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# Efficacy and safety of weight-adjusted heparin prophylaxis for the prevention of acute venous thromboembolism among obese patients undergoing bariatric surgery: A systematic review and meta-analysis

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ABSTRACT

*Background:* The bariatric surgical population is a particularly high risk population for VTE. It is unclear if standard (i.e. non-adjusted) thromboprophylaxis doses of low-molecular weight or unfractionated heparin provide adequate protection for obese patients undergoing bariatric surgery, or if higher doses are required. We sought to determine whether a weight based thromboprophylactic dosing regimen is safe and effective in the post-operative period for obese patients undergoing bariatric surgery.
*Methods:* A systematic literature search strategy was conducted using MEDLINE, EMBASE, the Cochrane Register of Controlled Trials and all EBM Reviews. Pooled proportions for the different outcomes were calculated.
*Results:* A total of 6 studies (1 RCT, 4 cohort studies and one quasi experimental trial) containing 1,858 patients were include in the systematic review. Post bariatric surgery patients receiving weight-adjusted prophylactic doses of heparin products, had an in hospital rate of VTE of 0.54% (95% CI: 0.2 to 1.0%) compared to 2.0% (95% CI: 0.1 to 6.4%) for those that did not weight adjust doses. Rates of major bleeding were similar for both groups: 1.6% (95% CI: 0.6 to 3.0%) for patients receiving weight-adjusted dosing compared to 2.3% (95% CI: 1.1% to 3.9%) for those receiving standard doses of heparin products.
*Conclusions:* Adjusting the dose of heparin products for thromboprophylaxis post-bariatric surgery seems to be associated with a lower rate of in hospital VTE compared to a strategy of not adjusting the dose, although this did not reach statistical significance. This practice does not lead to an increase in adverse major bleeding events.


## Introduction

The prevalence of obesity in society is rapidly increasing with the United States leading the world with a prevalence of 34% of adults now being classified as obese [1]. Obesity and surgery are known risk factors for venous thrombosis [2–4] and therefore, the bariatric surgical population is a particularly high risk population for VTE [5].

The data regarding the use of pharmacological thromboprophylaxis in the post-operative period following bariatric surgery is scarce. The most recent version of the American College of Chest Physicians guidelines does not report specific recommendation for this population [6]. More importantly, it is unclear if standard (i.e. non-adjusted) thromboprophylaxis doses of low-molecular weight heparin (LMWH) or unfractionated heparin (UFH) provide adequate protection for obese patients undergoing bariatric surgery, or if weight-adjusted doses are required. Obese patients have several proposed mechanisms of altered drug distribution and metabolism, including, altered renal clearance, metabolic derangements affecting handling of drugs by the liver and changes in the volume of distribution and absorption of medications [7]. In pharmacokinetic studies of LMWH actual body weight was inversely correlated with measured Anti-Xa level [8]. Therefore it would seem to make sense that a higher dose of LMWH would be required to obtain the same therapeutic effect. Conversely, it must be acknowledged that LMWHs have a low volume of distribution [9] and generally do not distribute well to adipose tissue there are concerns that truly basing doses on weight may result in overdosing of this patient group. To attempt to bridge this important knowledge gap, we conducted a systematic review of the literature to determine whether a weight-based thromboprophylactic dosing regimen of heparin products is safe and effective in the post-operative period for obese patients undergoing bariatric surgery.

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## Methods

A systematic literature search was performed in MEDLINE (1946-July 6, 2012), EMBASE (1947-July 6, 2012), the Cochrane Register of Controlled Trials and all EBM Reviews using an OVID interface. We also sought publications through a hand-search of potentially relevant journals and International Society of Thrombosis and Haemostasis conference proceedings (2003-2011). We also reviewed the references of included studies and previous systematic reviews for additional potential studies. There were no restrictions on language, publication type or publication year applied. The Medline search strategy is depicted in Appendix 1 (on-line).

### *Study Selection and Data Extraction*

Two reviewers (R.I. and M.C.) independently screened all abstracts records using a standardized extraction form to find potential relevant articles. Discrepancies between the reviewers on which studies should be included were resolved by consensus after discussion. The two investigators (R.I. and M.C.) then reviewed potentially relevant articles in full length to ensure that they satisfied these criteria: 1) patients undergoing bariatric surgery; 2) patients received post-operative pharmacological thromboprophylaxis using LMWH, unfractionated heparin (UFH) or fondaparinux; and 3) outcome measures available. Studies were excluded if they included pregnant or pediatric patients.

The primary outcome measures were VTE and major bleeding events. Venous thromboembolism was defined as symptomatic proximal lower limbs (popliteal vein or more proximal) deep vein thrombosis or objectively diagnosed pulmonary embolism. Weight-adjusted thromboprophylactic LMWH dosing was defined as the use of a higher than standard recommended dose set as enoxaparin 30 mg subcutaneously q12 hr or equivalent. Weight-adjusted UFH was defied as doses higher than 5000 IU subcutaneously q8hr or as the use of a subcutaneously UFH protocol that adjusted the dose based on weight and the level of anticoagulation (anti-Xa). Major bleeding was defined as clinically overt bleeding associated with one or more of the requirements for hospitalization; transfusion of at least 2 units of packed red blood cells; intracranial or retroperitoneal bleeding or bleeding involving a body cavity; bleeding related death; or as defined by the individual studies [10]. Outcome measures were independently extracted by each of the reviewers using a standard data extraction form. We attempted to contact authors but failed to retrieve any additional information. Corresponding author of manuscript were contacted if primary or secondary outcomes could not be extracted from the original manuscript.

### *Quality Assessment*

Observational study quality was assessed using the Newcastle Ottawa Quality Assessment Scale for observational studies. Randomized controlled trials were assessed using the Risk of Bias Assessment Tool from the Cochrane Handbook [11].

### *Data Synthesis and Statistical Analysis*

Pooled proportions using random effect model were calculated for the different outcome measure. Ninety-five percent confidence intervals (95% CI) were calculated for each proportion using the averaged, inverse variance-weighted estimates from each study. (Stats Direct software, version 2.7.9). $I^2$ was calculated to assess heterogeneity among the pooled estimates. It was set that an $I^2$ value of less than 25% was low-level heterogeneity, 25 to 50% was considered moderate and greater than 50% was a high degree of heterogeneity [12].

## Results

A total of 6 studies (1 randomized controlled trial, 4 cohort studies and 1 quasi-experimental trial) containing 1,858 patients met the inclusion criteria and were included in the analysis (see Fig. 1). Baseline characteristics of the included studies are depicted in Table 1.

A wide range of prophylaxis regimens are used by the studies the most aggressive of which was that used in the study by Borkgren-Okonek of up to enoxaparin 60 mg subcutaneous q12hours. Other studies used either an alternative regimen of enoxaparin (30-40 mg q12), nadroparin(5700 units vs 9500 units) or a unfractionated heparin prophylaxis protocol.

Of the included studies, the Scholten study is the only one demonstrating superiority of a weight based regimen and the Kalfarentzos study is the only study to demonstrate a signal for possible harm of a higher dosing regimen.

A total of 1428 patients received weight-adjusted prophylactic doses of heparin products whereas 430 patients did not. Placebo patients from the Cossu study were not included within the analyses. Post bariatric surgery patients receiving weight-adjusted prophylactic doses of heparin products, had an in hospital rate of VTE of 0.54% (95% CI: 0.2 to 1.0%) $I^2 = 0\%$ (0% to 64.1%). The rate of VTE was 2.0% (95% CI: 0.1 to 6.4%) $I^2 = 71.8\%$ (0% to 89.5%) for those that did not weight adjust doses (Fig. 2). Rates of major bleeding were for both groups: 1.6% (95% CI: 0.6 to 3.0%) $I^2 = 63.3\%$ (0% to 84.0%) for patients receiving weight-adjusted dosing compared to 2.3% (95% CI: 1.1% to 3.9%) $I^2 = 0\%$ (0% to 72.9%) for those receiving standard doses of heparin products (Fig. 2).

The quality of the included studies is depicted in Appendices 2 and 3 (on-line). All cohort studies were adequately representative. Follow up duration was deemed to be adequate for all cohort studies with the exception of one study [13] for which follow up was not able to be determined from the paper (Appendix 2). The included randomized controlled trial did not report the procedures for sequence generation, allocation concealment and blinding (Appendix 3) limiting bias assessment (Appendix 3).

## Discussion

According to the results of the pooled data of our systematic review, weight adjusted thromboprophylaxis after bariatric surgery shows a non-significant trend towards a lower rate of inpatient VTE complication without an increased rate of major bleeding.

Our reported rate of in-hospital VTE in patients receiving weight adjusted thromboprophylaxis is similar to those previously reported in the literature for non surgical obese patients which are theoretically a lower risk population [14]. This may suggest that a more aggressive thromboprophylaxis dosing strategy would be more effective at preventing thrombosis. Similarly, our rates of major bleeding episodes are similar to those previously reported. A recently published study assessing the use of non dose adjusted thromboprophylaxis for 2 weeks post bariatric surgery reported a 1% rate of bleeding requiring cessation of therapy [15] and another study found a 30 day rate of major bleeding between 1.65-1.86% [16] which are similar to our weight adjusted group and suggestive that the practice of weight adjusting heparin prophylaxis in this patient population does not lead to an increase in adverse bleeding outcomes. Finally, the clinical outcomes in our systematic review are supported by the pharmacokinetic study by Frederiksen [8] as his analysis suggests that higher doses of LMWH are needed to obtain the same pharmacologic activity in obese patients. However, future trials are needed to confirm the efficacy and safety of weight-adjusted parenteral thromboprophylaxis following bariatric surgery.

There are several limitations to interpretation of the results of this study. First, the low to moderate quality of the studies may have introduced bias into the review. Given that the primary outcome is objectively confirmed, it is likely that the bias was minimized, however, patient