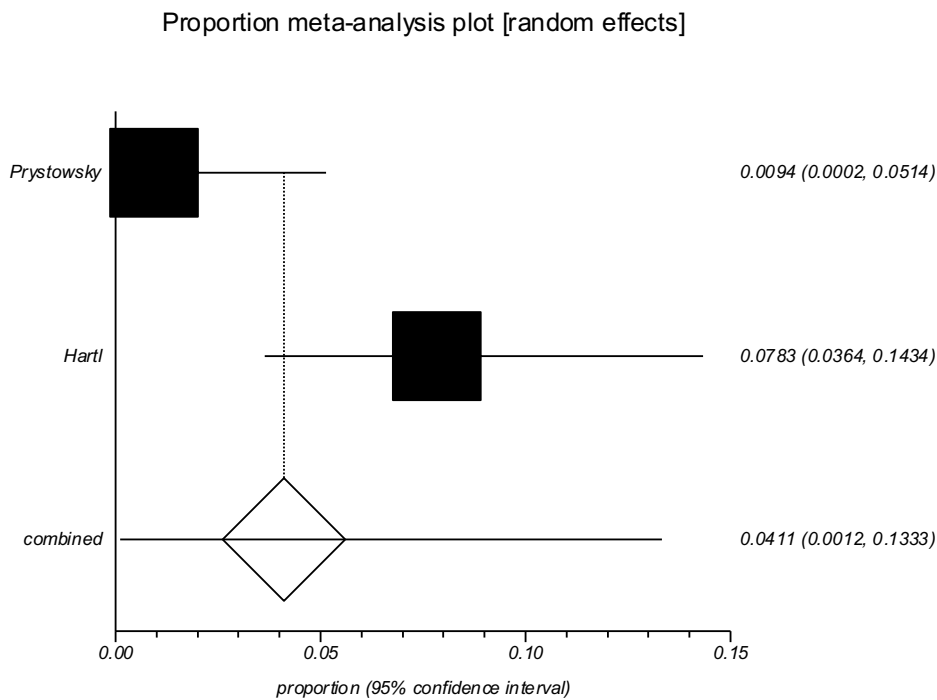
**Figure 38 Forest plot of the pooled proportion for wound infection post major abdominal surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

A total of 221 patients from one RCT and one prospective cohort study were used for this analysis. There were a total of 10 wound infections post-surgery corresponding to pooled proportion of 4.11% (95% CI = 0.12 to 13.33). Figure 39 shows the forest plot of the analysis.

**Figure 39 Forest plot of the pooled proportion for wound infection post major abdominal surgery in patient receiving low dose UFH for 7-10 days post-surgery.**

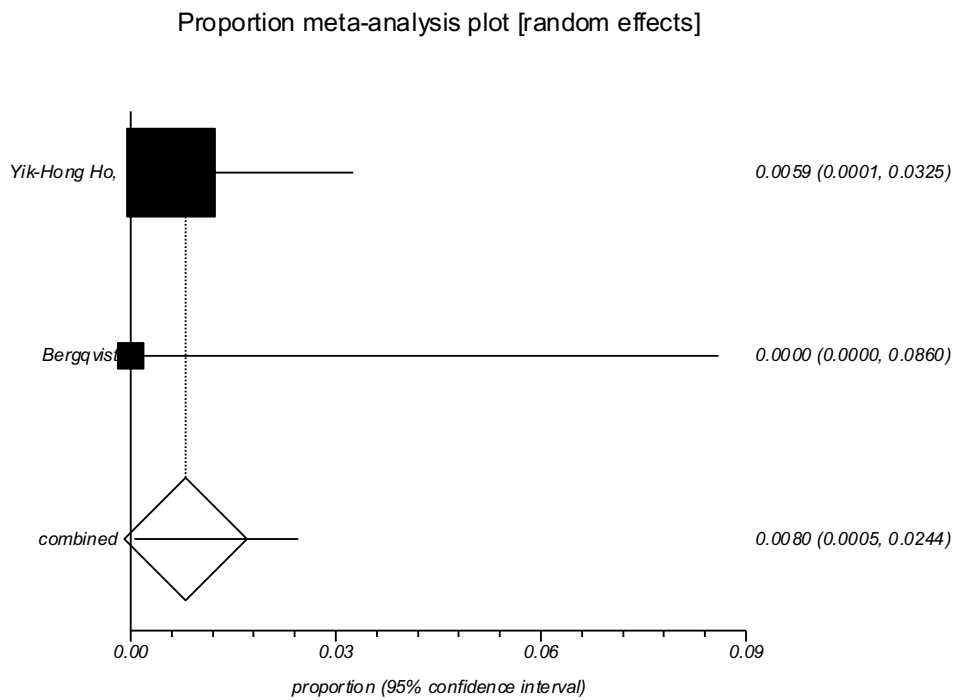


## **Placebo, non-pharmacological thromboprophylaxis or no treatment**

A total of 210 patients from 2 RCTs were used for this analysis. There were a total of 1 wound infection post-surgery corresponding to pooled proportion of 0.80% (95% CI = 0.05 to 2.44).

Figure 40 shows the forest plot of the analysis.

**Figure 40 Forest plot of the pooled proportion for wound infection post major abdominal surgery in patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment.**



## Pooled Proportion of wound oozing

### Fondaparinux (2.5mg s/c daily)

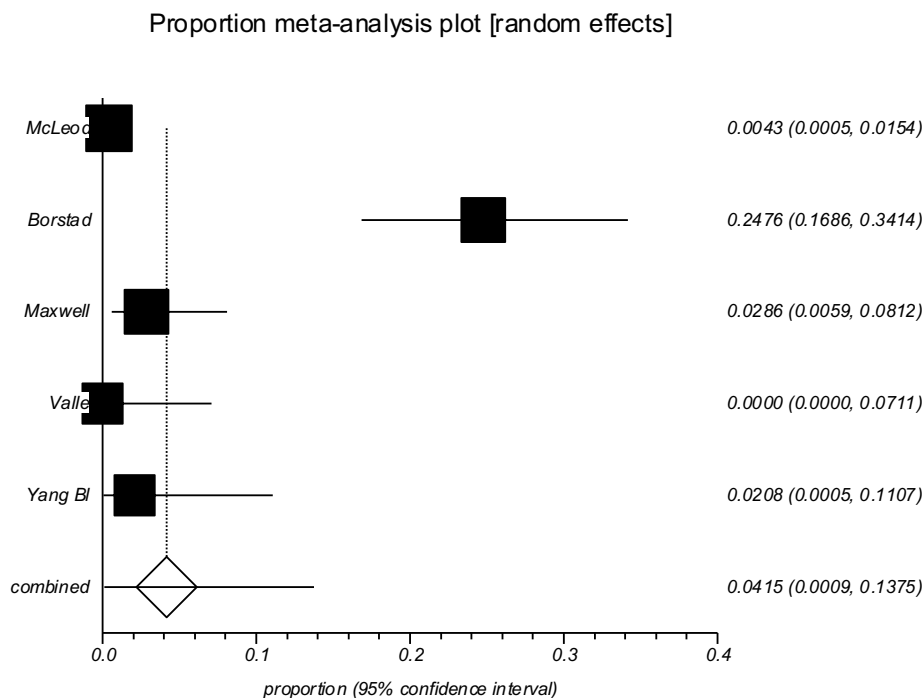
None of the fondaparinux studies reported on wound oozing.

### High thromboprophylactic dose of low molecular weight heparin

#### (≥4000 IU)

A total of 776 patients from 5 RCTs were included in this analysis. There were a total 32 wound oozing events post-surgery corresponding to pooled proportion of 4.15% (95% CI = 0.09 to 13.75) with considerable heterogeneity ( $I^2 = 94.5\%$ ). Figure 41 shows the forest plot of the analysis.

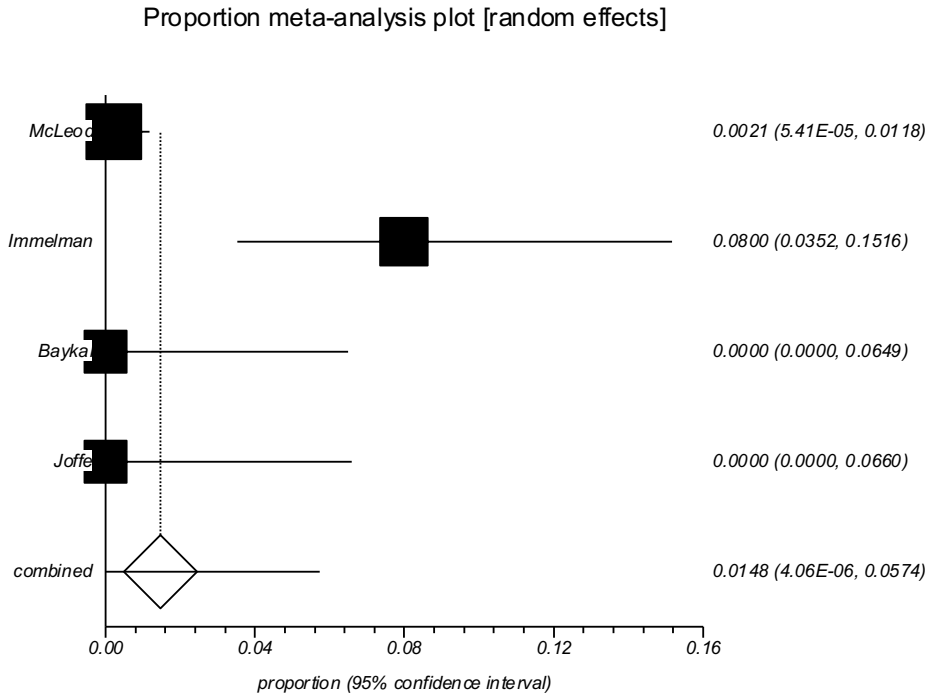
**Figure 41 Forest plot of the pooled proportion for wound oozing post major abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery**



**High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

A total of 677 patients from 4 RCTs were used for this analysis. There were a total of 9 wound oozing events post-surgery corresponding to pooled proportion of 1.48% (95% CI = 0.0004 to 5.74) with a considerable heterogeneity ( $I^2 = 84.4\%$ ). Figure 42 shows the forest plot of the analysis.

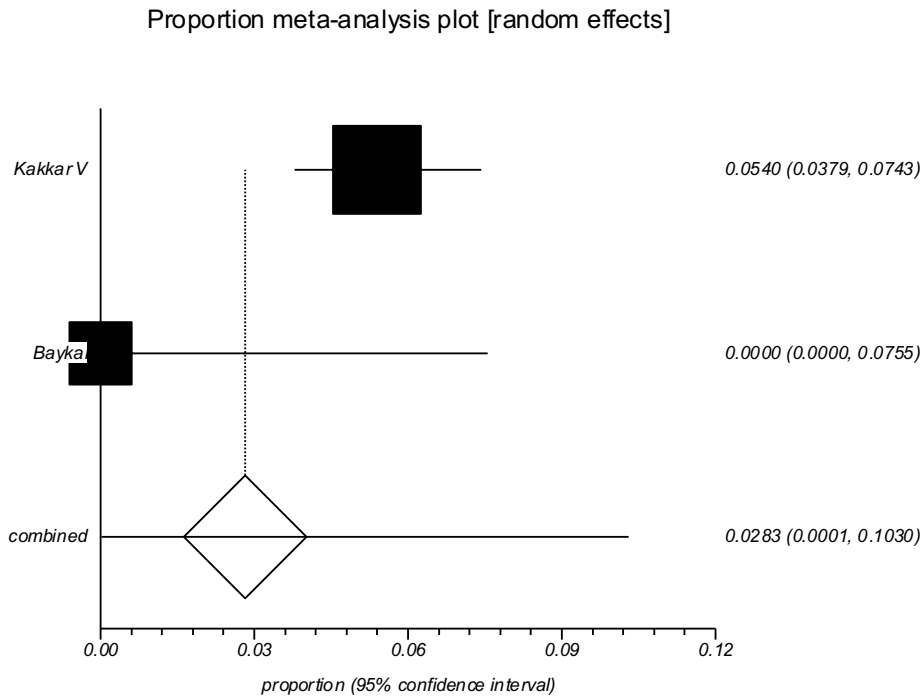
**Figure 42 Forest plot of the pooled proportion of wound oozing events post major abdominal surgery in patients receiving high dose UFH for 7-10 days post-surgery.**



## **Low prophylactic dose of low molecular weight heparin (<4000 IU)**

A total of 695 patients from 2 RCTs were included in this analysis. There were a total of 35 wound oozing events post-surgery corresponding to pooled proportion of 2.83% (95% CI = 0.01 to 0.030). Figure 43 shows the forest plot of the analysis.

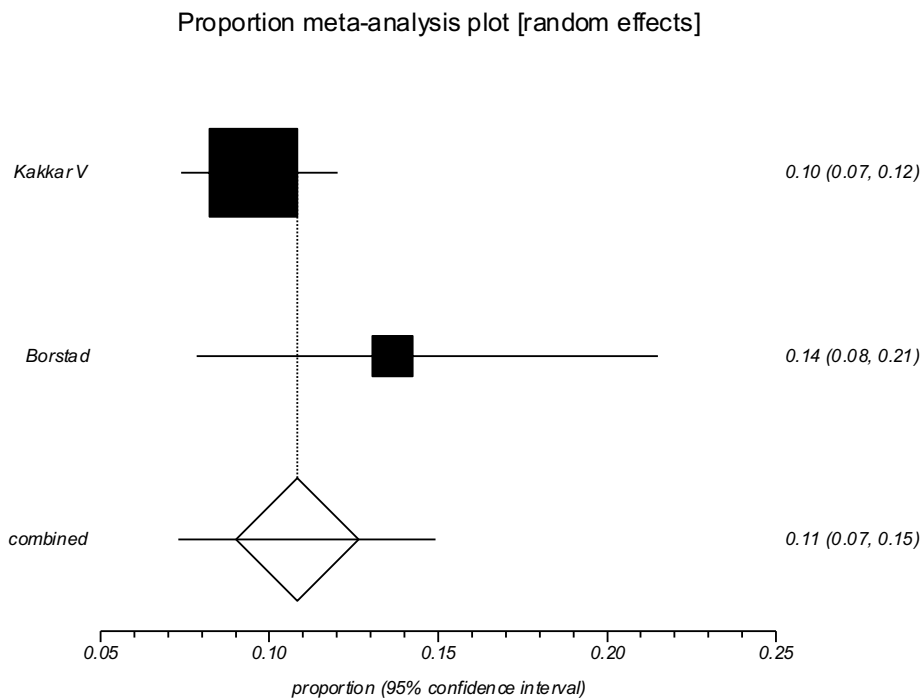
**Figure 43 Forest plot of the pooled proportion for wound oozing events post major abdominal surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**



**Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)**

A total of 773 patients from 2 RCT were used for this analysis. There were a total of 78 wound oozing events post-surgery corresponding to pooled proportion of 10.81 (95% CI = 7.29 to 14.92). Figure 44 shows the forest plot of the analysis.

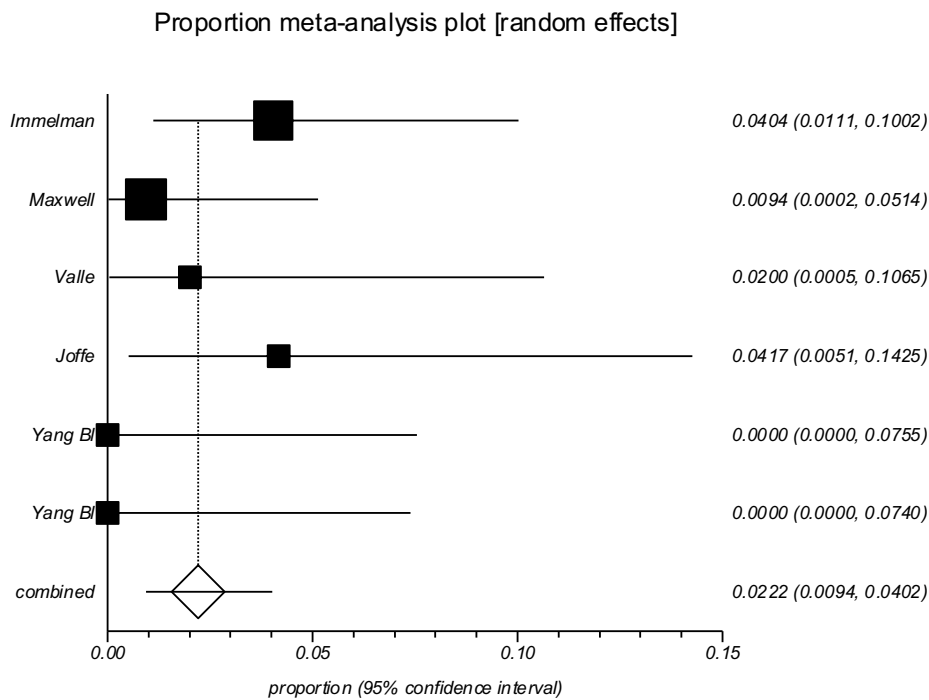
**Figure 44 Forest plot of the pooled proportion for wound oozing events post major abdominal surgery in patient receiving low dose UFH for 7-10 days post-surgery.**



## **Placebo, non-pharmacological thromboprophylaxis or no treatment**

A total of 398 patients from 6 RCTs were used for this analysis. There were a total of 8 wound oozing events post-surgery corresponding to pooled proportion of 2.22% (95% CI = 0.94 to 4.02) with low heterogeneity ( $I^2 = 11.8\%$ ). Figure 45 shows the forest plot of the analysis.

**Figure 45 Forest plot of the pooled proportion for wound oozing events post major abdominal surgery in patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment.**



## ***Appendix 6: Subgroup Analysis for Laparoscopic Surgery***

### ***Fondaparinux (2.5mg s/c daily)***

None of the fondaparinux studies reported on laparoscopic surgery.

### ***High thromboprophylactic dose of low molecular weight heparin***

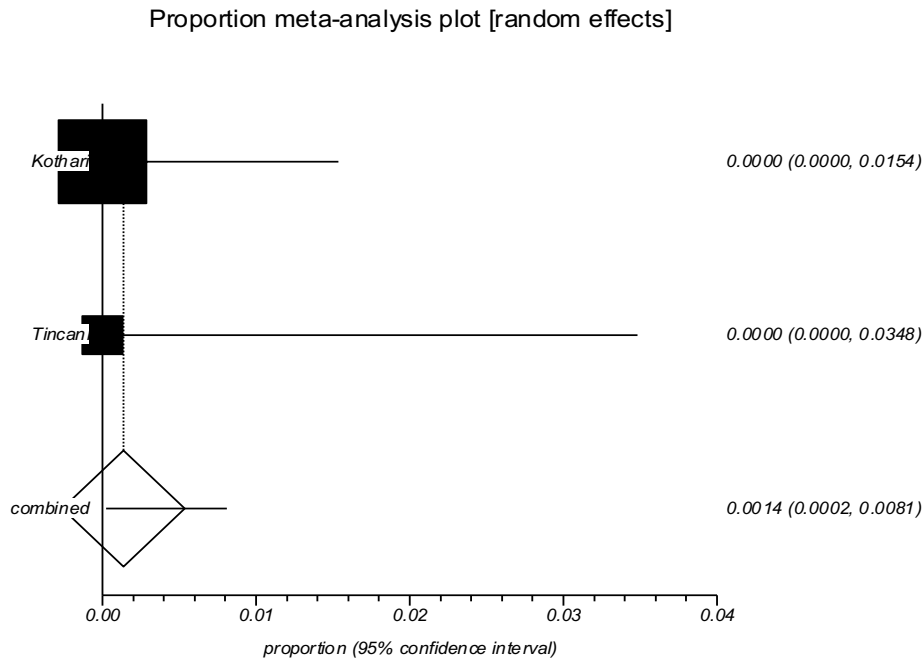
#### ***(≥4000 IU)***

There was one RCT and one prospective cohort study reported in laparoscopic surgery were used for this analysis.

## **Pooled proportion of VTE, DVT and PE**

A total of 342 patients from the two studies were included in this analysis. The two studies reported no VTE, DVT or PE events. This was translated to pooled proportion of 0.14% (95% CI = 0.02 to 0.81). Figure 46 shows the forest plot of the analysis.

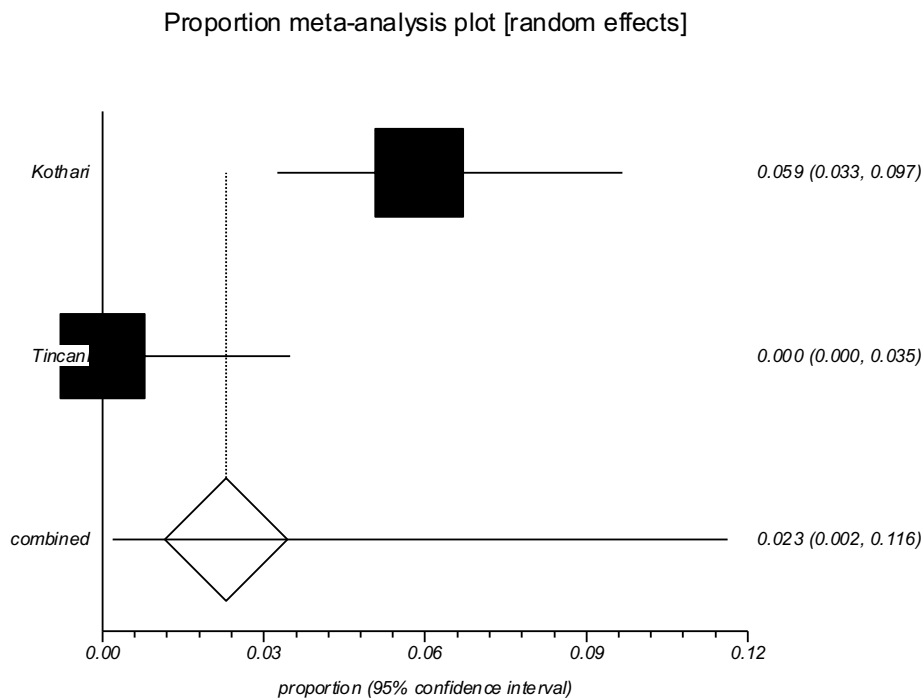
**Figure 46 Forest plot of the pooled proportion for VTE post major laparoscopic abdominal surgery in patient receiving high dose LMWH for 7-10 days post laparoscopic surgery.**



## **Pooled proportion of major bleeding events**

A total of 342 patients from the two studies used for this analysis. There were a total of 14 major bleeding events post-surgery corresponding to pooled proportion of 2.30 (95% CI = 0.19 to 11.63). Figure 47 shows the forest plot of the analysis.

**Figure 47 Forest plot of the pooled proportion for major bleeding post major laparoscopic abdominal surgery in patient receiving high dose LMWH for 7-10 days post laparoscopic surgery**



## **High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)**

Only one prospective cohort study (*Kothari*) included patients only undergoing laparoscopic surgery. There were a total of 238 patients received high doses UFH. There was one event of VTE (one PE, no DVT) and 3 major bleeding events.

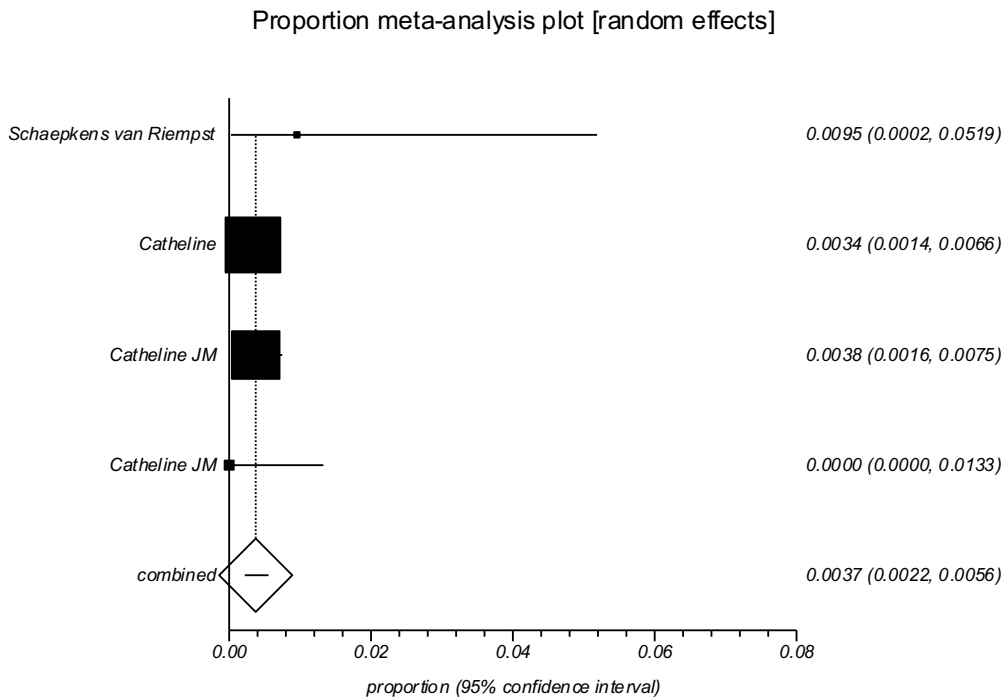
## ***Low prophylactic dose of low molecular weight heparin (<4000***

***IU)***

### ***Pooled proportion of VTE and DVT***

A total of 4873 patients from 4 prospective cohort studies were used for this analysis. There were a total of 17 VTE and DVT events corresponding to pooled proportion of 0.37% (95% CI = 0.22 to 0.56) with no heterogeneity ( $I^2 = 0\%$ ). Figure 48 shows the forest plot of the analysis.

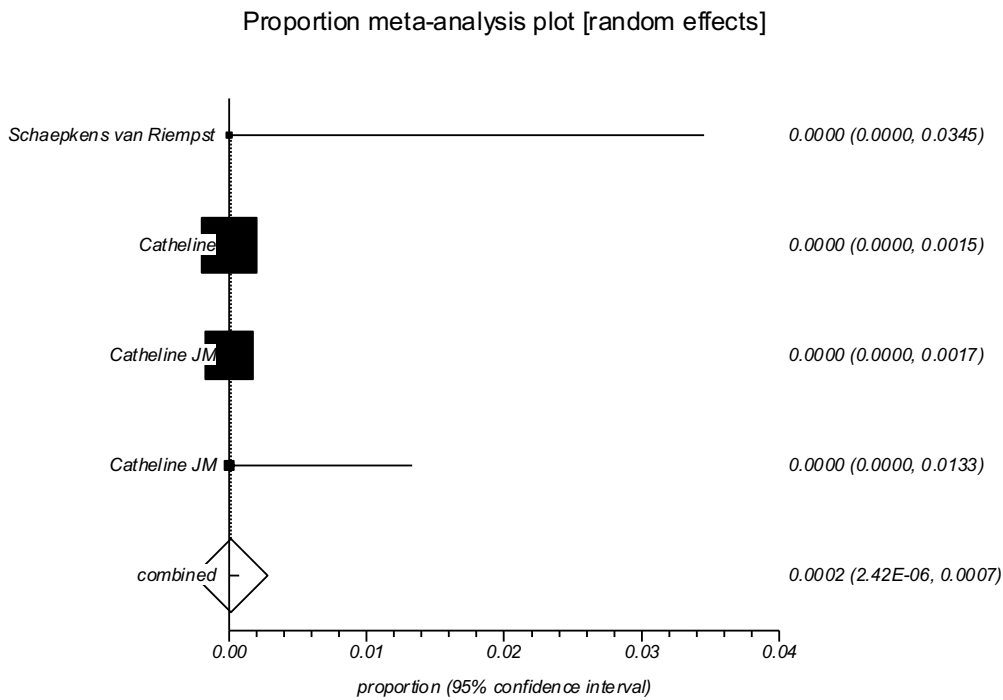
***Figure 48 Forest plot of the pooled proportion of VTE and DVT events post major laparoscopic abdominal surgery in patient receiving low dose LMWH for 7-10 days post-surgery.***



## **Pooled proportion of PE**

A total of 4873 patients from 4 prospective cohort studies were used for this analysis. There were no PE events corresponding to pooled proportion 0.02 (95% CI = 0.0002 to 0.07) with no heterogeneity ( $I^2 = 0\%$ ). Figure 49 shows the forest plot of the analysis.

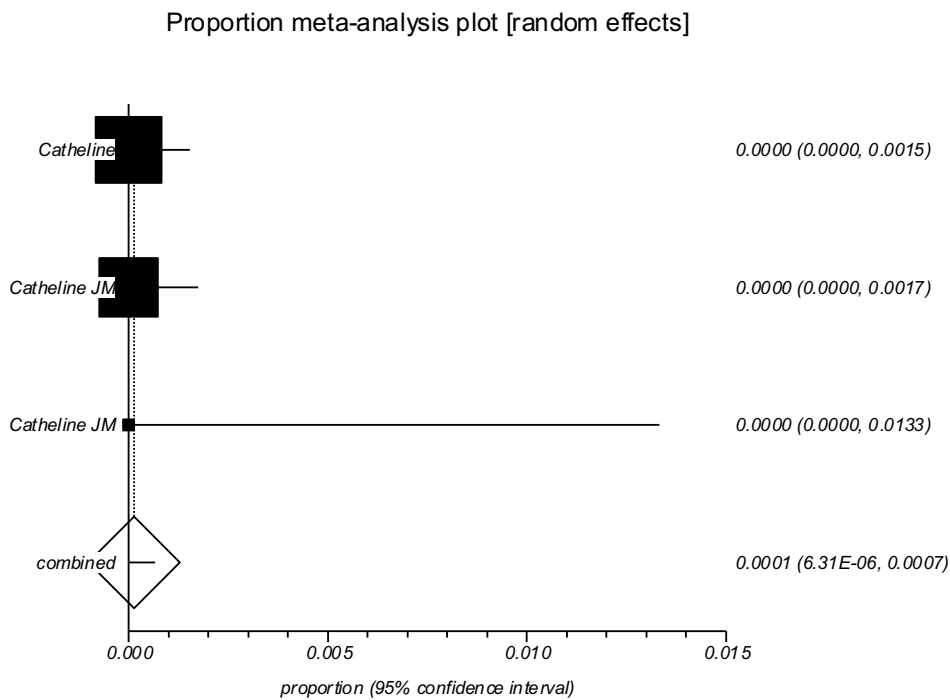
**Figure 49 Forest plot of the pooled proportion of PE events post major laparoscopic abdominal surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**



## **Pooled proportion of major bleeding**

A total of 4768 patients from 3 prospective cohort studies were used for this analysis. There were no major bleeding events corresponding to pooled proportion 0.01 (95% CI = 0.0006 to 0.07) with no heterogeneity ( $I^2 = 0\%$ ). Figure 50 shows the forest plot of the analysis.

**Figure 50 Forest plot of the pooled proportion of major bleeding events post major laparoscopic abdominal surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**

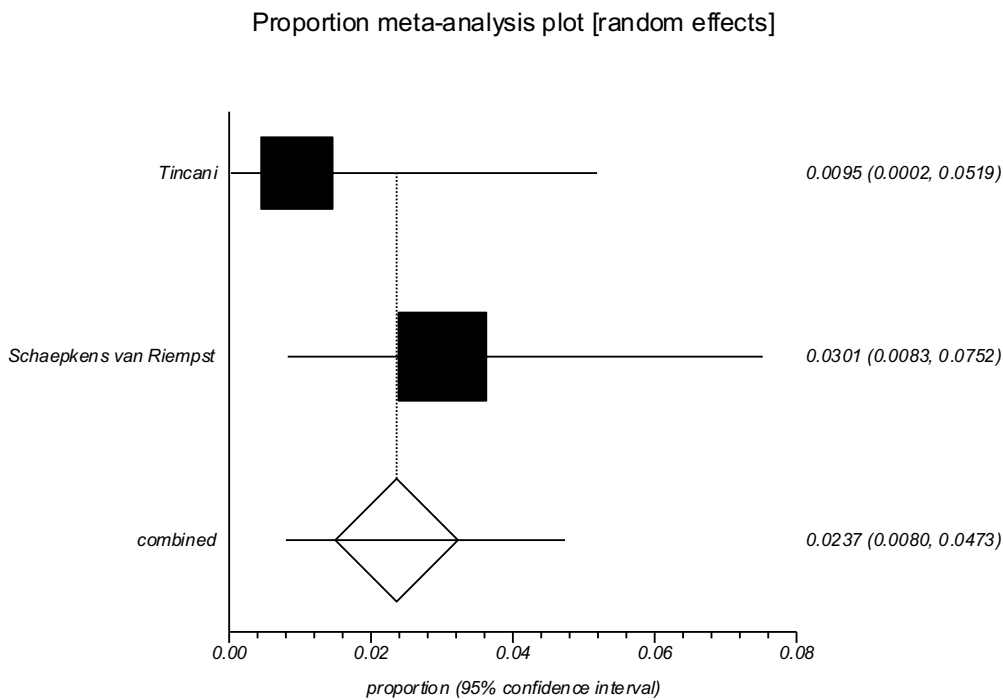


## ***Placebo, non-pharmacological thromboprophylaxis or no treatment***

### **Pooled proportion of VTE and DVT**

A total of 238 patients from one RCTs and one prospective cohort study were used for this analysis. There were a total of 5 VTE and DVT events post laparoscopic surgery corresponding to pooled proportion of 2.37 (95% CI = 0.80 to 4.73). Figure 51 shows the forest plot of the analysis.

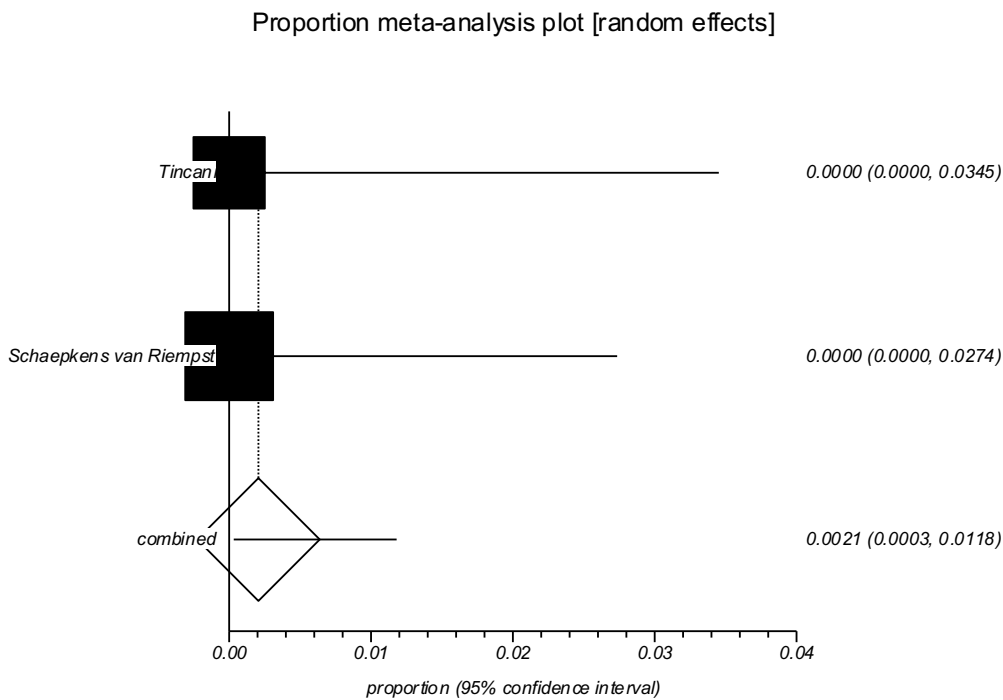
***Figure 51 Forest plot of the pooled proportion for VTE and DVT events post major laparoscopic abdominal surgery in patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment.***



## **Pooled proportion of PE**

A total of 238 patients from one RCTs and one prospective cohort study were used for this analysis. There were no PE events post laparoscopic surgery corresponding to pooled proportion of 0.21 (95% CI = 0.03 to 1.18) Figure 52 shows the forest plot of the analysis.

**Figure 52 Forest plot of the pooled proportion for PE events post major laparoscopic abdominal surgery in patients receiving placebo, non-pharmacological thromboprophylaxis or no treatment.**



## **Pooled proportion of major bleeding**

A total of 105 patients from one RCT were used for this analysis. There were no major bleeding events post laparoscopic surgery reported in the study.

## ***Appendix 7: Subgroup Analysis for Bariatric Surgery Surgery***

### ***Fondaparinux (2.5mg s/c daily)***

None of the fondaparinux studies reported on bariatric surgery.

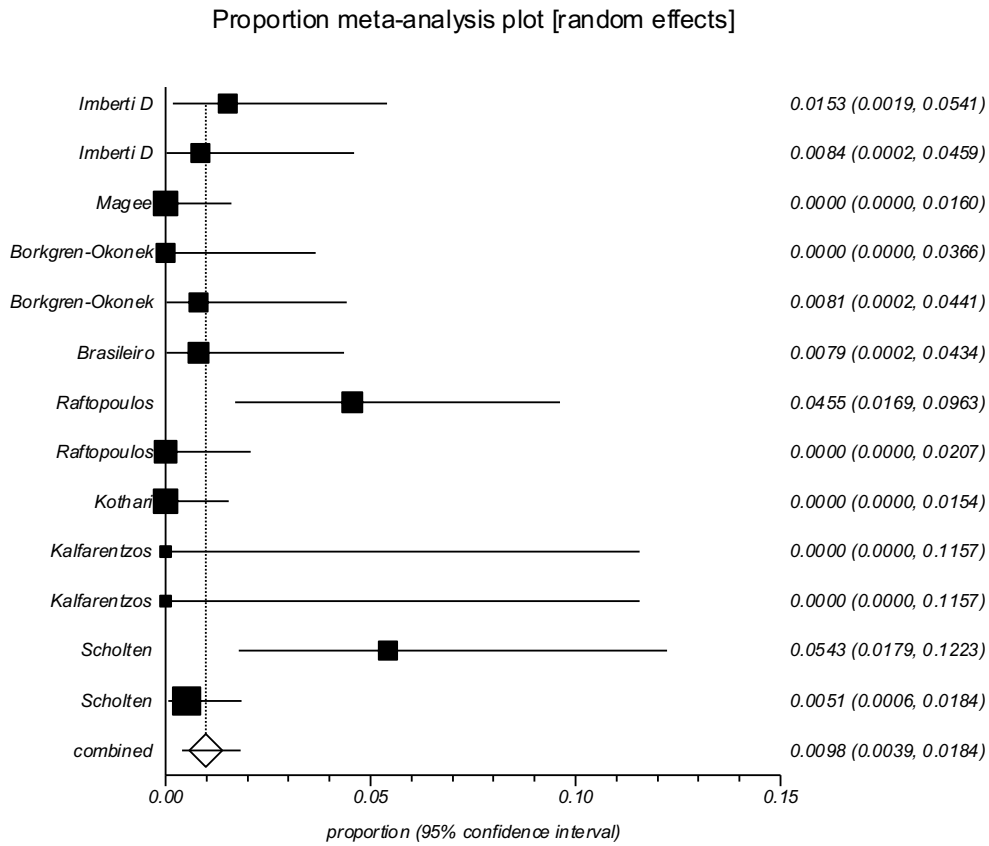
### ***High thromboprophylactic dose of low molecular weight heparin***

#### ***(≥4000 IU)***

#### ***Pooled proportion of VTE***

A total of 1915 patients from 4 RCTs and 9 prospective cohort studies were used for this analysis. There were a total 18 VTE events post-surgery corresponding to pooled proportion of 0.98% (95% CI = 0.39 to 1.84) with moderate heterogeneity ( $I^2 = 58.6\%$ ). Figure 53 shows the forest plot of the analysis.

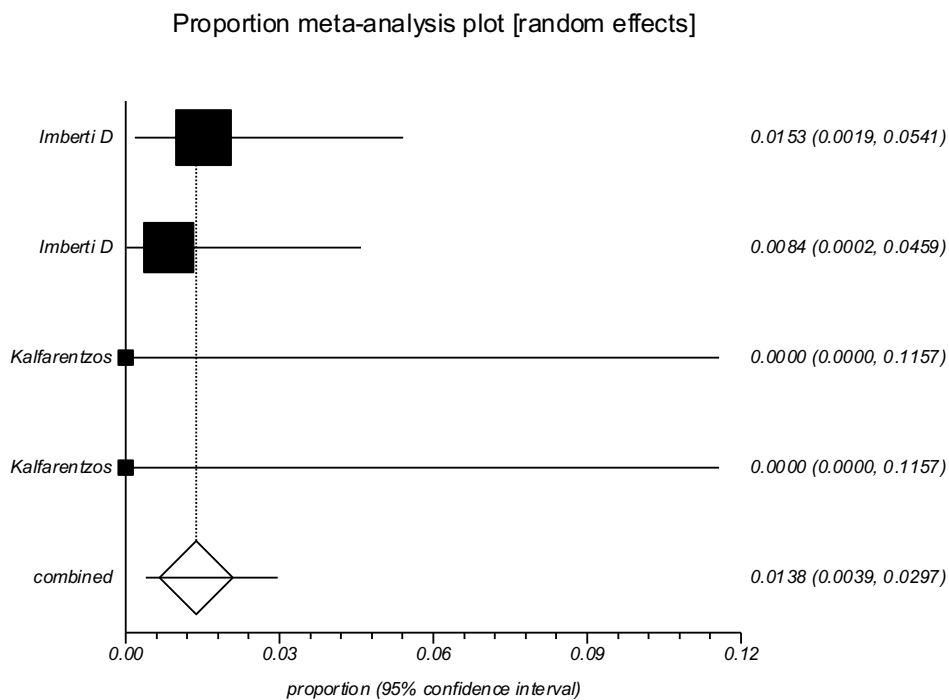
**Figure 53 Forest plot of the pooled proportion for VTE post major bariatric abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery.**



## **Pooled proportion of VTE using only RCTs**

A total of 310 patients from 4 RCTs (4 treatment arms of 2 RCTs) were used for this analysis. There were a total 3 VTE events post-surgery corresponding to pooled proportion of 1.38% (95% CI=0.39 to 2.97) with no heterogeneity ( $I^2 = 0\%$ ). Figure 54 shows the forest plot of the analysis.

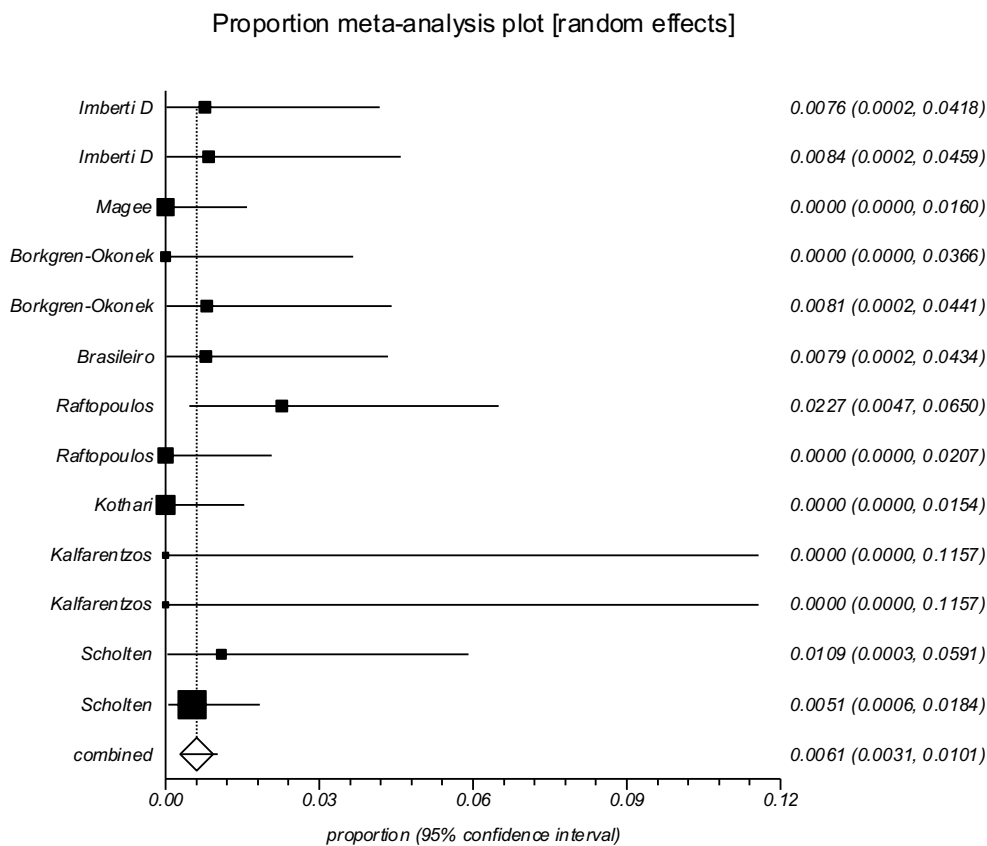
**Figure 54 Forest plot of the pooled proportion for VTE post major bariatric abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery. (RCT only)**



## **Pooled proportion of DVT**

A total of 1915 patients from 4 RCTs and 9 prospective cohort studies were used for this analysis. There were a total 10 DVT events post bariatric surgery corresponding to pooled proportion of 0.61% (95% CI = 0.31 to 1.01) with no heterogeneity ( $I^2 = 0\%$ ). Figure 55 shows the forest plot of the analysis.

**Figure 55 Forest plot of the pooled proportion for DVT post major bariatric abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery**

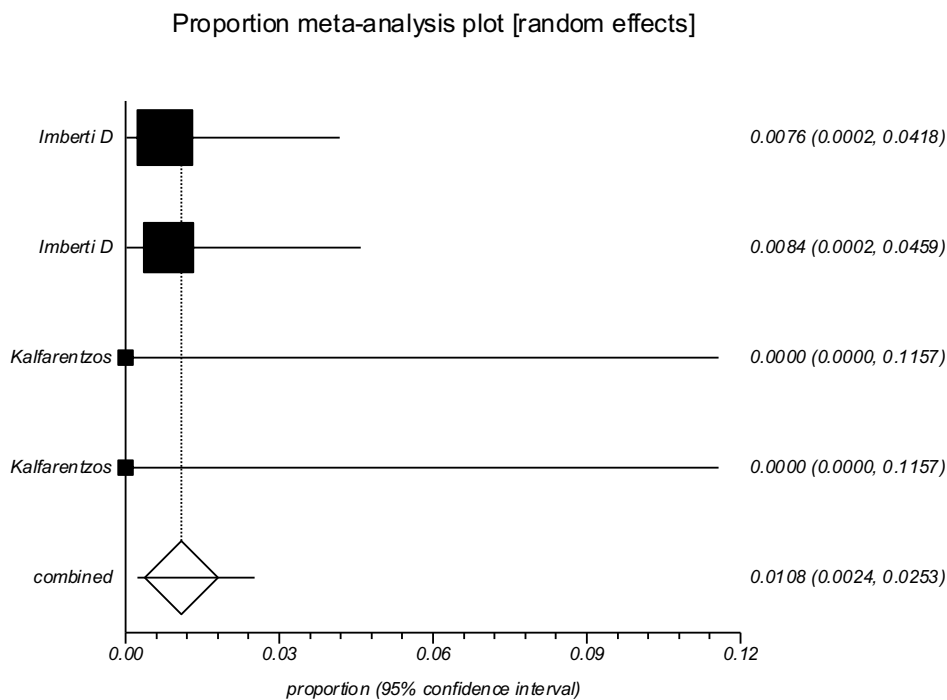


## **Pooled proportion of DVT using only RCTs**

A total of 310 patients from 4 RCTs (4 treatment arms of 2 RCTs) were used for this analysis.

There were a total 2 DVT events post-surgery corresponding to pooled proportion of 1.08 % (95% CI= 0.24 to 2.53) with no heterogeneity ( $I^2 = 0\%$ ). Figure 56 shows the forest plot of the analysis.

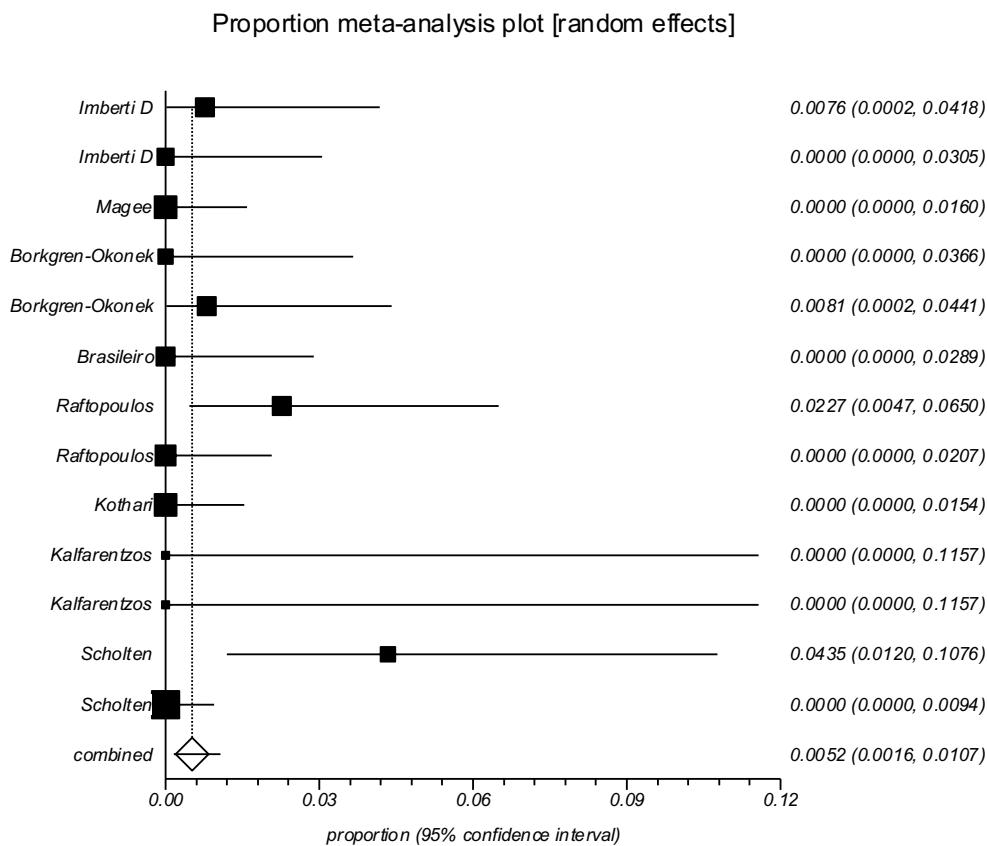
**Figure 56 Forest plot of the pooled proportion for DVT post major bariatric abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery. (RCT only)**



## **Pooled proportion of PE**

A total of 1915 patients from 4 RCTs and 9 prospective cohort studies were used for this analysis. There were a total 9 PE events post bariatric surgery corresponding to pooled proportion 0.52% (95% CI = 0.16 to 1.07) with moderate heterogeneity ( $I^2 = 44.3\%$ ). Figure 57 shows the forest plot of the analysis.

**Figure 57 Forest plot of the pooled proportion for PE post major bariatric abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery**

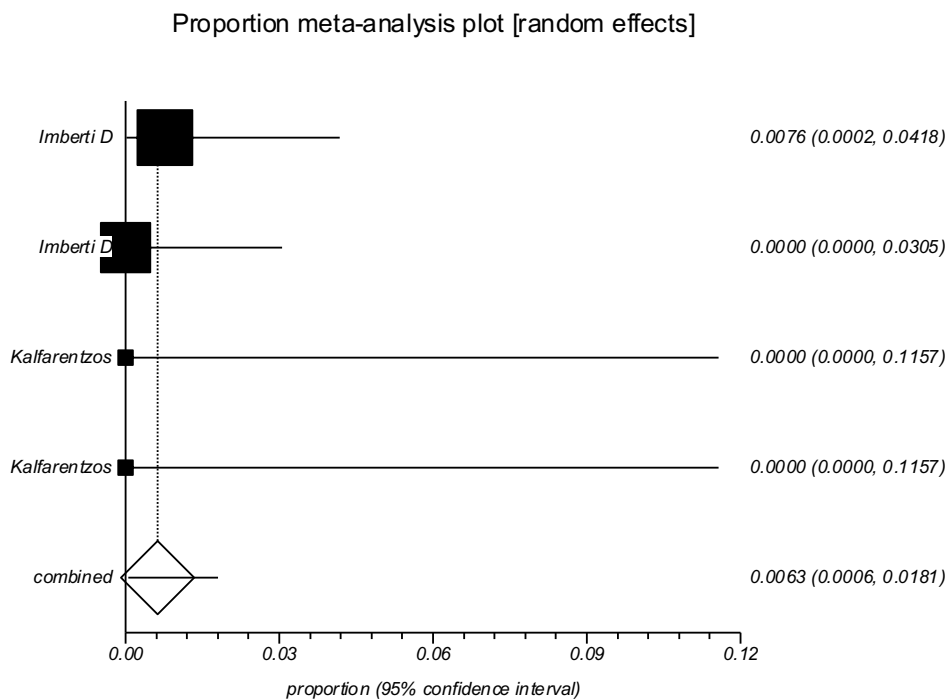


## **Pooled proportion of DVT using only RCTs**

A total of 310 patients from 4 RCTs (4 treatment arms of 2 RCTs) were used for this analysis.

There were a total 1 PE event post-surgery corresponding to pooled proportion of 0.63 % (95% CI= 0.06 to 1.81) with no heterogeneity ( $I^2 = 0\%$ ). Figure 58 shows the forest plot of the analysis.

**Figure 58 Forest plot of the pooled proportion for PE post major bariatric abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery. (RCT only)**

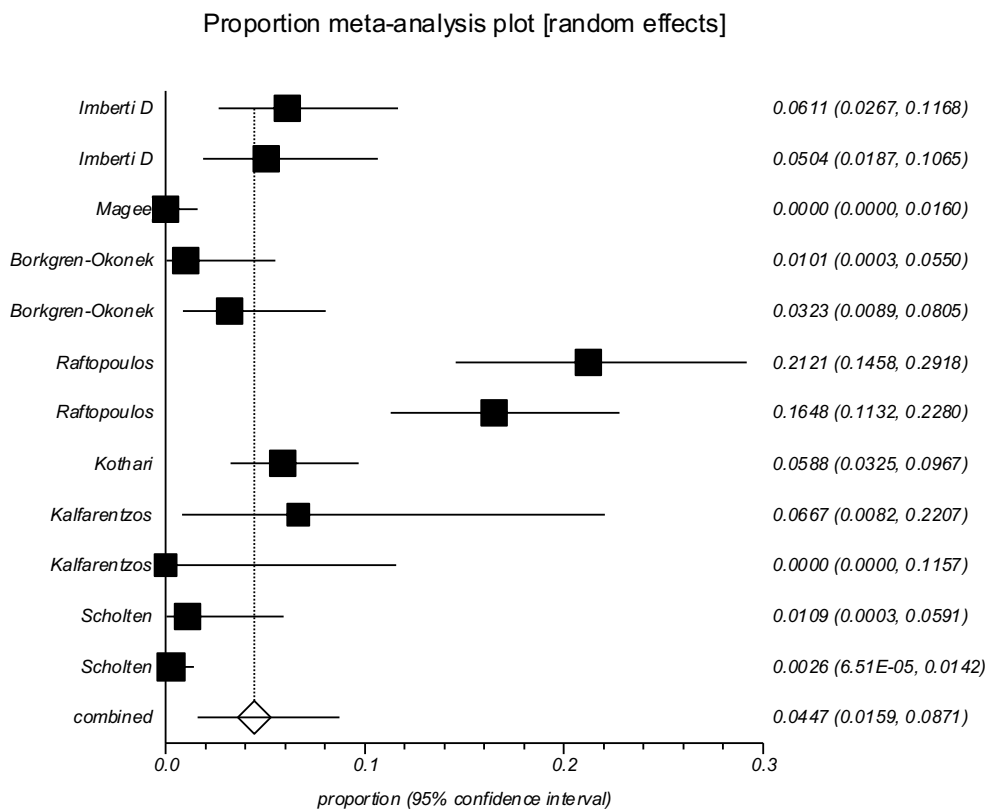


## **Pooled proportion of major bleeding**

A total of 1789 patients from 4 RCTs and 8 prospective cohort studies were used for this analysis. There were a total 94 major bleeding events post bariatric surgery corresponding to pooled proportion 4.47% (95% CI = 1.59 to 8.71) with considerable heterogeneity ( $I^2 = 92.3\%$ ).

Figure 59 shows the forest plot of the analysis.

**Figure 59 Forest plot of the pooled proportion for major bleeding post major bariatric abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery**

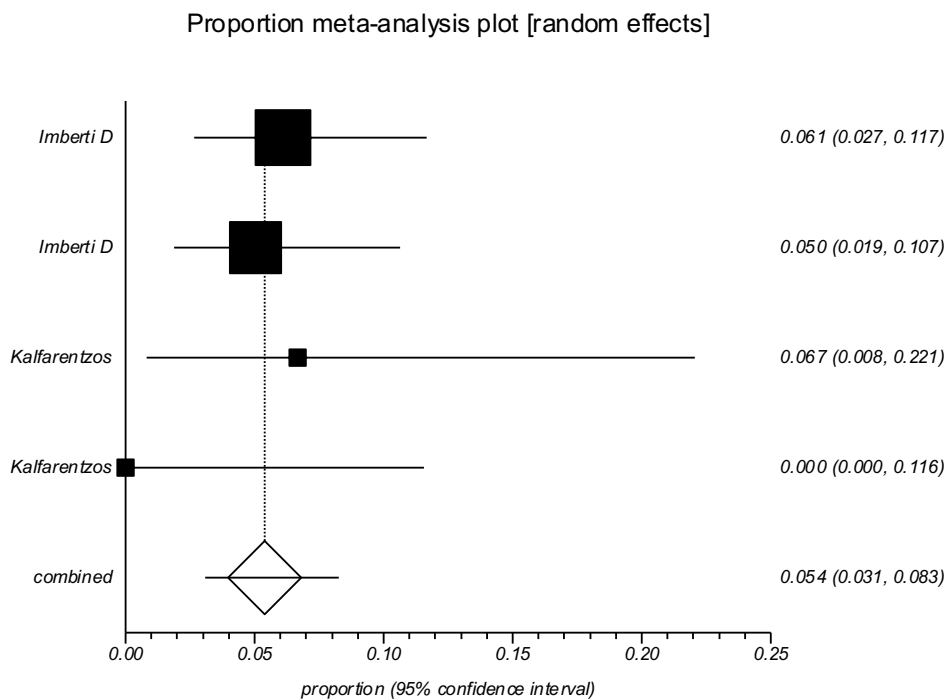


## **Pooled proportion of major bleeding events using only RCTs**

A total of 310 patients from 4 RCTs (4 treatment arms of 2 RCTs) were used for this analysis.

There were a total 16 major bleeding event post-surgery corresponding to pooled proportion of = 5.38% (95% CI=3.08 to 8.27) with negligible heterogeneity ( $I^2 = 5.3\%$ ). Figure 60 shows the forest plot of the analysis.

**Figure 60 Forest plot of the pooled proportion for PE post major bariatric abdominal surgery in patient receiving high dose LMWH for 7-10 days post-surgery. (RCT only)**



***High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)***

Only one prospective cohort study (*Kothari*) included only bariatric surgery. There were a total of 238 patients received high doses UFH. There was one event of VTE (one PE, no DVT) and 3 major bleeding events.

***Low prophylactic dose of low molecular weight heparin (<4000 IU)***

None of the bariatric surgery studies used low dose LMWH.

***Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)***

Only one prospective cohort study (*Prystowsky*) included only bariatric surgery and used low dose UFH. There were a total of 106 patients received low doses UFH. There were 3 event of VTE (0 PE, 3 DVT) and 2 major bleeding events.

***Placebo, non-pharmacological thromboprophylaxis or no treatment***

None of the bariatric surgery studies used placebo, non-pharmacological thromboprophylaxis alone or no treatment

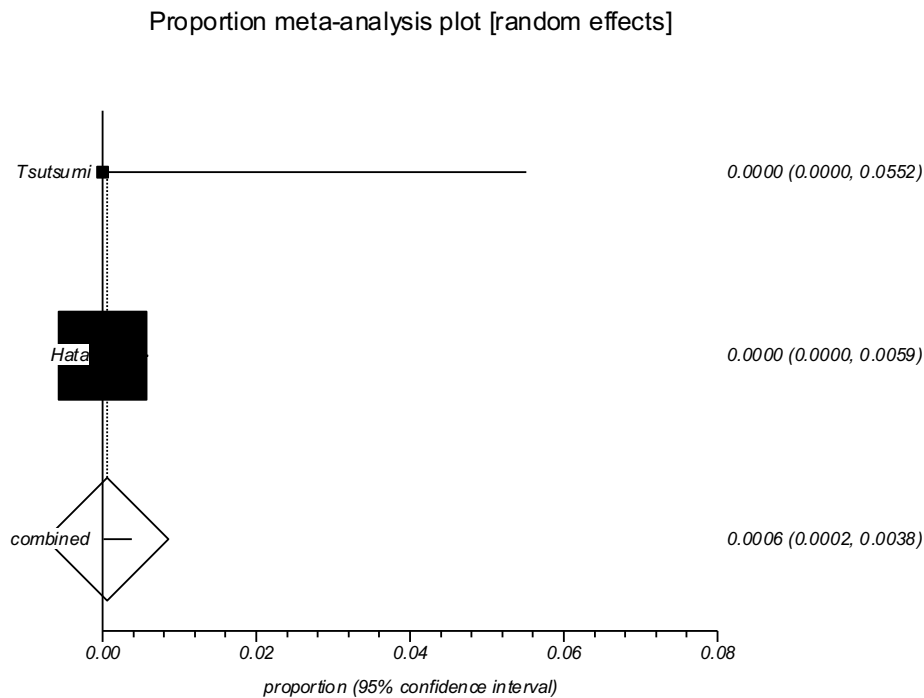
## Appendix 8: Subgroup Analysis for Bariatric Surgery Surgery

### Fondaparinux (2.5mg s/c daily)

#### Pooled proportion of VTE

A total of 684 patients from one RCT and one prospective cohort study were used for this analysis. There were no VTE events corresponding to pooled proportion of 0.06% (95% CI = 0.02 to 0.38). Figure 61 shows the forest plot of the analysis.

**Figure 61 Forest plot of the pooled proportion of the venous thromboembolic events post major abdominal cancer surgery in patient receiving Fondaparinux for 7-10 days post-surgery.**



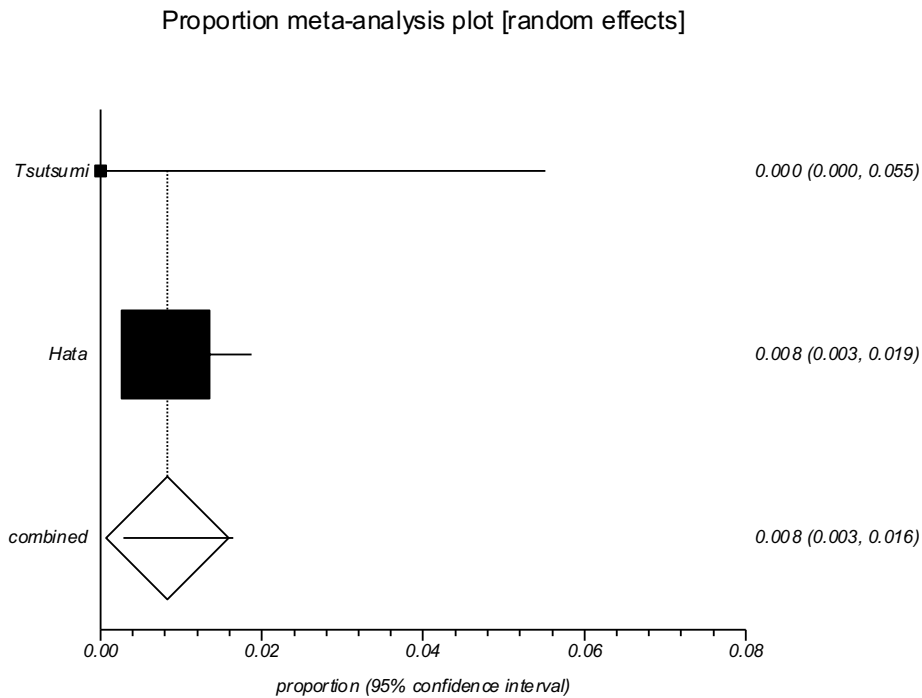
### **Pooled proportion of DVT and PE**

Only one prospective cohort study (*Hata*) included in this analysis. There were a total of 619 patients received fondaparinux post major abdominal surgeries. There were no DVT or PE events reported.

### **Pooled proportion of major bleeding**

A total of 684 patients from one RCT and one prospective cohort study were used for this analysis. There were 5 major bleeding events corresponding to pooled proportion of 0.83% (95% CI = 0.29 to 1.64) Figure 62 shows the forest plot of the analysis.

**Figure 62 Forest plot of the pooled proportion of major bleeding events post major abdominal cancer surgery in patient receiving Fondaparinux for 7-10 days post-surgery**

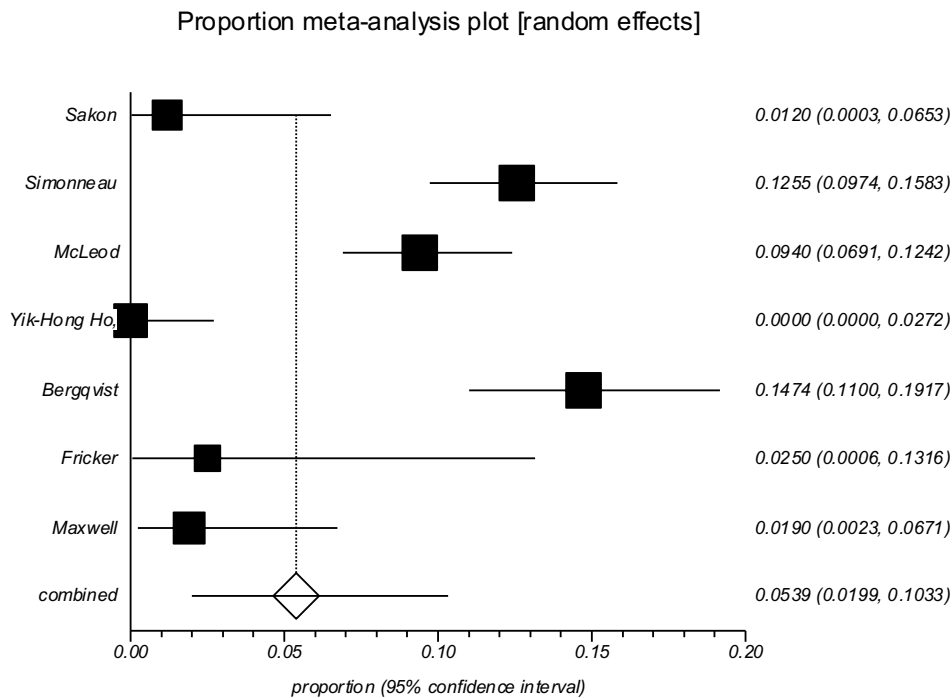


## ***High thromboprophylactic dose of low molecular weight heparin (≥4000 IU)***

### **Pooled proportion of VTE**

A total of 1628 patients from 7 RCTs were used for this analysis. There were a total 155 VTE events post cancer surgery corresponding to pooled proportion of 5.39% (95% CI = 1.99 to 10.33) with considerable heterogeneity ( $I^2 = 92.1\%$ ). Figure 63 shows the forest plot of the analysis.

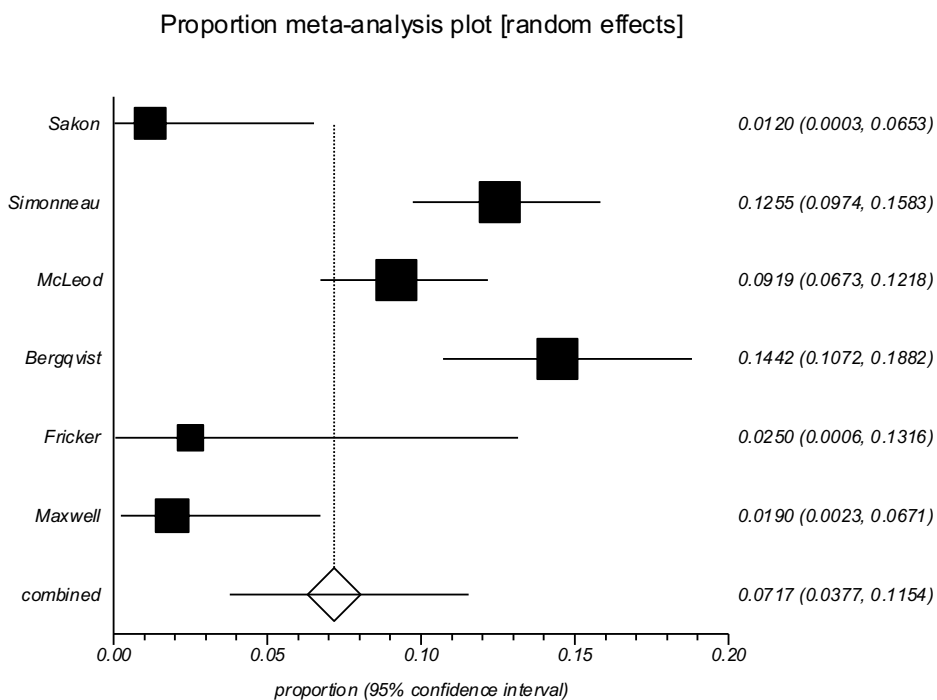
***Figure 63 Forest plot of the pooled proportion for VTE post major abdominal cancer surgery in patient receiving high dose LMWH for 7-10 days post-surgery.***



## **Pooled proportion of DVT**

A total of 1494 patients from 6 RCTs were used for this analysis. There were a total 153 DVT events post cancer surgery corresponding to pooled proportion of 7.17% (95% CI =3.77 to 11.54) with considerable heterogeneity ( $I^2 = 86.3\%$ ). Figure 64 shows the forest plot of the analysis.

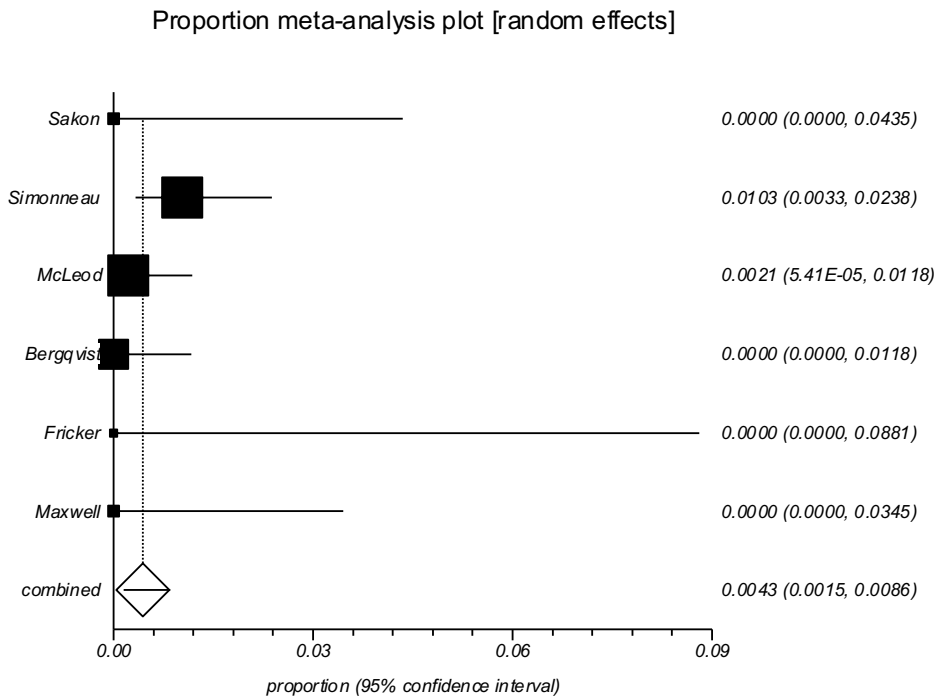
**Figure 64 Forest plot of the pooled proportion for DVT post major abdominal cancer surgery in patient receiving high dose LMWH for 7-10 days post-surgery.**



## **Pooled proportion of PE**

A total of 1494 patients from 6 RCTs were used for this analysis. There were a total 6 PE events post cancer surgery corresponding to pooled proportion of 0.43% (95% CI = 0.15 to 0.86) with low heterogeneity ( $I^2 = 6.5\%$ ). Figure 65 shows the forest plot of the analysis.

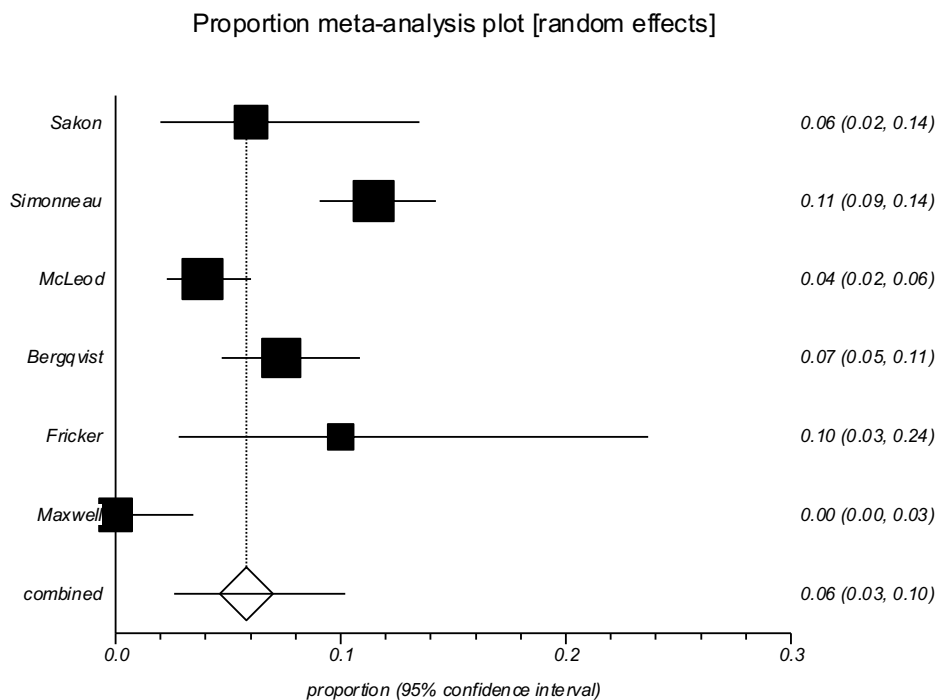
**Figure 65 Forest plot of the pooled proportion for PE post major abdominal cancer surgery in patient receiving high dose LMWH for 7-10 days post-surgery.**



## **Pooled proportion of major bleeding events**

A total of 1636 patients from 6 RCTs were used for this analysis. There were a total 122 major bleeding events post cancer surgery corresponding to pooled proportion of 5.82% (95% CI = 2.62 to 10.21) with considerable heterogeneity ( $I^2 = 89\%$ ). Figure 66 shows the forest plot of the analysis.

**Figure 66 Forest plot of the pooled proportion for major bleeding post major abdominal cancer surgery in patient receiving high dose LMWH for 7-10 days post-surgery.**

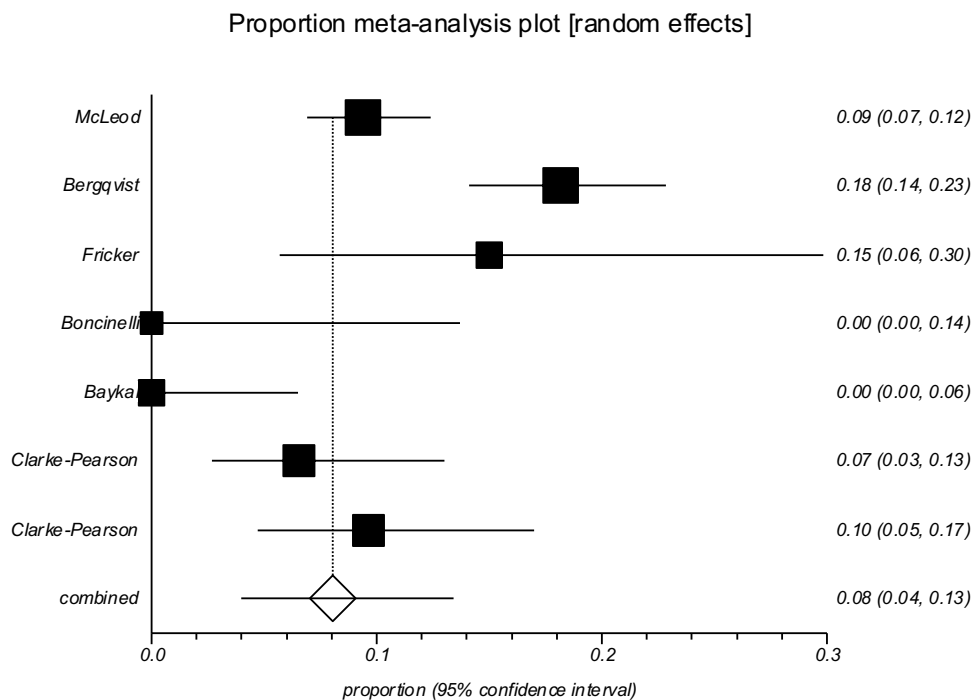


## ***High thromboprophylactic dose of unfractionated heparin (UFH 5000 units every 8 hours)***

### **Pooled proportion of VTE**

A total of 1118 patients from 7 RCTs were used for this analysis. There were a total 125 VTE events post cancer surgery corresponding to pooled proportion of 8.06 (95% CI =3.99 to 13.40) with considerable heterogeneity ( $I^2 = 85.1\%$ ). Figure 67 shows the forest plot of the analysis.

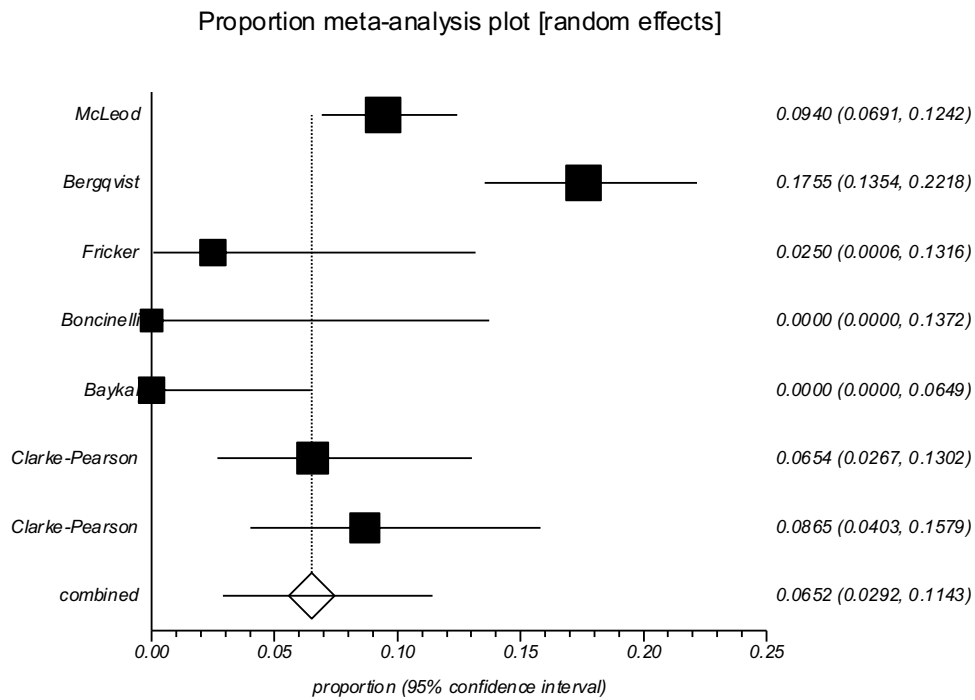
***Figure 67 Forest plot of the pooled proportion for VTE post major abdominal cancer surgery in patient receiving high dose UFH for 7-10 days post-surgery.***



## **Pooled proportion of DVT**

A total of 1118 patients from 7 RCTs were used for this analysis. There were a total 117 DVT events post cancer surgery corresponding to pooled proportion of 6.52 (95% CI = 2.92 to 11.43) with considerable heterogeneity ( $I^2 = 85.1\%$ ). Figure 68 shows the forest plot of the analysis.

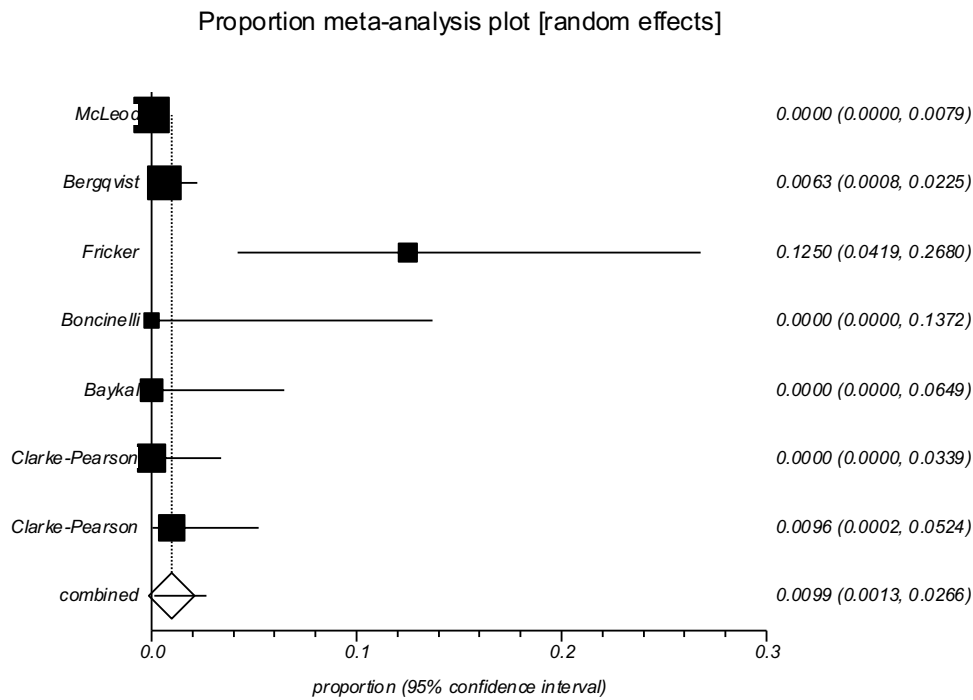
**Figure 68 Forest plot of the pooled proportion for DVT post major abdominal cancer surgery in patient receiving high dose UFH for 7-10 days post-surgery.**



## **Pooled proportion of PE**

A total of 1118 patients from 7 RCTs were used for this analysis. There were a total 8 PE events post cancer surgery corresponding to pooled proportion of 0.99 (95% CI = 0.13 to 2.66) with considerable heterogeneity ( $I^2 = 71.5\%$ ). Figure 69 shows the forest plot of the analysis.

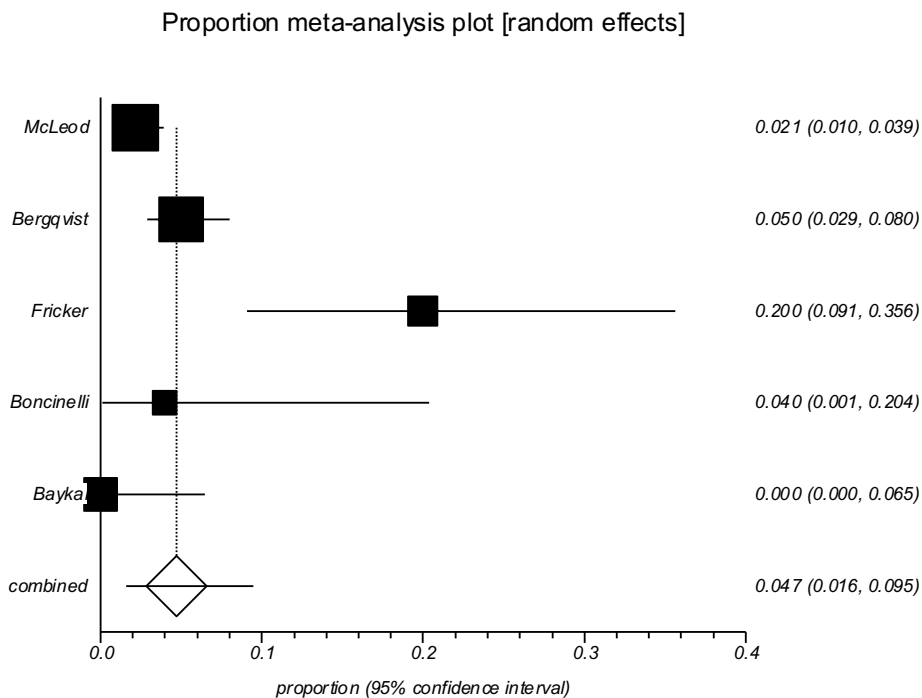
**Figure 69 Forest plot of the pooled proportion for PE post major abdominal cancer surgery in patient receiving high dose UFH for 7-10 days post-surgery.**



## **Pooled proportion of major bleeding**

A total of 907 patients from 5 RCTs were used for this analysis. There were a total 35 major bleeding events post cancer surgery corresponding to pooled proportion of 4.72 % (95% CI = 1.57 to 9.45) with considerable heterogeneity ( $I^2 = 81.5\%$ ). Figure 70 shows the forest plot of the analysis.

**Figure 70 Forest plot of the pooled proportion for major bleeding post major abdominal cancer surgery in patient receiving high dose UFH for 7-10 days post-surgery.**



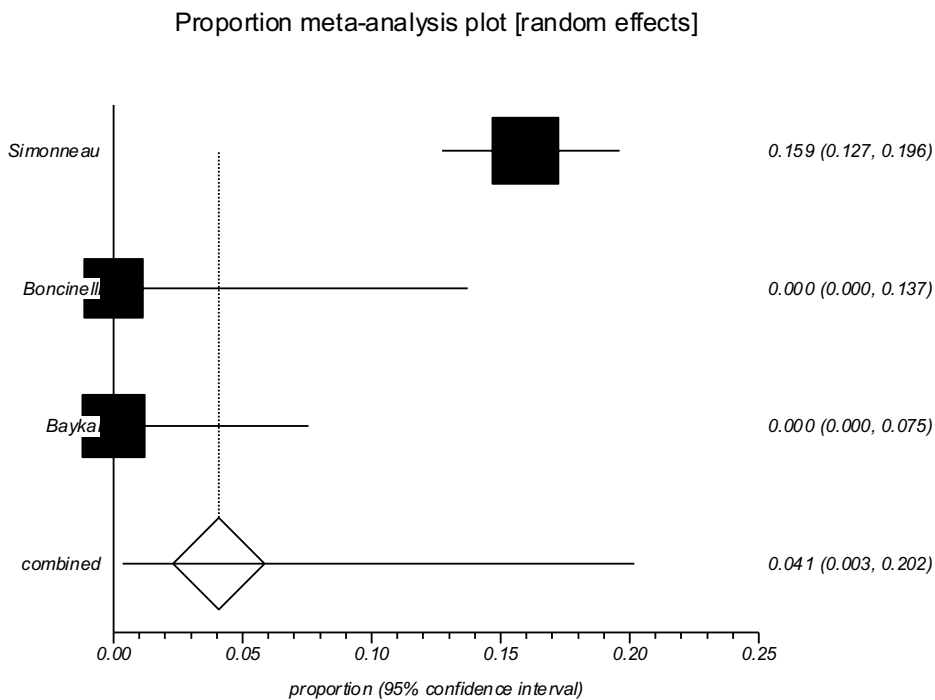
## ***Low prophylactic dose of low molecular weight heparin (<4000***

***IU)***

### ***Pooled proportion of VTE***

A total of 536 patients from 3 RCTs were used for this analysis. There were a total 74 VTE events post cancer surgery corresponding to pooled proportion of 4.08 (95% CI = 0.35 to 20.18) with considerable heterogeneity ( $I^2 = 92.8\%$ ). Figure 71 shows the forest plot of the analysis.

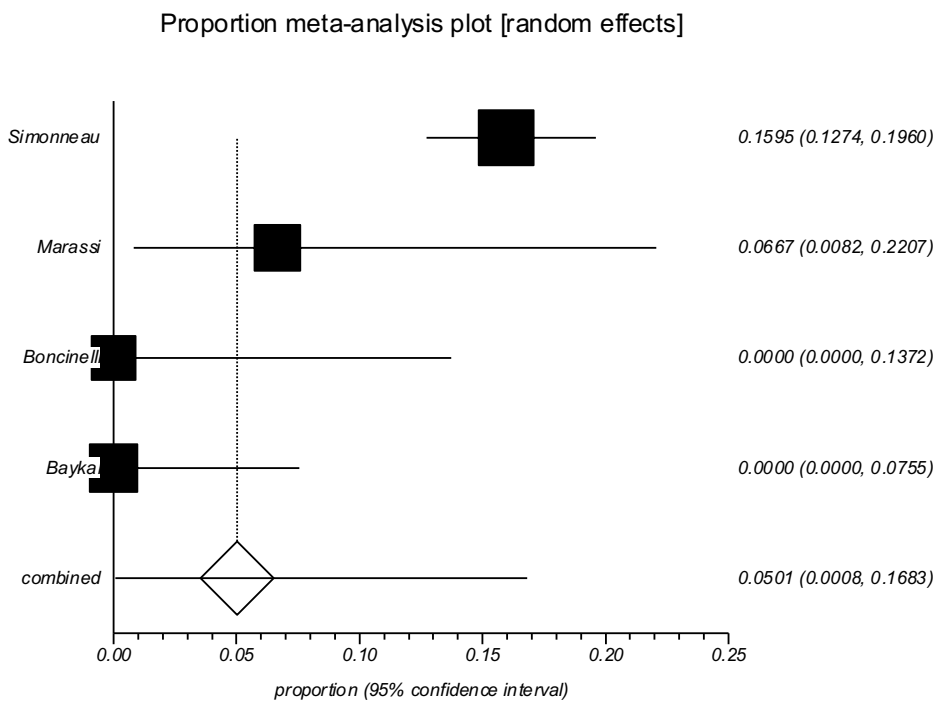
***Figure 71 Forest plot of the pooled proportion for VTE post major abdominal cancer surgery in patient receiving low dose LMWH for 7-10 days post-surgery.***



## **Pooled proportion of DVT**

A total of 566 patients from 4 RCTs were used for this analysis. There were a total 76 DVT events post cancer surgery corresponding to pooled proportion of 5.01% (95% CI = 0.08 to 16.83) with considerable heterogeneity ( $I^2 = 89.5\%$ ). Figure 72 shows the forest plot of the analysis.

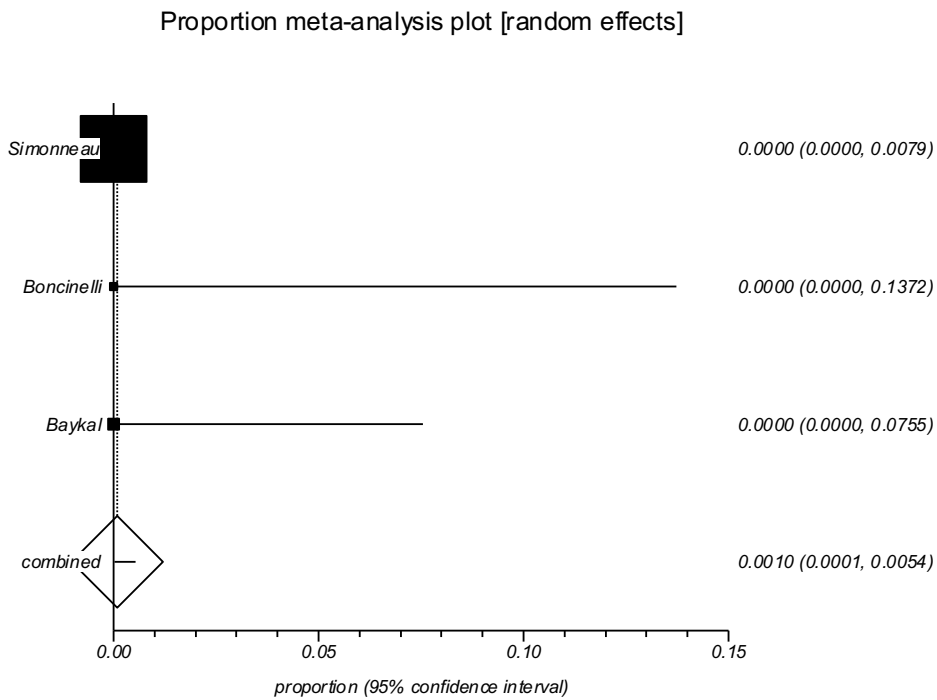
**Figure 72 Forest plot of the pooled proportion for DVT post major abdominal cancer surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**



## **Pooled proportion of PE**

A total of 536 patients from 3 RCTs were used for this analysis. There were no PE events reported post cancer surgery corresponding to pooled proportion of 0.10% (95% CI = 0.01 to 0.54) with no heterogeneity ( $I^2 = 0\%$ ). Figure 73 shows the forest plot of the analysis.

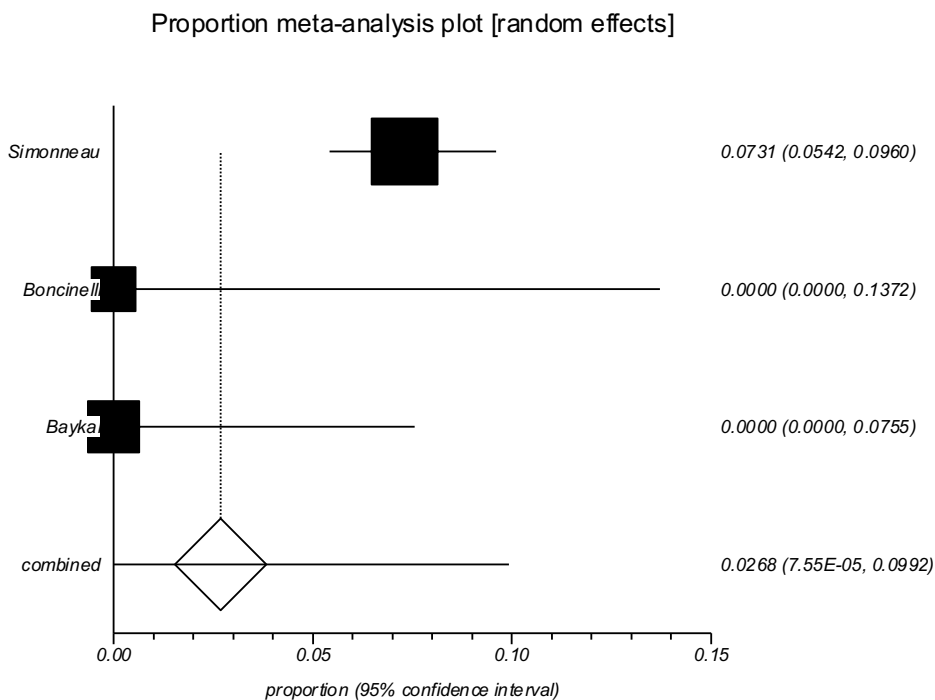
**Figure 73 Forest plot of the pooled proportion for PE post major abdominal cancer surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**



## **Pooled proportion of major bleeding**

A total of 715 patients from 3 RCTs were used for this analysis. There were a total of 47 major bleeding events reported post cancer surgery corresponding to pooled proportion of 2.68 %(95% CI = 0.008 to 9.92) with considerable heterogeneity ( $I^2 = 79.9\%$ ). Figure 74 shows the forest plot of the analysis.

**Figure 74 Forest plot of the pooled proportion for PE post major abdominal cancer surgery in patient receiving low dose LMWH for 7-10 days post-surgery.**

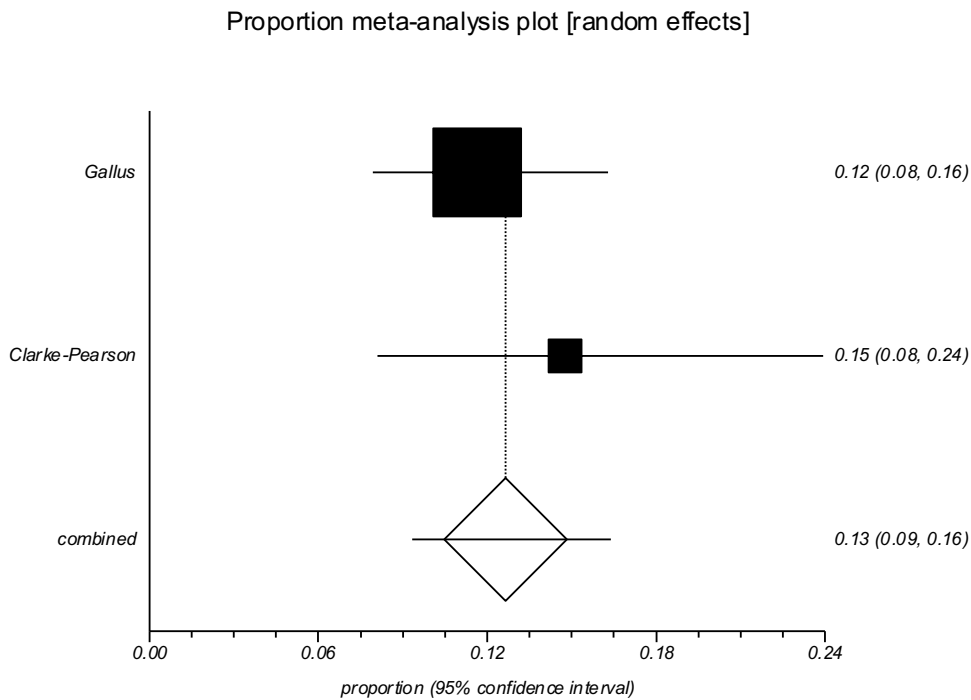


***Low prophylactic dose of unfractionated heparin (UFH 5000 units every 12 hours)***

***Pooled proportion of VTE***

A total of 337 patients from 2 RCTs were used for this analysis. There were a total 42 VTE events post cancer surgery corresponding to pooled proportion of 12.65% (95% CI = 9.33 to 16.39). Figure 75 shows the forest plot of the analysis.

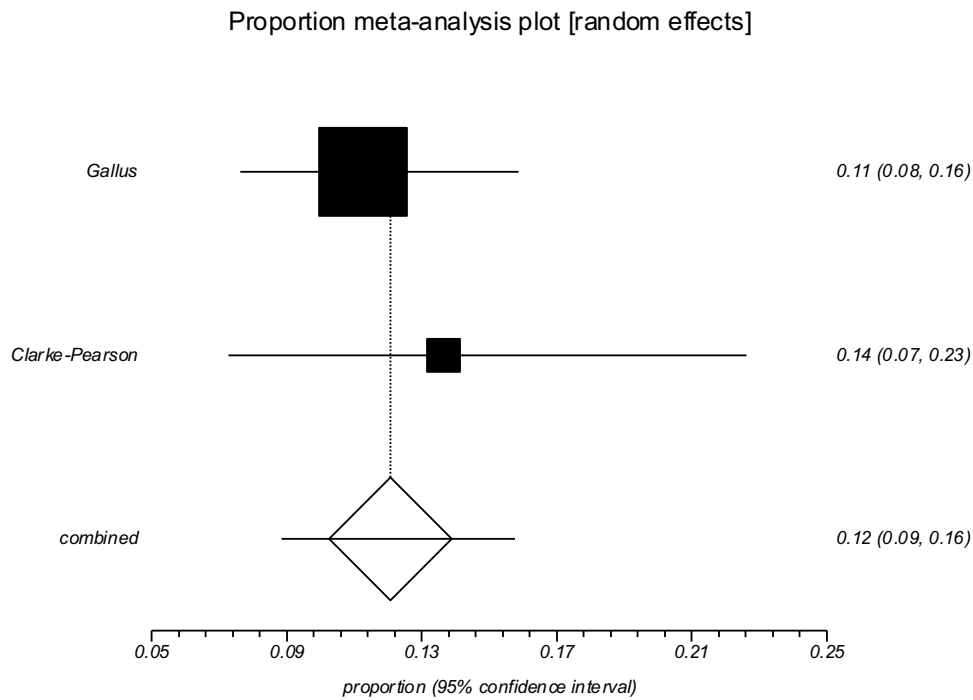
***Figure 75 Forest plot of the pooled proportion for VTE post major abdominal cancer surgery in patient receiving low dose UFH for 7-10 days post-surgery.***



## **Pooled proportion of DVT**

A total of 337 patients from 2 RCTs were used for this analysis. There were a total 40 DVT events post cancer surgery corresponding to pooled proportion of 12.07% (95% CI = 8.82 to 15.75). Figure 76 shows the forest plot of the analysis.

**Figure 76 Forest plot of the pooled proportion for DVT post major abdominal cancer surgery in patient receiving low dose UFH for 7-10 days post-surgery.**

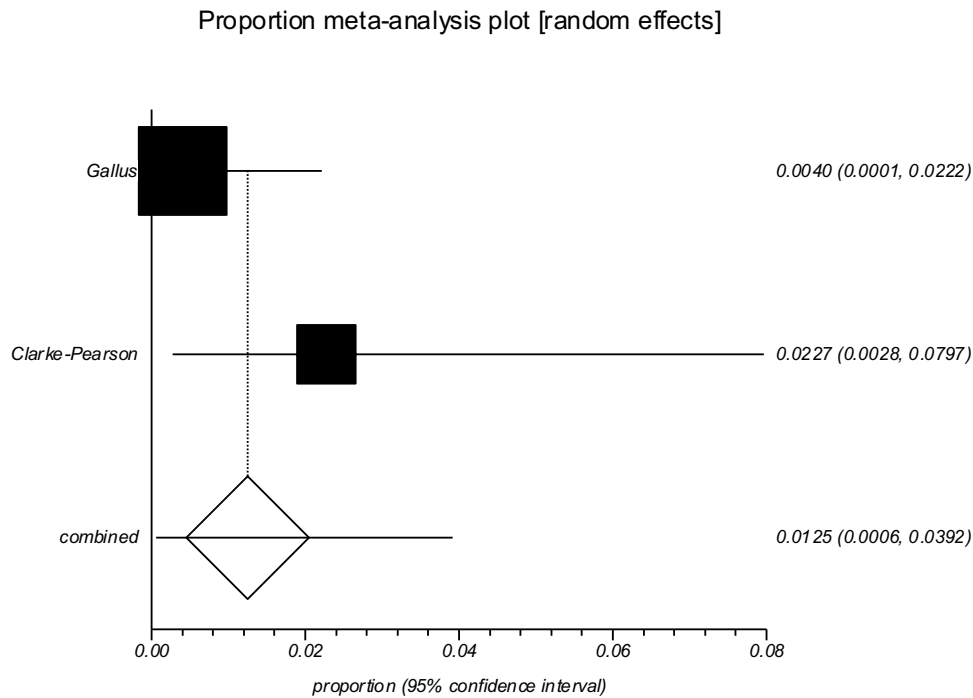


## **Pooled proportion of PE**

A total of 337 patients from 2 RCTs were used for this analysis. There were a total 3 PE events post cancer surgery corresponding to pooled proportion of 1.25% (95% CI = 0.06 to 3.92).

Figure 77 shows the forest plot of the analysis.

**Figure 77 Forest plot of the pooled proportion for PE post major abdominal cancer surgery in patient receiving low dose UFH for 7-10 days post-surgery.**



## **Pooled proportion of major bleeding**

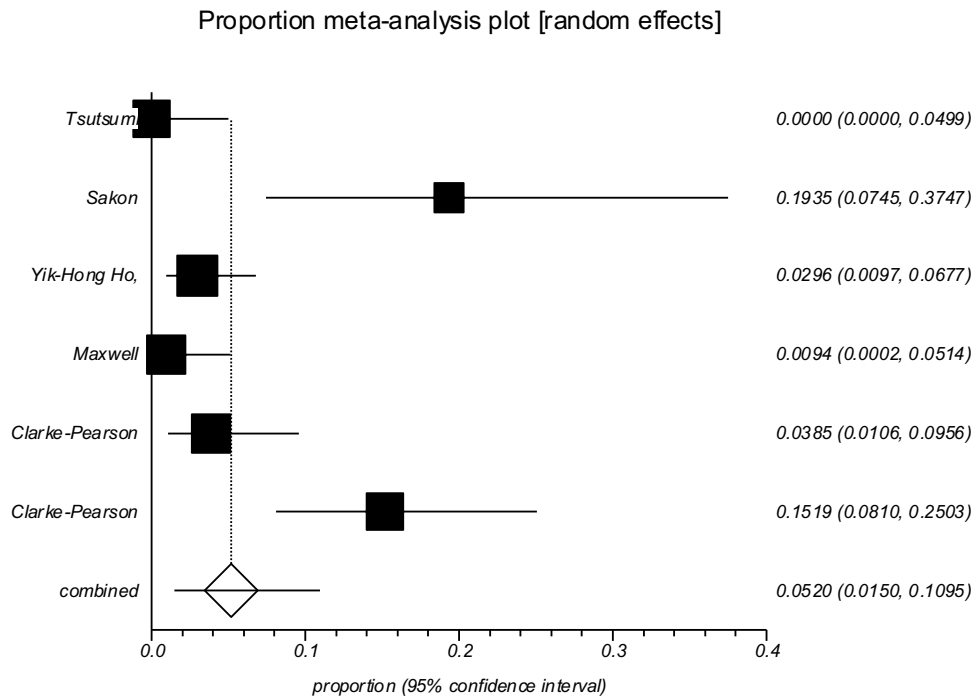
Only one RCT (*Gallus*) reported major bleeding events in cancer surgery. There were a total of 5 major bleeding events among 256 patients used for the analysis.

# ***Placebo, non-pharmacological thromboprophylaxis or no treatment***

## **Pooled proportion of VTE**

A total of 561 patients from 6 RCTs were used for this analysis. There were a total 28 VTE events post cancer surgery corresponding to pooled proportion of 5.20% (95% CI = 1.50 to 10.95) with considerable heterogeneity ( $I^2 = 84.2\%$ ). Figure 78 shows the forest plot of the analysis.

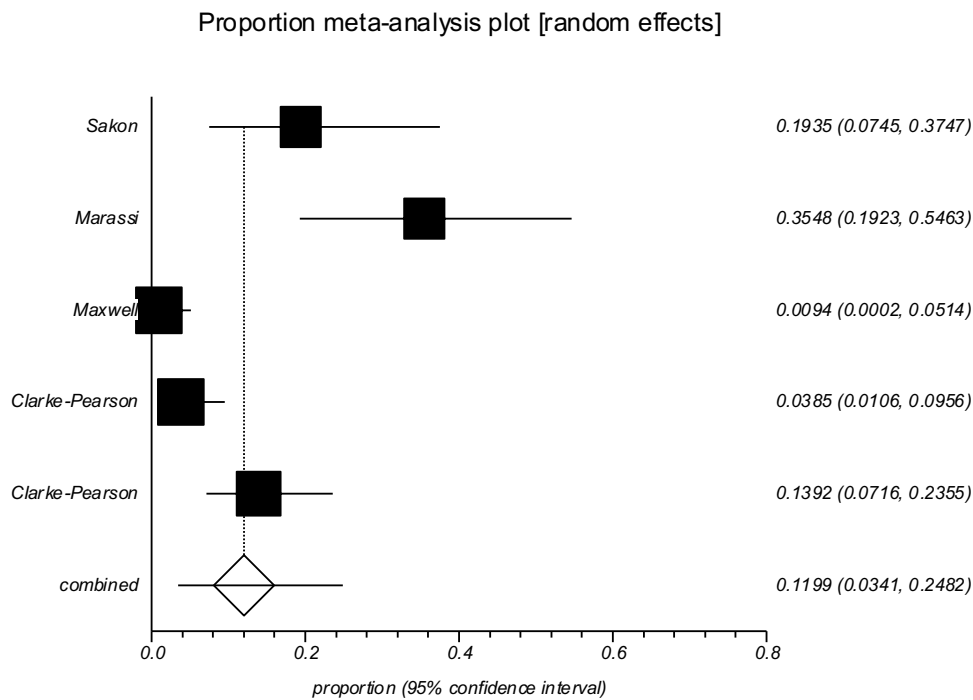
***Figure 78 Forest plot of the pooled proportion for VTE post major abdominal cancer surgery in patient receiving placebo, non-pharmacological thromboprophylaxis or no treatment for 7-10 days post-surgery.***



## **Pooled proportion of DVT**

A total of 351 patients from 5 RCTs were used for this analysis. There were a total 33 DVT events post cancer surgery corresponding to pooled proportion of 11.99 (95% CI = 3.41 to 24.82) with considerable heterogeneity ( $I^2 = 89.6\%$ ). Figure 79 shows the forest plot of the analysis.

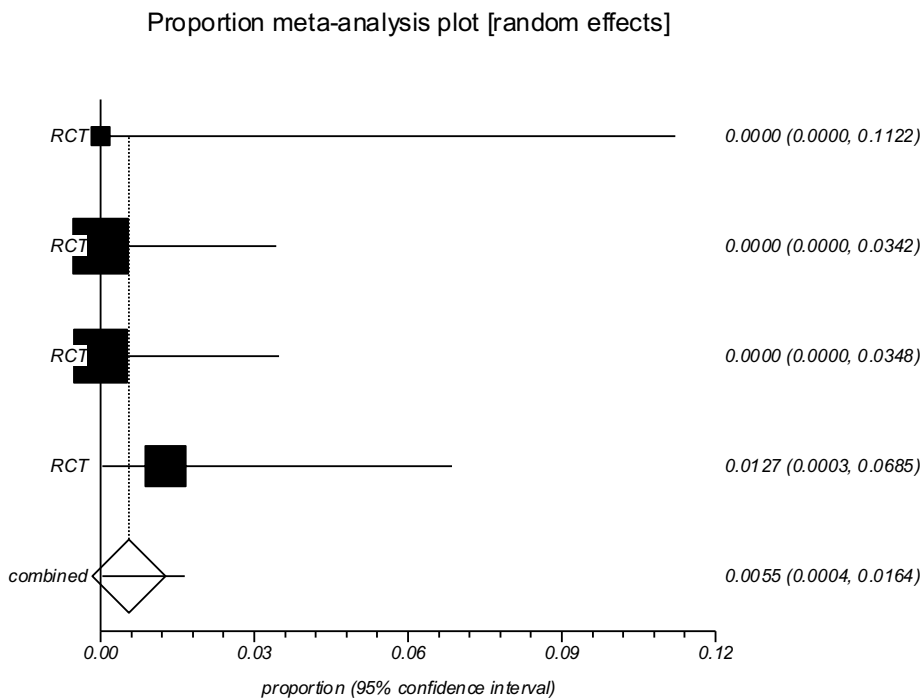
**Figure 79 Forest plot of the pooled proportion for DVT post major abdominal cancer surgery in patient receiving placebo, non-pharmacological thromboprophylaxis or no treatment for 7-10 days post-surgery.**



## **Pooled proportion of PE**

A total of 320 patients from 4 RCTs were used for this analysis. There were a total 1 PE event post cancer surgery corresponding to pooled proportion of 0.55% (95% CI = 0.04 to 1.64) with no heterogeneity ( $I^2 = 0\%$ ). Figure 80 shows the forest plot of the analysis.

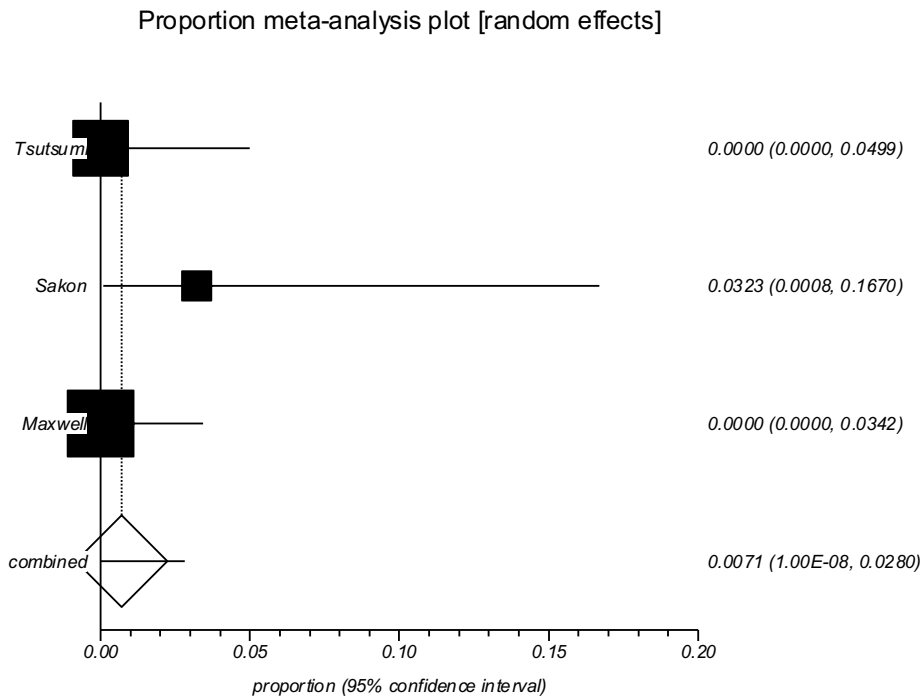
**Figure 80 Forest plot of the pooled proportion for PE post major abdominal cancer surgery in patient receiving placebo, non-pharmacological thromboprophylaxis or no treatment for 7-10 days post-surgery.**



## **Pooled proportion of major bleeding**

A total of 209 patients from 3 RCTs were used for this analysis. There was only one major bleeding event post cancer surgery corresponding to pooled proportion of 0.71% (95% CI =0.000001 to 2.81) with low heterogeneity ( $I^2 = 30.9\%$ ). Figure 81 shows the forest plot of the analysis.

**Figure 81 Forest plot of the pooled proportion for major bleeding post major abdominal cancer surgery in patient receiving placebo, non-pharmacological thromboprophylaxis or no treatment for 7-10 days post-surgery.**



## ***Appendix 9: Contact email send for Survey Participants***

### ***Initial email***

October 29 2015

Dear Doctor;

You are being asked to participate in a research study titled “***A Cross Sectional Survey: A Survey Of Thrombosis Experts And General Surgeons Evaluating Practices And Opinions Regarding Venous Thromboprophylaxis In Patients Post Major Abdominal Surgery***”.

Please find below a link to a survey regarding the role of thromboprophylaxis post major abdominal surgery. The survey should take about 5-10 minutes to complete. Please note that the survey is only available in English.

Your valuable participation will contribute towards identifying the risk and benefit of thromboprophylaxis post major abdominal surgery, and help to identify future research priorities in this area. We would be very grateful if you would consider helping us with our important research.

Filling out the online survey will be viewed as implied consent.

Your participation is voluntary. You can withdraw from the study at any point prior to submitting your answer. Once you’ve submitted your answer, the information cannot be removed as it will be anonymous. All the survey answers are kept confidential.

There are no risks, and you will not receive any benefits by participating in this study.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed the plans for this research study.

The survey can be found here: <https://www.surveymonkey.com/r/CanThrombosis>

Thank you for your consideration.

Sincerely,

## ***Reminder email***

October 29<sup>th</sup> 2015

**REMINDER: *A Cross Sectional Survey: A Survey Of Thrombosis Experts And General Surgeons Evaluating Practices And Opinions Regarding Venous Thromboprophylaxis In Patients Post Major Abdominal Surgery***".

Dear Doctor;

You may have already received an e-mail asking you to participate in this survey. If you have already completed and returned the survey, please accept our thanks and ignore this e-mail as no further involvement is required. If you have not completed the survey, please take the time to consider helping us with this important research.

You are being asked to participate in a research study titled "***A Cross Sectional Survey: A Survey Of Thrombosis Experts And General Surgeons Evaluating Practices And Opinions Regarding Venous Thromboprophylaxis In Patients Post Major Abdominal Surgery***".

Please find below a link to a survey regarding the role of thromboprophylaxis post major abdominal surgery. The survey should take about 5-10 minutes to complete. Please note that the survey is only available in English.

Your valuable participation will contribute towards identifying the risk and benefit of thromboprophylaxis post major abdominal surgery, and help to identify future research priorities in this area. We would be very grateful if you would consider helping us with our important research.

Filling out the online survey will be viewed as implied consent.

Your participation is voluntary. You can withdraw from the study at any point prior to submitting your answer. Once you've submitted your answer, the information cannot be removed as it will be anonymous. All the survey answers are kept confidential.

The survey can be found here: <https://www.surveymonkey.com/r/CanThrombosis>

Thank you for your consideration.

Sincerely,

## ***Appendix 10: The Survey***

### ***Survey sent to the Thrombosis Canada***

#### ***A Cross Sectional Survey: A Survey Of Thrombosis Experts Evaluating Practices And Opinions Regarding Venous Thromboprophylaxis In Patients Post Major Abdominal Surgery+***

Major abdominal surgery: include any abdominal surgery that is laparoscopic or open, performed under general anaesthesia and lasted for at least 30 minutes.

A. Questions 1 and 2 are about your clinical practice

A 49 year-old male (BMI = 30 kg/m<sup>2</sup>) undergoing laparoscopic colon resection (> 45 minutes) for ulcerative colitis that is refractory to medical therapy. He is to be hospitalized for 1-2 days after surgery (Caprini score of 5).

**1. Currently in your practice would you recommend the use of pharmacological thromboprophylaxis for this patient?**

- Yes. While admitted to hospital only
- Yes. For a total of 7 to 10 days
- Yes. For a total of 28 days
- I would not recommend any pharmacological thromboprophylaxis
- Other? Please specify: -----.

**2. Which types/dose/schedules of pharmacological thromboprophylaxis do you recommend (weight = 70 kg and normal renal function)? (please mark all that apply)**

- Unfractionated Heparin (UFH) 5,000 units, subcutaneous (SC), twice a day.
- UFH 5,000 units, SC, three times a day.
- Enoxaparin 30mg, SC, twice a day.
- Enoxaparin 40mg, SC, daily.
- Dalteparin 5,000 units, SC, daily.
- Tinzaparin 4,500 units or 75 units/kg, SC, daily.
- Fondaparinux 2.5mg, SC, daily.

- Aspirin 75-325 mg, PO, daily.
- Never
- Other? Please specify: -----.

B. Questions 3-11 are about your opinion and use of clinical practice guidelines for thromboprophylaxis in adult patients post major abdominal surgery:

A 49 year-old male (BMI = 30 kg/m<sup>2</sup>) undergoing laparoscopic colon resection (> 45 minutes) for ulcerative colitis that is refractory to medical therapy. He is to be hospitalized for 1-2 days after surgery (Caprini score of 5).

**3. In your opinion, in the case above, what is the probability (incidence) of overall venous thromboembolism (VTE) (symptomatic and asymptomatic VTE (i.e. including screening ultrasound or venography) at 7 to 10 days post-operatively if this patient does not receive thromboprophylaxis?**

- 1-3%.
- 4-6%.
- 7-9%.
- 10-12%.
- >=13%.

**4. In your opinion, in the case above, what do you think is the probability (without thromboprophylaxis) of symptomatic pulmonary embolism at 7 to 10 days post-op?**

- 0.5-1%.
- 2-3%.
- 4-5%.
- 6-7%.
- >=8%.

**5. In your opinion, in the case above, what is the incidence of a major bleeding episode\* if the patient receiving 7 to 10 days of pharmacological thromboprophylaxis in the post-operative period?**

\*Major bleeding: Fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/l or more, or leading to transfusion of two or more units of whole blood or red cells and/or bleeding required reoperation to stop the bleeding.

- 0.5-1%.

- 2-3%.
- 4-5%.
- 6-7%.
- >=8%.

**6. We performed a systematic review of the literature on the efficacy and safety of pharmacological thromboprophylaxis in patients undergoing major abdominal surgery. A large majority of clinical studies assessed pharmacological thromboprophylaxis for a total of 7 to 10 days. There are no clinical trials comparing a course of pharmacological thromboprophylaxis during the hospitalization only to a total duration of 7 to 10 days in this patient population. Therefore, some clinical practice guidelines suggest to consider a minimum 7 to 10 days of pharmacological thromboprophylaxis (including post-discharge prescription if applicable) for high risk patients undergoing major abdominal surgery. In your opinion, do you think that the benefits of using pharmacological thromboprophylaxis for 7 to 10 days in high risk patients outweigh the risk of bleeding in adult patients post major abdominal surgery?**

- Always.
- Most of the time
- Sometimes.
- Never.
- Other? Please specify: -----.

**7. Do you believe that there is clinical equipoise around the use of thromboprophylaxis post discharge (up to 7 to 10 days) in high risk adult patients post major abdominal surgery??**

- Yes.
- No.

**8. Would you consider allowing your patients to participate in a randomized trial assessing the use of thromboprophylaxis in adult patients post major abdominal surgery (please choose only one answer)?**

- Yes, comparing thromboprophylaxis to placebo.
- Yes, comparing different duration (e.g. during hospitalization only vs. 10 days) of thromboprophylaxis or agents.
- No, I would not enroll patients post major abdominal surgery in a clinical trial.

C Questions 9-14 are about you and your clinical practice:

**9. You are a:**

- Hematologist.

- Internist.
- Family Doctor
- Other? Please specify\_\_\_\_\_.

**10. You are a:**

- Male.
- Female.

**11. Your age is:**

- 25-35.
- 36-45.
- 46-55.
- 56-65.
- over 65

**12. You have been in independent practice for \_\_\_\_\_years.**

**13. You practice >50% of your time in the province of:**

- NF.
- NS.
- NB.
- PE.
- QC.
- ON.
- MB.
- SK.
- AB.
- BC.
- YT/NT /Nunavut

**14. You practice >50% of your time at:**

- A non-academic (community) hospital.
- An academic (teaching) hospital.
- Private Practice Office.
- Other? Please specify\_\_\_\_\_.

## ***Survey sent to the Canadian Association of General Surgeons***

### ***A Cross Sectional Survey: A Survey Of General Surgeons Evaluating Practices And Opinions Regarding Venous Thromboprophylaxis In Patients Post Major Abdominal Surgery+***

Major abdominal surgery: include any abdominal surgery that is laparoscopic or open, performed under general anaesthesia and lasted for at least 30 minutes.

#### **B. Questions 1 and 4 are about your clinical practice**

**1. Are you a surgeon who performs major abdominal surgery?**

- Yes.
- No.

**2. Are you familiar with the Caprini score for estimating the risk of postoperative venous thromboembolism?**

- Yes.
- No.

A 49 year-old male (BMI = 30 kg/m<sup>2</sup>) undergoing laparoscopic colon resection (> 45 minutes) for ulcerative colitis that is refractory to medical therapy. He is to be hospitalized for 1-2 days after surgery (Caprini score of 5).

**3. Currently in your practice would you recommend the use of pharmacological thromboprophylaxis for this patient?**

- Yes. While admitted to hospital only
- Yes. For a total of 7 to 10 days
- Yes. For a total of 28 days
- I would not recommend any pharmacological thromboprophylaxis
- Other? Please specify: -----.

**4. Which types/dose/schedules of pharmacological thromboprophylaxis do you recommend (weight = 70 kg and normal renal function)? (please mark all that apply)**

- Unfractionated Heparin (UFH) 5,000 units, subcutaneous (SC), twice a day.

- UFH 5,000 units, SC, three times a day.
- Enoxaparin 30mg, SC, twice a day.
- Enoxaparin 40mg, SC, daily.
- Dalteparin 5,000 units, SC, daily.
- Tinzaparin 4,500 units or 75 units/kg, SC, daily.
- Fondaparinux 2.5mg, SC, daily.
- Aspirin 75-325 mg, PO, daily.
- Never
- Other? Please specify: -----.

B. Questions 5-10 are about your opinion and use of clinical practice guidelines for thromboprophylaxis in adult patients post major abdominal surgery:

A 49 year-old male (BMI = 30 kg/m<sup>2</sup>) undergoing laparoscopic colon resection (> 45 minutes) for ulcerative colitis that is refractory to medical therapy. He is to be hospitalized for 1-2 days after surgery (Caprini score of 5).

**5. In your opinion, in the case above, what is the probability (incidence) of overall venous thromboembolism (VTE) (symptomatic and asymptomatic VTE (i.e. including screening ultrasound or venography) at 7 to 10 days post-operatively if this patient does not receive thromboprophylaxis?**

- 1-3%.
- 4-6%.
- 7-9%.
- 10-12%.
- >=13%.

**6. In your opinion, in the case above, what do you think is the probability (without thromboprophylaxis) of symptomatic pulmonary embolism at 7 to 10 days post-op?**

- 0.5-1%.
- 2-3%.
- 4-5%.
- 6-7%.
- >=8%.

**7. In your opinion, in the case above, what is the incidence of a major bleeding episode\* if the patient receiving 7 to 10 days of pharmacological thromboprophylaxis in the post-operative period?**

\*Major bleeding: Fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/l or more, or leading to transfusion of two or more units of whole blood or red cells and/or bleeding required reoperation to stop the bleeding.

- 0.5-1%.
- 2-3%.
- 4-5%.
- 6-7%.
- >=8%.

**8. We performed a systematic review of the literature on the efficacy and safety of pharmacological thromboprophylaxis in patients undergoing major abdominal surgery. A large majority of clinical studies assessed pharmacological thromboprophylaxis for a total of 7 to 10 days. There are no clinical trials comparing a course of pharmacological thromboprophylaxis during the hospitalization only to a total duration of 7 to 10 days in this patient population. Therefore, some clinical practice guidelines suggest to consider a minimum 7 to 10 days of pharmacological thromboprophylaxis (including post-discharge prescription if applicable) for high risk patients undergoing major abdominal surgery. In your opinion, do you think that the benefits of using pharmacological thromboprophylaxis for 7 to 10 days in high risk patients outweigh the risk of bleeding in adult patients post major abdominal surgery?**

- Always.
- Most of the time
- Sometimes.
- Never.
- Other? Please specify: -----.

**9. Do you believe that there is clinical equipoise around the use of thromboprophylaxis post discharge (up to 7 to 10 days) in high risk adult patients post major abdominal surgery??**

- Yes.
- No.

**10. Would you consider allowing your patients to participate in a randomized trial assessing the use of thromboprophylaxis in adult patients post major abdominal surgery (please choose only one answer)?**

- Yes, comparing thromboprophylaxis to placebo.
- Yes, comparing different duration (e.g. during hospitalization only vs. 10 days) of thromboprophylaxis or agents.

- No, I would not enroll patients post major abdominal surgery in a clinical trial.

C Questions 11-16 are about you and your clinical practice:

**11. You are a:**

- General Surgeon.  
 Subspecialty surgeon (e.g. colorectal, bariatric, etc.).  
 Other? Please specify\_\_\_\_\_.

**12. You are a:**

- Male.  
 Female.

**13. Your age is:**

- 25-35.  
 36-45.  
 46-55.  
 56-65.  
 over 65

**14. You have been in independent practice for \_\_\_\_\_years.**

**15. You practice >50% of your time in the province of:**

- NF.  
 NS.  
 NB.  
 PE.  
 QC.  
 ON.  
 MB.  
 SK.  
 AB.  
 BC.  
 YT/NT /Nunavut

**16. You practice >50% of your time at:**

- A non-academic (community) hospital.  
 An academic (teaching) hospital.  
 Private Practice Office.  
 Other? Please specify\_\_\_\_\_.