Review

Pharmacologic and Mechanical Strategies for Preventing Venous Thromboembolism After Bariatric Surgery
A Systematic Review and Meta-analysis

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We sought to assess the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent venous thromboembolism (VTE) in patients undergoing bariatric surgery. We searched (through August 2012) for primary studies that had at least 2 different interventions. Of 30 902 citations, we identified 8 studies of pharmacologic strategies and 5 studies of filter placement. No studies randomized patients to receive different interventions. One study suggested that low-molecular-weight heparin is more efficacious than unfractionated heparin in preventing VTE (0.25% vs 0.68%, $P < .001$), with no significant difference in bleeding. One study suggested that prolonged therapy (after discharge) with enoxaparin sodium may prevent VTE better than inpatient treatment only. There was insufficient evidence supporting the hypothesis that filters reduce the risk of pulmonary embolism, with a point estimate suggesting increased rates with filters (pooled relative risk [RR], 1.21 95% CI, 0.57-2.56). There was low-grade evidence that filters are associated with higher mortality (pooled RR, 4.30 95% CI, 1.60-11.54) and higher deep vein thrombosis rates (2.94 1.35-6.38). There was insufficient evidence to support that augmented subcutaneous enoxaparin doses (>40 mg daily or 30 mg twice daily) are more efficacious than standard dosing, with a trend toward increased bleeding. Of note, for both filters and augmented pharmacologic dosing strategies, patients at highest risk for VTE were more likely to receive more intensive interventions, limiting our ability to attribute outcomes to prophylactic strategies used.

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Prophylaxis to prevent venous thromboembolism (VTE) is recommended for patients undergoing abdominal surgery and may include pharmacologic prophylaxis or mechanical measures, sometimes in combination.[1] Because patients undergoing bariatric surgery are often morbidly obese, it has been suggested that they may require more aggressive VTE prophylaxis than other surgical patients.[2] Obesity itself is a risk factor for VTE[3] and may lead to restricted mobility and conditions associated with VTE, such as hypertension, diabetes mellitus, and venous stasis.[4] Also, drug regimens used to prevent thrombosis in surgical patients generally are given in fixed doses that do not account for body weight.[5]

Strategies to augment VTE protection in patients undergoing bariatric surgery may include higher-than-standard (ie, augmented) dosing of usual pharmacotherapy (eg, >40 mg daily or 30 mg twice daily of enoxaparin sodium) and placement of inferior vena cava filters before surgery. The optimal approach to prophylaxis, however, remains unclear.[6] Based on the varying practice patterns among surgeons and limited guideline recommendations addressing this population specifically, we performed a systematic review to address the comparative effectiveness of pharmacologic and mechanical VTE prevention strategies in patients undergoing bariatric surgery.

Methods

This report describes strategies for preventing VTE in patients undergoing bariatric surgery. Additional methodologic details are in our evidence report prepared for the Agency for Healthcare Research and Quality[7] the full protocol was posted online (http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=928#4369).

Data Sources and Search

We searched the following databases for primary studies through August 2012: MEDLINE, EMBASE, Scopus, CINAHL, International Pharmaceutical Abstracts, clinicaltrials.gov, and the Cochrane Library. Our search strategy was defined a priori (eAppendix in Supplement). We reviewed reference lists of all included articles, relevant

review articles, and related systematic reviews to identify additional publications. We reviewed Scientific Information Packets from pharmaceutical manufacturers and requested that the Agency for Healthcare Research and Quality peer reviewers alert us to any published or unpublished data that we may have missed.

Study Selection

Two investigators independently reviewed titles and then abstracts abstracts were excluded if both investigators agreed that the article met 1 or more of the exclusion criteria. All investigators participated in this process. We included only studies that described 2 or more interventions, including devices, drugs, varying doses, or varying durations of therapy. We studied only drugs available in the United States in 2011. We included only studies that focused on clinical end points (rather than pharmacokinetic end points or subjective end points such as satisfaction).

Outcomes

Prospectively identified outcomes included (1) pulmonary embolism (PE), fatal and nonfatal (2) deep vein thrombosis (DVT), including vena cava thrombosis (3) bleeding as defined by the investigators of each study (4) all-cause mortality (5) filter complications and (6) adverse drug reactions.

Data Abstraction and Quality Assessment

We used a data extraction tool (DistillerSR, 2010 version Evidence Partners) to manage the screening and review process. Paired investigators reviewed all extracted data, with disagreements resolved by consensus. We assessed the risk of bias for each study independently and in duplicate, using 10 items from the Downs and Black[8] instrument that we found most relevant to this review. Studies could be considered to have low risk of bias only if allocation to interventions was randomized and blinded.

Data Synthesis and Analysis

For outcomes reported in 3 or more studies, we used I^2 values to assess heterogeneity (with >50% defined as high heterogeneity). We used random-effects models to estimate pooled effect sizes, with 95% CIs for individual studies.

Grading the Evidence and Applicability

We graded the quantity, quality, and consistency of evidence by adapting a grading scheme recommended in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[9] We placed evidence into 4 categories: high, moderate, and low (reflecting the degree of confidence that the evidence reflects a true effect) and insufficient.

Results

Study Characteristics

There were 30 902 unique citations identified by the electronic search (**Figure 1**). Two additional articles were identified by an Agency for Healthcare Research and Quality peer reviewer that were not yet published but provided updated analyses from a large multicenter registry.[10,11] To avoid double-counting patients, we eliminated an earlier report from the same registry.[12] We ultimately included 13 articles,[11,13-24] including 5 that included patients with and without filters (**Table 1**)[11,15,17,19,24] and 8 that included patients receiving different pharmacologic regimens (**Table 2**).[10,13,14,16,18,22,23,25] All included studies used an observational cohort design.

Participant Characteristics

Patients underwent bariatric procedures, including Roux-en-Y gastric bypass (predominantly laparoscopic), sleeve gastrectomy, adjustable laparoscopic gastric banding, and biliary-pancreatic diversion. Patient characteristics were generally consistent across studies. Most reports did not describe the prevalence of prior VTE. Duration of follow-up was generally 2 to 6 weeks however, one study reported follow-up of more than 2 years.[23]

Patient and hospitalization characteristics varied by treatment allocation. More intensive prophylaxis often was targeted toward patients at higher thrombosis risks. In the registry studies by Birkmeyer et al[10,11] and Li et al,[24] patients receiving filters tended to have lower baseline mobility, be men, and have a prior history of VTE. Overby et al[15] offered filters to patients with elevated levels of coagulation markers, impaired mobility, severe sleep apnea or hypoventilation, prior VTE, and more severe obesity. Obeid et al[17] preferentially placed filters in the most obese patients and in those with prior VTE.

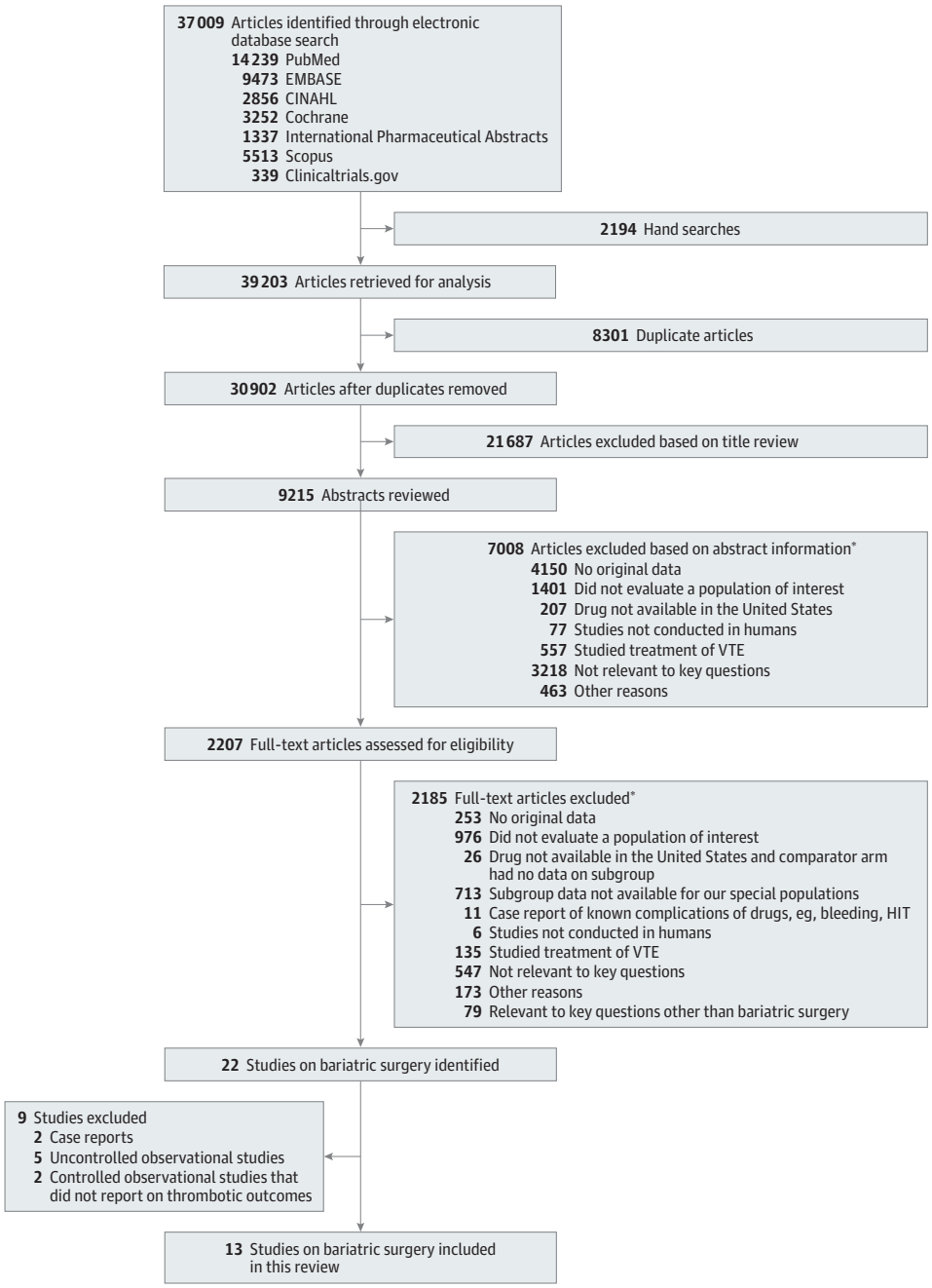
Higher-intensity pharmacologic regimens were prescribed preferentially for higher-risk surgical patients depending on type of surgery (laparoscopic vs open), duration of surgery, or length of hospital stay. Of the 3 studies[16,22,23] of pharmacologic prophylaxis that used enoxaparin doses of 60 mg twice daily, 2 studies[22,23] did so only in the most obese patients. In the single study[14] of prolonged pharmacologic prophylaxis vs inpatient prophylaxis alone, 132 patients who underwent surgery between 2003 and 2005 received 30 mg twice daily of enoxaparin subcutaneously starting 1 hour preoperatively and continuing through hospitalization, which averaged 3.0 days. A second group of 176 patients who underwent surgery in 2006 and 2007 received enoxaparin starting 12 hours postoperatively, continuing throughout hospitalization (averaging 2.2 days) and for 10 days after discharge. In addition to the significantly shorter length of stay in the second group, patients in this group had fewer open procedures (0 vs 4 patients) and fewer conversions to open procedures after failed laparoscopic interventions (0 vs 5 patients).

Interventions

Filter types varied according to physician practice and preference and included the retrievable Gunther Tulip (Cook Medical), Bard Recovery (Bard), OptEase (Cordis Corporation), Cook Celect (Cook Medical), and Bard G2 (Bard), as well as filters that generally are not intended for retrieval, including the Greenfield stainless steel (Boston Scientific), Simon Nitinol (Bard), and Cordis TRAPEASE (Cordis) filters. The registry studies by Birkmeyer et al[11] and Li et al[24] did not report specific filter types. Concurrent use of sequential compression devices and pharmacotherapy (enoxaparin, heparin sodium, or warfarin sodium) was described by some authors.[15,17] Only one study[15] reported filter retrieval rates, at 92%.

Enoxaparin and unfractionated heparin were the only drugs evaluated specifically however, one registry study[10] combined patients taking any low-molecular-weight heparin (LMWH) into a single group. Five studies[13,16,18,22,23] featured varying doses of

Figure 1. Flow Diagram of Studies Included in the Systematic Review



HIT indicates heparin-induced thrombocytopenia and VTE, venous thromboembolism. *Total exceeds the number in the exclusion box because reviewers were allowed to mark more than 1 reason for exclusion.

enoxaparin, 2 studies[22,23] of which used weight-based dosing. In the study[25] that included patients receiving either enoxaparin or unfractionated heparin, one group of patients received 40 mg of enoxaparin subcutaneously twice daily and another group received 5000 U of unfractionated heparin subcutaneously every 8 hours. In one study,[14] all patients received 30 mg of enoxaparin subcutaneously twice daily, but the timing and duration of prophylaxis differed between the 2 comparison groups. Dosing regimens of enoxaparin ranged from 30 mg once daily to 60 mg twice daily (Table 2). We categorized doses as standard prophylactic dosing (enoxaparin, 30 mg twice daily or 40 mg once daily, and heparin, 5000 U every 8 hours) or augmented dosing, including enoxaparin, 40 mg, 50 mg, and 60 mg twice daily. According to this classification, 3 studies[13,18,23] included groups of patients receiving standard vs augmented dosing, and 3 studies[16,22,23] compared 2 or more augmented dosing regimens. One of these studies[18] also

Table 1. Characteristics of Studies of Inferior Vena Cava Filters Among Patients Undergoing Bariatric Surgery

Source	Design	Arm	No. of Patients	Age, Mean, y	Male Sex, %	BMI
Gargiulo et al,[19] 2006	Retrospective-prospective	Filter	58	NR	41.3[a]	>55 in 100%
		No filter	351	NR	41.3[a]	>55 in 12%
Birkmeyer et al,[11]2013	Retrospective cohort with propensity-matched controls	Filter	1077	48	32	58
		No filter	1077	49	31	57
Obeid et al,[17] 2007	Retrospective cohort	Filter	246	46.6	23.6	60.0
		No filter	1847	44.7	14.0	48.8
Overby et al,[15] 2009	Retrospective cohort	Filter	160	NR	14.55[a]	51.42[a]
		No filter	170	NR	14.55[a]	51.42[a]
Li et al,[24] 2012	Retrospective cohort	Filter	322	47	31.4	45.3
		No filter	96 806	46	21.1	44.5

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NR, not reported.

[a] Data for entire cohort rather than specific subgroup.

Table 2. Characteristics of Studies of Pharmacologic Comparisons Among Patients Undergoing Bariatric Surgery

Source	Design	Intervention and Comparator	No.	Age, Mean, y	Male Sex, %	BMI
Kothari et al,[25] 2007	Prospective cohort	Enoxaparin, 40 mg subcutaneously twice daily, and SCD, ambulation (A)	238	42[a]	NR	48.7
		Heparin, 5000 U subcutaneously every 8 h, and SCD, ambulation (S)	238	44[a]	NR	47
Borkgren-Okonek et al,[22] 2008	Prospective cohort	Enoxaparin, 40 mg subcutaneously twice daily, SCD, ambulation and preoperative heparin 5000 U subcutaneously, BMI <50 and once daily for 10 d after discharge (A)	124	44.7	22.6	44.9
		Enoxaparin, 60 mg subcutaneously twice daily, SCD, ambulation and preoperative heparin subcutaneously, BMI >50 and once daily for 10 d after discharge (A)	99	44.3	27.3	57.4
Raftopoulos et al,[14] 2008	Prospective cohort	Enoxaparin, 30 mg subcutaneously twice daily, extended for 10 d after discharge (S)	176	44.1	18.75	46.1
		Enoxaparin, 30 mg subcutaneously twice daily, during hospital stay, SCD (S)	132	42.6	15.2	47.8
Scholten et al,[13] 2002	Prospective cohort	Enoxaparin, 40 mg subcutaneously twice daily, SCD, and ambulation (A)	389	44.3	15.8	50.4
		Enoxaparin, 30 mg subcutaneously twice daily, and SCD, ambulation (S)	92	43.7	20.2	51.7
Singh et al,[23] 2012	Prospective cohort	Enoxaparin, 40 mg subcutaneously twice daily, ambulation for BMI 41-49 (A)	145	43[a]	53[a]	48
		Enoxaparin, 50 mg subcutaneously twice daily, ambulation for BMI 50-59 (A)	9	43[a]	53[a]	51
		Enoxaparin, 60 mg subcutaneously twice daily, ambulation for BMI >60 (A)	5	43[a]	53[a]	65
		Enoxaparin, 30 mg subcutaneously twice daily, ambulation for BMI <40 (S)	11	43[a]	53[a]	39
Hamad and Choban,[18] 2005	Prospective cohort	Enoxaparin, 40 mg subcutaneously twice daily (A)	180	39.7	3	46
		Enoxaparin, 40 mg subcutaneously once daily, (S) postoperatively for 12-120 h	84	47.5	29	56.8
		Enoxaparin, 40 mg subcutaneously once daily, (S) postoperatively for 12-24 h	180	41.9	10	49.9
		Enoxaparin, 30 mg subcutaneously once daily, (R) preoperatively	100	39.5	25	47
		Enoxaparin, 30 mg subcutaneously once daily, (R) after discharge	124	42.1	18	51.5
Ojo et al,[16] 2008	Prospective cohort	Enoxaparin, 40 mg subcutaneously twice daily (S)	59	48	33.9	57
		Enoxaparin, 60 mg subcutaneously, twice daily (A)	68	46	61.8	58
Birkmeyer et al,[10] 2012	Prospective cohort	Preoperative and postoperative UFH	4402	>60 y, 13%	23	>60, 9%
		Preoperative UFH and postoperative LMWH	4482	>60 y, 10%	20	>60, 10%
		Preoperative and postoperative LMWH	15 891	>60 y, 12%	23	>60, 9%

Abbreviations: A, augmented dose; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); LMWH, low-molecular-weight heparin; NR, not reported; R, reduced dose; S, standard dose given for venous thromboembolism prophylaxis; SCD, sequential compression devices; UFH, unfractionated heparin.

[a] Data for entire cohort rather than specific subgroup.

Table 3. Venous Thromboembolism Outcomes Among Patients Undergoing Bariatric Surgery Who Received Inferior Vena Cava Filters vs Control

Source	Design	Arm	No.	No. (%) PE	No. (%) DVT, Including Device-Related DVT	No. (%) Total Mortality
Birkmeyer et al,[11] 2013	Retrospective cohort with propensity-matched controls	Filter	1077	9 (0.8)	13 (1.2)	7 (0.7)[a]
		No filter	1077	5 (0.5)	4 (0.4)	1 (0.09)
Obeid et al,[17] 2007	Retrospective cohort	Filter	246	2 (0.8)	3 (1.2)	2 (0.81)
		No filter	1847	11 (0.59)	12 (0.65)	4 (0.22)
Overby et al,[15] 2009	Retrospective cohort	Filter	160	1 (0.63)	5 (3.13)	3 (0.9)
		No filter	170	5 (2.94)	4 (2.35)	
Gargiulo et al,[19] 2006	Retrospective-prospective	Filter	58	0	2 (3)	0[b]
		No filter	351	9 (2.56)	NR	5 (1.42)[b]
Li et al,[24] 2012	Retrospective cohort	Filter	322	1 (0.31)	3 (0.93)	1 (0.31)
		No Filter	96 806	116 (0.12)	116 (0.12)	29 (0.03)

Abbreviations: DVT, deep vein thrombosis; NR, not reported; PE, pulmonary embolism.

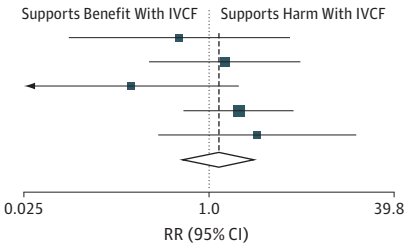
[a] Among the 7 inferior vena cava filter patients who died, 4 had PE and 2 had inferior vena cava filter thrombosis/occlusion the cause of death for the seventh patient was not reported.

[b] Authors reported PE-related mortality.

Figure 2. Relative Risk (RR) Meta-analysis of inferior Vena Cava Filters (IVCFs) in Preventing Pulmonary Embolism in Patients Undergoing Bariatric Surgery

Source	IVCF Events	IVCF Total	No IVCF Events	No IVCF Total	RR (95% CI)	Weight
Gargiulo et al,[19] 2006	0	58	9	351	0.55 (0.06-4.96)	11.19
Obeid et al,[17] 2007	2	246	11	1847	1.37 (0.30-6.12)	22.87
Overby et al,[15] 2009	1	160	5	170	0.21 (0.03-1.80)	11.79
Birkmeyer et al,[11] 2013	9	1077	5	1077	1.80 (0.61-5.35)	40.32
Li et al,[24] 2012	1	322	116	96 806	2.59 (0.36-18.50)	13.82
Total	13	1863	146	100 251	1.21 (0.57-2.56)	100.00

Overall: $I^2 = 6.9\%$, $P = .37$
Note: Weights are from random-effects analysis
Test of RR = 1: $z = 0.50$; $P = .62$



The shaded box sizes are proportional to the weight of each study blue diamond shows the CI of the pooled effect size. Black bars denote CIs for individual studies, and dotted line indicates the pooled effect estimate.

included patients receiving reduced enoxaparin dosing (30 mg once daily). One registry study[10] compared unfractionated heparin with LMWH but did not account for different dosing strategies. Four studies[13,14,23,25] initiated pharmacotherapy prior to surgery, and 2 studies[16,22] initiated pharmacotherapy after surgery the timing was variable in the 5-center study by Hamad and Choban.[18] The planned duration of pharmacotherapy was for the entire hospital stay in 2 studies,[14,25] until "fully ambulatory" or hospital discharge in 1 study,[13] for 2 weeks postoperatively in 1 study,[16] for 10 days following discharge in 1 study,[22] was not clearly specified in 2 publications,[11,23] and varied by center in another investigation.[18] Some studies described concurrent mechanical prophylaxis, including pneumatic compression[13,14,22,23,25] and early ambulation.[13,22,23] None of the reports indicated that these nonpharmacologic prophylactic measures were delivered to only 1 treatment arm.

Outcomes

Most studies relied on clinically diagnosed (symptomatic) thrombosis and did not use routine surveillance for VTE prior to hospital discharge. However, one study[15] reported using ultrasonography and/or computed tomographic venography prior to filter removal, and another[14] reported performing bilateral lower extremity ultrasonography before discharge.

Inferior Vena Cava Filter vs No Inferior Vena Cava Filter

In studies of filter use, there was substantial variability with regard to PE and mortality (**Table 3** and **Figures 2**, **3**, and **4**). Gargiulo et al[19] reported no PEs among 58 patients receiving filters and 9 PEs among 351 patients who did not receive filters, of which 5 PEs were fatal. However, the large registry studies by Li et al[24] and Birkmeyer et al[11,12] found higher PE rates among patients with filters. There also was consistency in that filters were associated with higher rates of DVT (Table 3 and Figure 3).

Reported filter complications included filter migration to the heart requiring heart valve replacement (1 patient),[11] fatal inferior vena cava thrombosis (2 patients),[11] pneumothorax (1 patient),[15] hemopericardium (1 patient),[15] contrast nephropathy (1 patient),[11] incision site infection (1 patient),[11] and the inability to perform transvenous ablation of a cardiac accessory pathway because of the filter (1 patient).[15]

LMWH vs Unfractionated Heparin

Two studies compared unfractionated heparin with LMWH[11,25] (**Table 4** and **Table 5**). In the study by Kothari et al[25] comparing enoxaparin, 40 mg administered subcutaneously twice daily, with unfractionated heparin, 5000 U administered every 8 hours, a single PE occurred in the heparin-treated patients (0.42%), with no thrombotic events in the enoxaparin-treated patients. Bleeding events re-

Figure 3. Relative Risk (RR) Meta-analysis of Inferior Vena Cava Filters (IVCFs) and Deep Vein Thrombosis in Patients Undergoing Bariatric Surgery

Source	IVCF Events	IVCF Total	No IVCF Events	No IVCF Total	RR (95% CI)	Weight
Obeid et al,[17] 2007	3	246	12	1847	1.88 (0.53-6.61)	23.60
Overby et al,[15] 2009	5	160	4	170	1.33 (0.36-4.86)	22.72
Birkmeyer et al,[11] 2013	13	1077	4	1077	3.25 (1.06-9.94)	27.15
Li et al,[24] 2012	3	322	116	96806	7.78 (2.48-24.33)	26.52
Total	24	1805	136	99900	2.94 (1.35-6.38)	100.00

Overall: I^2 = 40.3%, P = .17
Note: Weights are from random-effects analysis
Test of RR = 1: z = 2.72; P = .007

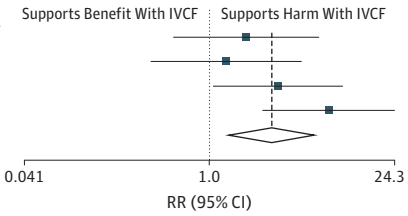
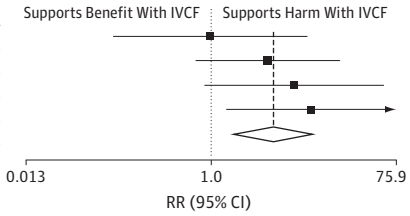


Figure 4. Relative Risk (RR) Meta-analysis of Inferior Vena Cava Filters (IVCFs) and Mortality in Patients Undergoing Bariatric Surgery

Source	IVCF Events	IVCF Total	No IVCF Events	No IVCF Total	RR (95% CI)	Weight
Gargiulo et al,[19] 2006	0	58	5	351	0.98 (0.10-9.49)	18.97
Obeid et al,[17] 2007	2	246	4	1847	3.75 (0.69-20.39)	34.10
Birkmeyer et al,[11] 2013	7	1077	1	1077	7.00 (0.86-56.80)	22.28
Li et al,[24] 2012	1	322	29	96806	10.37 (1.42-75.87)	24.65
Total	10	1703	39	100081	4.30 (1.60-11.54)	100.00

Overall: I^2 = 0%, P = .45
Note: Weights are from random-effects analysis
Test of RR = 1: z = 2.89; P = .004



quiring transfusion and reoperation were higher among enoxaparin-treated patients. The registry study by Birkmeyer et al[10] compared patients receiving LMWH regimens with those receiving unfractionated heparin regimens (doses not specified) and found that patients who received prophylaxis with LMWH preoperatively and postoperatively had a lower adjusted rate of VTE (0.25%) than did those receiving unfractionated heparin preoperatively and postoperatively (0.68%) (P < .001). Bleeding occurred in a similar percentage of patients receiving unfractionated heparin and LMWH (adjusted rates, 1.69% and 1.65%, respectively adjusted odds ratio, 0.94 95% CI, 0.63-1.41 P = .78), with major bleeding (>4 U of blood transfused or reoperation) in 0.46% and 0.38%, respectively (adjusted OR, 0.75 95% CI, 0.38-1.47 P = .40).

Enoxaparin vs Extended-Duration Enoxaparin

Raftopoulos et al[14] reported thrombotic events in 6 of 132 patients (4.5%) receiving short-term enoxaparin prophylaxis and none of 176 patients receiving extended prophylaxis (P = .006) (Tables 4 and 5). This difference remained statistically significant after excluding patients who required conversion to open procedures (P = 0.03). Bleeding requiring reoperation occurred in 1 patient from each group.

Enoxaparin at Standard vs Augmented Dosing

Three studies[13,18,23] reported on VTE outcomes in patients receiving standard vs augmented enoxaparin dosing (Tables 4 and 5). In the study by Scholten et al,[13] among 92 patients receiving enoxaparin, 30 mg twice daily (standard dosing), there were 5 thrombotic events (5.4%), whereas among 389 patients who received 40 mg twice daily (augmented), there were 2 thrombotic events (0.5%). In the studies by Singh et al[23] and Hamad and Choban,[18] rates of VTE were comparable for patients receiving different doses of enoxaparin. None of the 3 studies reported any perioperative deaths. Bleeding events were infrequent but slightly more common overall with augmented dosing.

Strength of Evidence

All included studies were rated as having a high risk of bias except 2 of them[10,11] that we rated as having a moderate risk of bias (**Table 6** and **Table 7**). The preference of the surgical team or the protocol used at the center during a particular time frame usually defined the prophylactic strategy, and interventions often were allocated on the basis of real or perceived risk factors for postoperative VTE, such as prior VTE, age, degree of immobility, or severity of obesity. This targeted approach would tend to bias toward poorer efficacy with more aggressive prophylactic strategies because these were used in patients at higher risk. None of the studies performed multivariable adjustments to account for patient differences according to intervention allocation except the 2 that we rated as having moderate risk of bias.[10,11] None of the studies focusing on differing intensity, timing, or duration of pharmacologic prophylaxis used multivariable adjustment to account for differences between patients receiving different prophylactic strategies.

For filters, there was consistency suggesting a higher risk of DVT in patients receiving the intervention however, based on the limitations of the source data, we graded the strength of evidence as low. We also graded the strength of evidence that filters do not prevent PE or total mortality as low. We rated the strength of evidence as insufficient for all outcomes and comparisons in studies that evaluated pharmacologic interventions because of the inconsistencies and imprecision in the body of evidence.

Discussion

Overall, our findings support the use of "standard" doses of pharmacotherapy as prophylaxis for patients undergoing bariatric sur-

Table 4. Venous Thromboembolism Outcomes Among Bariatric Surgery Patients Undergoing Pharmacologic Prophylaxis

Source	Design	Arm	No.	Perioperative, No. (%)	
				PE	DVT
Kothari et al,[25] 2007	Retrospective cohort	Enoxaparin, 40 mg subcutaneously twice daily, and SCD, ambulation	238	0	0
		Heparin, 5000 U subcutaneously every 8 h, and SCD, ambulation	238	1 (0.42)	0
Raftopoulos et al,[14] 2008[a]	Retrospective cohort	Enoxaparin, 30 mg subcutaneously twice daily, SCD extended for 10 d after discharge	176	0	0
		Enoxaparin, 30 mg subcutaneously twice daily, SCD during hospital stay, SCD	132	3 (2.3)	3 (2.3)
Scholten et al,[13] 2002[b]	Retrospective cohort	Enoxaparin, 40 mg subcutaneously twice daily, SCD and ambulation (A)	389	0	2 (0.5)
		Enoxaparin, 30 mg subcutaneously twice daily, and SCD, ambulation (S)	92	4 (4.3)	1 (1.1)
Singh et al,[23] 2012	Retrospective cohort	Enoxaparin, 40 mg subcutaneously twice daily, SCD, ambulation for BMI 41-49 (A)	145	0	0
		Enoxaparin, 50 mg subcutaneously twice daily, SCD, ambulation for BMI 50-59 (A)	9	0	0
		Enoxaparin, 60 mg subcutaneously twice daily, SCD, ambulation for BMI >60 (A)	5	0	0
		Enoxaparin, 30 mg subcutaneously twice daily, SCD, ambulation for BMI <40 (S)	11	0	0
Hamad and Choban,[18] 2005	Retrospective cohort	Enoxaparin, 40 mg subcutaneously twice daily, (A)	180	1 (0.6)	0
		Enoxaparin, 40 mg subcutaneously once daily, (S) postoperatively for 12-120 h	84	1 (1)	0
		Enoxaparin, 40 mg subcutaneously once daily, (S) postoperatively for 12-24 h	180	0	0
		Enoxaparin, 30 mg subcutaneously once daily, (R) preoperatively	100	2 (2)	0
		Enoxaparin, 30 mg subcutaneously once daily, (R) after discharge	124	2 (1.6)	1 (0.8)
Borkgren-Okonek et al,[22] 2008	Retrospective cohort	Enoxaparin, 40 mg subcutaneously twice daily, SCD, ambulation and preoperative heparin subcutaneously, BMI ≤50, and once daily for 10 d after discharge	124	NR	NR
		Enoxaparin, 60 mg subcutaneously twice daily, SCD, ambulation and preoperative heparin subcutaneously, BMI >50, and once daily for 10 d after discharge	99	NR	NR
Ojo et al,[16] 2008	Retrospective cohort	Enoxaparin, 40 mg subcutaneously twice daily	59	NR	NR
		Enoxaparin, 60 mg subcutaneously twice daily	68	NR	NR
Birkmeyer et al,[10] 2013[c]	Retrospective cohort	Preoperative and postoperative UFH	4402	Total VTE	...
		Preoperative UFH and postoperative LMWH	4482	Total VTE	...
		Preoperative and postoperative LMWH	15 891	Total VTE	...

Abbreviations: A, augmented dose; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ellipsis, not applicable; LMWH, low-molecular-weight heparin; NR, not reported; PE, pulmonary embolism; R, reduced dose; S, standard dose given for VTE prophylaxis; SCD, sequential compression devices; UFH, unfractionated heparin; VTE, venous thromboembolism.

[a] Also reported a statistically significant difference in VTE outcomes between extended-duration vs short-term enoxaparin group, 6 vs 0 or 4.5% vs 0% $P = .006$.

[b] Also reported a statistically significant difference in VTE outcomes between standard dose and augmented dose, 5 vs 2 or 5.4% vs 0.6% $P < .01$.

[c] Reported a statistically significant difference in total VTE outcomes between UFH/UFH and UFH/LMWH, 0.29% vs 0.68% $P = .028$ (reference group, UFH/UFH) and between LMWH/LMWH vs UFH/UFH, 0.25% vs 0.68% $P < .0001$ (reference group, UFH/UFH).

gery, consistent with current American College of Chest Physicians guidelines,[1] which do not distinguish between patients undergoing bariatric surgery and those undergoing other types of abdominal surgery. Similarly, a position statement issued by the Clinical Issues Committee of the American Society for Metabolic and Bariatric Surgery[26] declined to recommend any specific anticoagulant or filter placement strategy in bariatric surgery patients but did recommend that those without contraindications to anticoagulation prophylaxis should generally receive it. We found no evidence to support filter placement as prophylaxis in patients undergoing bariatric surgery, with a trend toward higher DVT rates and higher mortality in patients receiving filters. Based on one study that evaluated LMWH vs unfractionated heparin and found that the rate of thrombosis was significantly lower with LMWH[10] and another study that evaluated prolonged prophylaxis for 10 days after hospital discharge and found that thrombosis rates were significantly lower with prolonged prophylaxis,[14] clinicians may consider either or both of these approaches. The rate of fatal PE appears to be low in patients receiv-

Table 5. Safety Profile of Pharmacologic Interventions to Prevent Venous Thromboembolism in Bariatric Surgical Patients

Source	Arm	No. of Patients	No. (%)			
			Bleeding Requiring			
			Packed Red Blood Cells	Surgery	Minor Bleeding	Total Perioperative Mortality
Enoxaparin vs unfractionated heparin						
Kothari et al,[25] 2007	Enoxaparin, 40 mg subcutaneously twice daily, and SCD, ambulation	238	14 (5.9)	4 (1.7)	NR	0
	Heparin, 5000 U subcutaneously every 8 h, and SCD, ambulation	238	3 (1.3)	0	NR	0
Enoxaparin vs extended-duration enoxaparin						
Raftopoulos et al,[14] 2008	Enoxaparin, 30 mg subcutaneously twice daily, extended for 10 d after discharge	176	0	1 (0.56)	NR	0
	Enoxaparin, 30 mg subcutaneously twice daily, during hospital stay, SCD	132	6 (4.5)	1 (0.75)	NR	0
Enoxaparin at standard vs augmented dosing						
Scholten et al,[13] 2002	Enoxaparin, 40 mg subcutaneously twice daily, SCD and ambulation (A)	389	NR	1 (0.26)	NR	NR
	Enoxaparin, 30 mg subcutaneously twice daily, SCD, and ambulation (S)	92	1 (1.1)	NR	NR	NR
Singh et al,[23] 2012	Enoxaparin, 40 mg subcutaneously twice daily, ambulation for BMI 41-49 (A)	145	4 (2.8)	1 (0.7)	NR	NR
	Enoxaparin, 50 mg subcutaneously twice daily, ambulation for BMI 50-59 (A)	9	0	0	NR	NR
	Enoxaparin, 60 mg subcutaneously twice daily, ambulation for BMI >60 (A)	5	1 (20)	0	NR	NR
	Enoxaparin, 30 mg subcutaneously twice daily, ambulation for BMI <40 (S)	11	0	0	NR	NR
Hamad and Choban,[18] 2005	Enoxaparin, 40 mg subcutaneously twice daily, (A)	180	3 (1.7)	NR	NR	NR
	Enoxaparin, 40 mg subcutaneously once daily, (S) postoperatively for 12-120 h	84	0	NR	NR	NR
	Enoxaparin, 40 mg subcutaneously once daily, (S) postoperatively for 12-24 h	180	3 (1.7)	NR	NR	NR
	Enoxaparin, 30 mg subcutaneously once daily, (R) preoperatively	100	0	NR	NR	NR
	Enoxaparin, 30 mg subcutaneously once daily, (R) after discharge	124	1 (0.8)	NR	NR	2 (1.6)
Differing augmented enoxaparin dosing regimens						
Borkgren-Okonek et al,[22] 2008	Enoxaparin, 40 mg subcutaneously twice daily, SCD, ambulation and preoperative heparin subcutaneously, BMI ≤50 and once daily for 10 d after discharge	124	4 (3.2)	1 (0.8)	NR	0
	Enoxaparin, 60 mg subcutaneously twice daily, SCD, ambulation and preoperative heparin subcutaneously, BMI >50 and once daily for 10 d after discharge	99	1 (1)	0	NR	1 (1)
Singh et al,[23] 2011	Enoxaparin, 40 mg subcutaneously twice daily, ambulation for BMI 41-49 (A)	145	4 (2.8)	1 (0.7)	NR	NR
	Enoxaparin, 50 mg subcutaneously twice daily, ambulation for BMI 50-59 (A)	9	0	0	NR	NR
	Enoxaparin, 60 mg subcutaneously twice daily, ambulation for BMI >60 (A)	5	1 (20)	0	NR	NR
	Enoxaparin, 30 mg subcutaneously twice daily, ambulation for BMI <40 (S)	11	0	0	NR	NR

(continued)

Table 5. Safety Profile of Pharmacologic Interventions to Prevent Venous Thromboembolism in Bariatric Surgical Patients (continued)

Source	Arm	No. of Patients	No. (%)			
			Bleeding Requiring			
			Packed Red Blood Cells	Surgery	Minor Bleeding	Total Perioperative Mortality
Ojo et al,[16] 2008	Enoxaparin, 40 mg subcutaneously twice daily	59	0	NR	NR	NR
	Enoxaparin, 60 mg subcutaneously twice daily	68	0	NR	NR	NR
Unspecified dosing regimens						
Birkmeyer et al,[10]2012	Preoperative and postoperative UFH	4402	20 (0.46)[a]	[b]	74 (1.69)	NR
	Preoperative UFH and postoperative LMWH	4482	27 (0.60)[a]	[b]	83 (1.86)	NR
	Preoperative and postoperative LMWH	15 891	60 (0.38)[a]	[b]	262 (1.65)	NR

Abbreviations: A, augmented dose; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); LMWH, low-molecular-weight heparin; NR, not reported; R, reduced dose; S, standard dose given for VTE prophylaxis; SCD, sequential compression devices; UFH, unfractionated heparin; VTE, venous thromboembolism.

[a] Authors described serious hemorrhage as that occurring within 30 days after surgery and requiring more than 4 U of blood products or reoperation.

[b] Not applicable because the outcomes of major bleeding requiring transfusion and requiring surgery were combined.

Table 6. Body of Evidence for IVCF vs Controls for the Prevention of PE in Patients Undergoing Bariatric Surgery[a]

Outcome, Source	Risk of Bias	Magnitude of Effect
PE	High	Insufficient evidence to support that prophylactic IVCFs reduce PE in patients undergoing bariatric surgery vs controls RR, 1.21 (95% CI, 0.57-2.56 P = .62 I^2 = 6.9%)
Obeid et al,[17] 2007	High	0.8 vs 0.6% P = .69
Overby et al,[15] 2009	High	0.6% vs 2.9% P = .22
Gargiulo et al,[19] 2006	High	0% vs 2.6%
Li et al,[24] 2012	High	0.31% vs 0.12% P = .33
Birkmeyer et al,[11] 2013	Moderate	0.8% vs 0.5% P = .23
Fatal PE	High	Insufficient evidence to comment on effectiveness of IVCF vs controls in reducing fatal PE in patients undergoing bariatric surgery
Gargiulo et al,[19] 2006	High	0% vs 11.1%
DVT	High	Low-grade evidence to support that IVCFs increase DVT in patients undergoing bariatric surgery vs controls RR, 2.94 (95% CI, 1.35 to 6.38 P = .007I^2 = 40.3%)
Obeid et al,[17] 2007	High	1.2% vs 0.65% P = .56
Overby et al,[15] 2009	High	3.1% vs 2.4% P = .74
Gargiulo et al,[19] 2006	High	3.4% vs NR
Li et al,[24] 2012	High	0.9% vs 0.1% P < .001
Birkmeyer et al,[11] 2013	Moderate	1.2% vs 0.4% P = .04
Mortality[b]	High	Low-grade evidence to support that prophylactic IVCFs are associated with higher total mortality in patients undergoing bariatric surgery vs controls RR, 4.30 (95% CI, 1.60-11.54 P = .004 I^2 = 0.0%)
Birkmeyer et al,[11] 2013	Moderate	0.7% vs 0.1% P = .07
Obeid et al,[17] 2007	High	0.8% vs 0.2% P = .37
Gargiulo et al,[19] 2006	High	0% vs 1.4%
Li et al,[24] 2012	High	0.31% vs 0.03% P = .003

Abbreviations: DVT, deep vein thrombosis; IVCF, inferior vena cava filters; PE, pulmonary embolism; RR, relative risk.

[a] There were no randomized clinical trials these reported on mortality and permanent disability.

[b] Mortality rated as insufficient despite the absence of statistical heterogeneity (I^2 = 0%) because of clinical heterogeneity with filters being channeled to high-risk patients.

ing pharmacologic prophylaxis when used in conjunction with compression devices or stockings and early ambulation. In addition, studies that focused on inferior vena cava filters generally included patients receiving concurrent pharmacologic prophylaxis.

Our systematic review identified important weaknesses in the literature. We found no randomized clinical trials addressing the comparative effectiveness of differing interventions to prevent VTE in patients undergoing bariatric surgery, and only 2 studies (one of filters[11]

Table 7. Body of Evidence for Pharmacologic Prophylaxis for the Prevention of Venous Thromboembolism in Patients Undergoing Bariatric Surgery

Outcome, Source	Risk of Bias	Magnitude of Effect
Enoxaparin vs UFH		
PE	High	Insufficient evidence to comment on effectiveness of enoxaparin vs UFH in reducing PE in patients undergoing bariatric surgery
Kothari et al,[25] 2007		0% vs 0.4% *P* = .99
DVT	High	Insufficient evidence to comment on effectiveness of enoxaparin vs UFH in reducing DVT in patients undergoing bariatric surgery
Kothari et al,[25] 2007	High	0% vs 0%
Major bleeding[a]	High	Insufficient evidence to comment on effectiveness of enoxaparin vs UFH in reducing major bleeding in patients undergoing bariatric surgery
Kothari et al,[25] 2007	High	5.9% vs 1.3% *P* = .011
Mortality	High	Insufficient evidence to comment on effectiveness of enoxaparin vs UFH in reducing mortality in patients undergoing bariatric surgery
Kothari et al,[25] 2007	High	0% vs 0%
Enoxaparin vs Extended-Duration Enoxaparin		
PE	High	Insufficient evidence to comment on effectiveness of enoxaparin vs extended duration enoxaparin in reducing PE in patients undergoing bariatric surgery
Raftopoulos et al,[14] 2008	High	2.3% vs 0%
VTE	High	Insufficient evidence to comment on effectiveness of enoxaparin vs extended duration enoxaparin in reducing VTE in patients undergoing bariatric surgery
Raftopoulos et al,[14] 2008	High	4.5% vs 0% *P* = .006
DVT	High	Insufficient evidence to comment on effectiveness of enoxaparin vs extended duration enoxaparin in reducing DVT in patients undergoing bariatric surgery
Raftopoulos et al,[14] 2008	High	2.3% vs 0%
Major bleeding[a]	High	Insufficient evidence to comment on effectiveness of enoxaparin vs extended duration enoxaparin in reducing major bleeding in patients undergoing bariatric surgery
Raftopoulos et al,[14] 2008	High	4.5% vs 0% *P* = .006
Mortality	High	Insufficient evidence to comment on effectiveness of enoxaparin vs extended duration enoxaparin in reducing mortality in patients undergoing bariatric surgery
Raftopoulos et al,[14] 2008	High	0% vs 0% *P* = NS
PE	High	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs augmented dosing in reducing PE in patients undergoing bariatric surgery
Scholten et al,[13] 2002	High	4.3% vs 0%
Singh et al,[23] 2012	High	0% vs 0%
Hamad and Choban,[18] 2005	High	0.4% vs 0.6%
DVT	High	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs augmented dosing in reducing DVT in patients undergoing bariatric surgery
Scholten et al,[13] 2002	High	1.1% vs 0.5%
Singh et al,[23] 2012	High	0% vs 0%
Hamad and Choban,[18] 2005	High	0% vs 0%
VTE	High	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs augmented dosing in reducing VTE in patients undergoing bariatric surgery
Scholten et al,[13] 2002	High	5.4% vs 0.5% *P* < .01
Bleeding	High	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs augmented dosing in reducing bleeding in patients undergoing bariatric surgery
Singh et al,[23] 2012	High	0% vs 3.1%
Hamad and Choban,[18] 2005	High	1.1% vs 1.7%
Scholten et al,[13] 2002	High	1.1% vs 0.26% *P* = NS
Unspecified Dosing Regimens, LMWH vs UFH		
Major bleeding	High	Insufficient evidence to comment on effectiveness of LMWH vs UFH in reducing bleeding in patients undergoing bariatric surgery
Birkmeyer et al,[10] 2012	Moderate	Adjusted rate, 0.38% vs 0.46% *P* = .40
Any VTE	High	Insufficient evidence to comment on effectiveness of LMWH vs UFH in preventing thrombosis in patients undergoing bariatric surgery
Birkmeyer et al,[10] 2012	Moderate	Adjusted rate, 0.25% vs 0.68% *P* < .001

Abbreviations: DVT, deep vein thrombosis; ILMWH, low-molecular-weight heparin; NS, not significant; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

[a] Requiring transfusion.

and the other of pharmacotherapy[10]) used multivariable analysis to account for differences between patients allocated to different interventions. As such, all studies were observational and most had a high risk of bias. The greatest risk to their validity was confounding

by indication in that sicker patients received more intense prophylaxis, with no or inadequate adjustment for differences between treatment groups. In the absence of randomized trials, we were unable to determine the comparative effectiveness and safety or the optimal timing and duration of prophylactic pharmacotherapy. The observational studies did not provide a clear association between the use of preoperative initiation of pharmacologic prophylaxis and perioperative bleeding or between postoperative initiation of pharmacologic prophylaxis and thrombosis.

Our findings are likely to be generalizable. Patient characteristics were consistent with those expected in the bariatric surgery population, including obese middle-aged individuals of both sexes. Types of surgeries included the types of bariatric procedures frequently performed in the United States most were laparoscopic. Most studies did not report race, so we cannot make conclusions related to potential interactions between race and prophylactic strategy. Although many studies reported single-center experiences, patient characteristics and surgery types appeared to be relatively consistent across study centers. The single-center design of these studies, by itself, is not a major factor limiting generalizability, since the characteristics of patients were similar to those in other centers.

In contrast to this comparative effectiveness review, which evaluated only comparative studies, Becattini et al[27] conducted a systematic review of pharmacologic strategies for VTE prevention in bariatric surgery that included uncontrolled single-arm studies of pharmacologic prophylaxis in an effort to define VTE incidence rates with varying pharmacotherapy regimens. They concluded that the incidence of symptomatic postoperative VTE appeared to be less than 1% with both prophylactic strategies, but that with active VTE surveillance, the rate was approximately 2%. Bleeding rates were approximately 1% for standard-dose regimens, and 1.6% for weight-adjusted (augmented) pharmacologic prophylaxis. The authors concluded that there might be a higher rate of bleeding with augmented dosing with no evidence of increased efficacy, similar to our findings.

Our systematic review has several limitations. Although our search strategy was comprehensive, we may have missed a few studies. We were unable to assess the possibility of publication bias or selective outcomes reporting and its effect on our findings. In addition, as noted above, our findings are limited because of the high overall risk of bias of the included studies.

In summary, despite the limitations of the existing literature, we did not find evidence to support the use of filters or augmented dosing of pharmacotherapy in patients undergoing bariatric surgery. We note that, despite the patient population, which might be assumed to be at particularly high risk of postoperative VTE because of their body habitus, rates of thrombosis and mortality were reassuringly low. Although we did not specifically evaluate the impact of minimally invasive operative techniques, early ambulation, and noninvasive mechanical measures to prevent thrombosis in these patients, most authors emphasized using these approaches. We suspect that these supplemental strategies may be one reason that overall VTE rates and associated mortality are acceptably low in the bariatric surgical population even when using the standard pharmacologic prophylactic approaches that are used in nonobese perioperative patients.

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