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REVIEW

Efficacy and Safety of Pharmacoprophylaxis for Venous Thromboembolism in Patients Undergoing Bariatric Surgery: a Systematic Review and Meta-analysis

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Abstract

This study aims to assess the efficacy and safety of pharmacoprophylaxis regimens for venous thromboembolism (VTE) in patients undergoing bariatric surgery. A total of 15 studies were included. Low molecular-weight heparins (LMWH) and fondaparinux may be equally effective in reducing VTE risk (OR 1.02, 95% confidence interval [CI] 0.14–7.39). Pooled estimate suggested uncertain effects of augmented LMWH dosing on VTE prophylaxis compared with standard dosing (OR 0.57, 95% CI 0.07–4.39), but may increase major bleeding (OR 3.03, 95% CI 0.38–23.96). Very low-quality evidence showed an inconclusive effect of extended prophylaxis on VTE (OR 0.54, 95% CI 0.15–1.90) and major bleeding (OR 1.24, 95% CI 0.92–1.68) compared with restricted prophylaxis. Standard LMWH dosing may be effective and safe. Current evidences are insufficient to support extended prophylaxis.

Keywords Bariatric surgery · Venous thromboembolism · Deep vein thrombosis · Pulmonary embolism · Pharmacological prophylaxis · Meta-analysis

Key points

- LMWH and fondaparinux are equally effective for reducing VTE in bariatric surgery.
- Standard LMWH dosing may be effective and safe in VTE prophylaxis.
- Current available evidences are still insufficient to support extended prophylaxis.

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Introduction

The prevalence of clinically severe obesity is increasing globally, leading to a significant increase in the number of bariatric surgery over the past decade [1, 2]. Although morbidity and mortality after bariatric surgery have decreased considerably due to improvements in both surgical techniques and multidisciplinary perioperative care, it is well recognized that venous thromboembolism (VTE), mainly including deep vein thrombosis (DVT), pulmonary embolism (PE), and portomesenteric venous thrombosis (PMVT), is one of the major contributors [3–5]. Reported incidence rates of VTEs after bariatric surgery varied from 0.5 to 6.4% [6–9], including 0.2 to 3% for DVT, 0.3 to 2% for PE, and 0.37 to 1% for PMVT [10]. The overall mortality rate after bariatric surgery is reported to be 0.18 to 1.8% [6], and VTE results in a 13.89-fold increase in unadjusted thirty-day mortality [7].

Given the significant risk of VTE in patients with obesity, pharmacoprophylaxis is recommended for moderate to high-risk bariatric surgery patients without contraindications in clinical practice guidelines [11–14]. However, optimal prophylactic regimen, especially the choice of dosing and

duration, remains controversial. Some studies have suggested that an augmented dosing for VTE prophylaxis is needed [13, 15], while other studies have shown equal effectiveness and less incidence of bleeding complications using a standard dosing [16–19]. Several studies demonstrated that the majority of VTEs after bariatric surgery occurs after discharge [6, 8, 20, 21], leading to the theory that extended prophylaxis may decrease the risk of VTE. However, these aggressive prophylaxis regimens, including both augmented dosing and extended duration, have been shown to increase the incidence of postoperative bleeding than standard regimens [18, 22].

In light of uncertain optimal VTE prophylactic regimens, we performed a systematic review and meta-analysis to compare the efficacy and safety of different pharmacoprophylaxis regimens, including pharmacological agents, dosing, and duration for preventing VTE in patients undergoing bariatric surgery.

Materials and Methods

The protocol of this study was registered with PROSPERO (CRD42021266650). We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) reporting guidelines for randomized controlled trials (RCTs) [23] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for observational studies [24].

Data Sources and Search Strategy

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Clinicaltrials.gov from inception to August 30, 2021 to identify eligible studies. We also identified other potentially eligible studies by manually searching the reference lists of included studies and published systematic reviews. There were no restrictions regarding the language, publication type, or publication date. Detailed search strategies were presented in Appendix 1.

Eligibility Criteria and Study Selection

Two reviewers independently assessed titles and abstracts, subsequently the full text for potentially eligible studies based on the following inclusion criteria: (1) studies included patients undergoing bariatric surgery; (2) RCTs or observational studies that comparing different pharmacological agents for VTE prophylaxis, including unfractionated heparin (UFH), low molecular-weight heparins (LMWHs), vitamin K antagonists (VKA), direct oral anticoagulants (DOACs), factor Xa inhibitors and direct thrombin inhibitors, antiplatelet agents, and fondaparinux; (3) studies that comparing different dosing and durations of pharmacoprophylaxis; and (4) studies reporting outcomes of interest. Exclusion criteria were (1) duplicated reports; (2) single-arm studies; and (3) studies that did not report sufficient information to pool data.

Primary outcome measures included incidences of VTE, major bleeding, and all-cause mortality. VTE was defined as objectively diagnosed asymptomatic and symptomatic DVT, PE, or PMVT. Major bleeding, when available, was defined by the investigators of each study. When not available, major bleeding was defined as reoperation, transfusion of at least 2 units of whole blood or red blood cells, intracranial or retroperitoneal bleeding, and fatal bleeding events according to the criteria of the International Society on Thrombosis and Haemostasis [25]. All other bleeding events were defined as minor bleeding. Secondary outcomes included incidences of DVT, PE, PMVT, and any bleeding and minor bleeding events. Standard dosing for VTE prophylaxis was defined as enoxaparin 40 mg *q.d.*, 50 mg *q.d.*, 60 mg *q.d.*, 30 mg *b.i.d.*, nadroparin 5700 IU, or UFH 5000 IU *q.8.h.* [26]. Augmented dosing was defined as higher dose than standard recommended prophylaxis dosing: enoxaparin 40 mg *b.i.d.*, 50 mg *b.i.d.*, or 60 mg *b.i.d.*, enoxaparin 90 mg *q.d.*, or nadroparin 9500 IU *q.d.*. Restricted duration VTE prophylaxis was defined as thromboprophylaxis only during hospitalization, and extended VTE prophylaxis was defined as thromboprophylaxis for 7 or more days after discharge.

Data Extraction

Two reviewers independently extracted data from each eligible study using a specifically designed form for the following items: study characteristics (publication year), patients characteristics (age, proportion of female, body mass index [BMI], operative time, length of stay, procedure type), description of interventions and comparators (name, dosing, and duration); and outcome measures and definitions (Appendix 2).

Risk of Bias Assessment

Two reviewers independently assessed risk of bias for each study with adjudication by a third reviewer, using a modified Cochrane criteria for RCTs, and a modified Newcastle–Ottawa instrument for cohort studies [27]. Each criterion was judged as definitely or probably low risk of bias, or probably or definitely high risk of bias. Disagreements were resolved by discussion or, if necessary, by consultation with a third reviewer to reach a consensus. We judged the overall risk of bias for each outcome in each study as "low risk" if all domains were rated as low risk of bias and otherwise as high risk of bias.

Data Synthesis and Analysis

For each comparison for each outcome, a meta-analysis was conducted using Mantel–Haenszel's random-effects model to calculate the odds ratio (OR), risk differences (RD), and corresponding 95% confidence intervals (CI) for all outcomes. For different study types, meta-analysis for RCTs and observational studies were performed separately. Statistical heterogeneity was assessed using the I^2 statistic [28]. All meta-analyses were performed with the Stata software (Version 17) or Review Manager (Version 5.4). We did not evaluate publication bias with funnel plots or statistical tests due to an insufficient number of trials. The small number of studies were not sufficient for subgroup meta-analyses.

Assessment of Quality of Evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the quality of evidence for each outcome as high, moderate, low, or very low [29]. The assessment included judgments addressing risk of bias [30], imprecision [31], inconsistency [32], indirectness [33], and publication bias [34]. We judged imprecision by comparing the confidence intervals to decision thresholds chosen by the review panel with 0.5% reduction for VTE, 0.5% for major bleeding, and 5% for minor bleeding both in dosing comparison group and duration comparison group. Consistent with GRADE guidance, when evidence is of moderate quality, we state that the intervention "likely" or "probably" will produce the putative effect. When the evidence is of low quality, we describe the intervention as "may" or "possibly" to produce the putative effect [35].

Results

Study and Patient Characteristics

Of 1,499 studies identified through literature search, 15 eligible studies were included in our review (Fig. 1). Among these, 3 were RCTs, and 12 were observational studies (Table 1). Sample sizes of included studies varied from 60 to 43,493, enrolling a total of 72,939 patients. Types of bariatric surgery included open or laparoscopic adjustable gastric band, sleeve gastrectomy, gastric bypass, and biliopancreatic diversion/duodenal switch. Laparoscopic bariatric surgery is generally predominant. Generally, patient characteristics were consistent across studies.

Risk of Bias

In RCTs, one (33.3%) was judged as low risk of bias (Appendix 3), and 6 (50%) observational studies as low risk of bias (Appendix 4).

Outcomes

VTE and bleeding outcomes are shown in Appendix 5 and Appendix 6, respectively. The GRADE summary of findings for primary and secondary outcomes is shown in Tables 2, 3, and 4 and Appendix 7–9 respectively.

Interventional Pharmacological Agents

Three studies comparing LMWHs with UFH or fondaparinux were identified, and no studies assessing VKAs or DOACs were found.

1) ***LMWH vs. UFH***

VTE: Two studies compared LMWH with UFH (Table 1). The prospective cohort study by Kothari et al. involved 476 patients and compared enoxaparin 40 mg *b.i.d.* with UFH 5000 units *q.8.h.* until discharge [36]. It reported one PE event occurred in UFH group (0.42%), while none of any VTE events in LMWH group (very low-quality evidence, Table 2). Another registry study by Birkmeyer et al. that enrolled 20,293 patients compared LMWH regimens with UFH regimens [37], suggesting that patients who received prophylaxis with LMWH may have less incidence of VTE events than with UFH (OR 0.34, 95% CI 0.19 to 0.62, RD 0.4% fewer, low-quality evidence, Table 2).

Bleeding: Evidence from the study by Kothari et al. [36] suggested that enoxaparin 40 mg *b.i.d.* may increase the incidence of major bleeding compared with UFH *q.8.h.* (OR 4.90, 95% CI 1.39 to 17.27, RD 4.6% more, low-quality evidence, Table 2). Birkmeyer et al. [37] showed uncertain results of LMWH versus UFH on major bleeding events (OR 0.94, 95% CI 0.63 to 1.41, RD 0.1% fewer, very low-quality evidence, Table 2).

Mortality: No mortality was reported in the study of Kothari et al. [36] (very low-quality evidence; Table 2).

2) ***LMWH vs. Fondaparinux***

VTE: One RCT compared enoxaparin 40 mg *b.i.d.* with fondaparinux 50 mg *q.d.* for the duration of hospital stay in 198 bariatric surgery patients [38]. The results suggested two regimens be equally effective at reducing the risk of

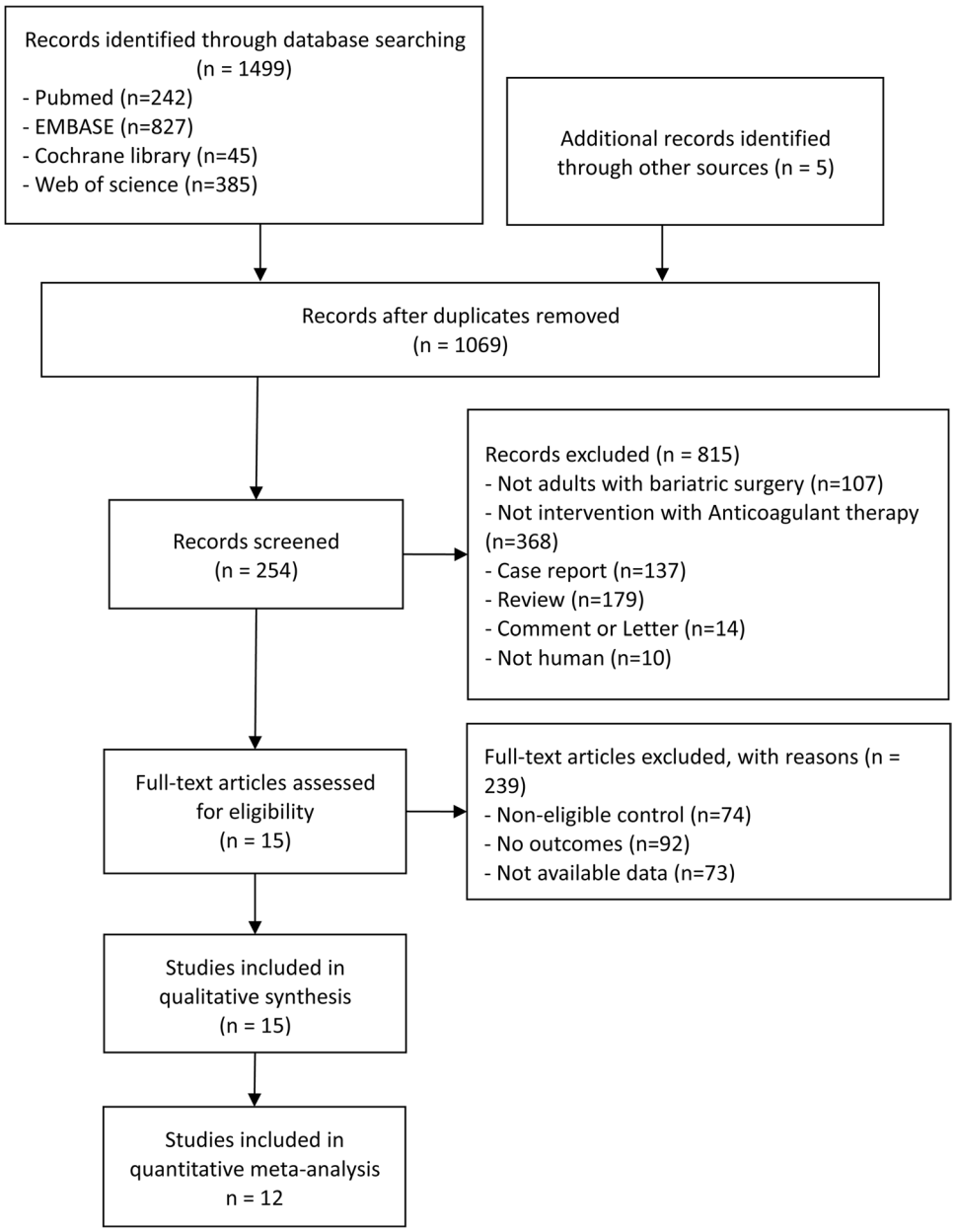

Fig. 1 PRISMA flow chart

DVT (OR 1.02 95% CI 0.14 to 7.39, low-quality evidence, Table 2).

Bleeding: As demonstrated by the included RCT, patients in both prophylaxis regimen groups had no major bleeding and mortality (Table 2). But a higher percentage of minor bleeding was seen in patients receiving twice daily enoxaparin than once daily fondaparinux (Appendix 7).

LMWH Augmented Dosing vs. Standard Dosing

VTE: Seven studies reported VTE outcomes in patients receiving augmented *vs.* standard LMWH dosing, including two RCTs [17, 39] and five observational studies [15, 16, 18, 19, 40] (Table 1). RCTs did not observe any VTE events in either augmented dosing group or standard dosing group (low-quality evidence, Table 3). Pooled estimate from observational studies (1966 patients) was essentially uninformative with wide confidence intervals, suggesting uncertain effects of augmented LMWH dosing on VTE prophylaxis compared with standard dosing (OR 0.57, 95% CI 0.07 to 4.39, RD 0.1% lower, very low-quality evidence, Table 3, Fig. 2A). The sensitivity analysis that took into account risk of bias did not appreciably change the results.

Likewise, pooled estimates for secondary outcomes (DVT and PE) suggested uncertain effects (very low-quality evidence, Appendix 8).

Table 1 Baseline characteristics of included studies

Reference	Study design	Country	Population	Intervention and comparator	No	Age, mean ± SD	Female Sex, %	BMI mean ± SD	Operative time (mins), mean ± SD	Length of stay (days), mean ± SD	Procedure type	Follow up (days)	If exclued previous VTE
LMWH vs UFH													
Birkmeyer 2013	Retrospective cohort	USA	Patients undergoing bariatric surgery	I: LMWH, doses unspecified, preoperatively and postoperatively (LMWH/LMWH)	15,891	> 60 y, 12%	77.0	> 60, 9%	NR	NR	Laparoscopic adjustable gastric band, SG, RYGB, BPD/DS	30	No
				C: UFH, doses unspecified, preoperatively and postoperatively (UFH/UFH)	4402	> 60 y, 13%	77.0	> 60, 9%	NR	NR			
Kothari 2007	Prospective cohort	USA	Patients undergoing laparoscopic gastric bypass bariatric surgery	I: Enoxaparin, 40 mg staring preoperatively, 40 mg on postoperative day 0, and b.i.d., until discharge	238	42 ± 9.6	NR	48.7 ± 6	129.5 ± 25.6	2.3 ± 1.3	Laparoscopic RYGB	30	Yes
				C: UFH, 5,000 units staring preoperatively, nothing on postoperative day 0, and 5,000 units t.i.d., until discharge	238	44 ± 8.8	NR	47 ± 6.2	160.1 ± 29.2	2.2 ± 0.7			
LMWH vs Fondaparinux													

Table 1 (continued)

Reference	Study design	Country	Population	Intervention and comparator	No	Age, mean ± SD	Female Sex, %	BMI mean ± SD	Operative time (mins), mean ± SD	Length of stay (days), mean ± SD	Procedure type	Follow up (days)	If exclued previous VTE
Steele 2015	RCT	USA	Patients undergoing laparoscopic SG or laparoscopic RYGB bariatric surgery	I: Enoxaparin, 40 mg on call to the operating room, starting on postoperative day 1, then 40 mg b.i.d., until discharge	98	41.8 ± 9.0	83.7	45.7 ± 5.2	183 ± 51	2.4 ± 0.8	Laparoscopic SG, laparoscopic RYGB	14	Yes
				C: Fondaparinux, 5 mg q.d., starting at six hours following surgery stop time, then 5 mg q.d. on postoperative day 1, until discharge	100	40.4 ± 10.2	84.0	45.1 ± 5.5	187 ± 49	2.5 ± 0.8			
LMWH Augmented dosing vs Standard dosing													
Goslan 2018	Prospective cross-sectional comparative study	Brazil	Patients undergoing gastric derivation surgery	I: Enoxaparin, 40 mg b.i.d., starting one day before surgery, for 10 days	26	33.8 ± 9.8	84.6	41.7 ± 5.2	50	NR	Laparoscopic RYGB	10	Yes
				C: Enoxaparin, 40 mg q.d., starting one day before surgery, for 10 days	34	33.3 ± 8.0	91.2	38.8 ± 3.2	50	NR			

Table 1 (continued)

Reference	Study design	Country	Population	Intervention and comparator	No	Age, mean ± SD	Female Sex, %	BMI mean ± SD	Operative time (mins), mean ± SD	Length of stay (days), mean ± SD	Procedure type	Follow up (days)	If exclued previous VTE
Hamad and Choban 2005	Retrospective cohort	USA	Patients undergoing bariatric surgery	I: Enoxaparin, 40 mg b.i.d., postoperatively, for 12–36 h	180	39.7 ± 9.1	97.0	46.0 ± 5.1	NR	2.5 ± 1.5	Open RYGB, vertical banded gastroplasty, or laparoscopic RYGB	14.6 ± 6.5	No
				C: Enoxaparin, 40 mg q.d., postoperatively, for 12–120 h§	84	47.5 ± 9.0	71.0	56.8 ± 10.1	NR	4.8 ± 5.3		18.0 ± 0.0	
				C: Enoxaparin, 40 mg q.d., postoperatively, for 12–24 h§	180	41.9 ± 9.5	90.0	49.9 ± 8.7	NR	2.9 ± 0.6		7.4 ± 4.6	

Table 1 (continued)

Reference	Study design	Country	Population	Intervention and comparator	No	Age, mean ± SD	Female Sex, %	BMI mean ± SD	Operative time (mins), mean ± SD	Length of stay (days), mean ± SD	Procedure type	Follow up (days)	If exclued previous VTE
Javanainen 2016	Prospective cohort	Finland	Patients undergoing both primary and revisional procedures	I: Enoxaparin, 40 mg b.i.d., one day before surgery, a dose both on the morning of the surgery and after the surgery, for 10 days (normal-risk patients) or for 10-14 days (high-risk patients)§	100	47.9 ± 8.9	60.0	49.0 ± 6.7	78 ± 29.8 for SG), 103 ± 31.2 for gastric bypass	9.3 ± 2.8 for major bleeding complications, 5.1 ± 7.5 for others	RYGB, SG, Band removal, BPD/DS	NR	NR
				I: Enoxaparin, 40 mg b.i.d., one day before surgery, and no dose on the morning of the surgery, for 10 days (normal-risk patients) or for 10-14 days (high-risk patients)§	100	47.8 ± 8.7	68.0	48.9 ± 6.8					
				C: Enoxaparin, 40 mg q.d., one day before surgery, for 10 days (normal-risk patients) or for 10-14 days (high-risk patients)	200	47.6 ± 9.3	70.0	48.4 ± 7.1					

Table 1 (continued)

Reference	Study design	Country	Population	Intervention and comparator	No	Age, mean ± SD	Female Sex, %	BMI mean ± SD	Operative time (mins), mean ± SD	Length of stay (days), mean ± SD	Procedure type	Follow up (days)	If exclued previous VTE
Kalfarentzos 2001	RCT	Greece	Patients undergoing RYGB bariatric surgery	I: Nadroparin, 9500 IU q.d., starting preoperatively, until discharge	30	35.7 ± 10.8	70.0	48.6 ± 7.3	196.7 (95–420) ‡	10.2 (8–20) ‡	RYGB	90 days, 180 days	No
				C: Nadroparin, 5700 IU q.d., starting preoperatively, until discharge	30	34 ± 10	86.7	48.8 ± 8	185.6 (135–360) ‡	9.4 (8–21) ‡			
Marie 2013*	Prospective cohort	USA	Patients undergoing bariatric surgery	I: Enoxaparin, 90 mg q.d., postoperatively, for 30 days	230	NR	NR	NR	NR	NR	NR	30	Yes
				C: Enoxaparin, 50 mg q.d., postoperatively, for 30 days	361	NR	NR	NR	NR	NR			
Scholten 2002	Prospective cohort	USA	Patients undergoing primary and revisional bariatric surgery	I: Enoxaparin, 40 mg b.i.d., 2 h prior to surgery, and until the patient was fully ambulatory or discharge	389	44.3	84.2	50.4	175	3.81	Open long limb RYGB (97.5%), BPD/DS (1%) and laparoscopic RYGB (1.5%). Revisional bariatric surgery (8.5%)	≥ 180	No
				C: Enoxaparin, 30 mg b.i.d., 2 h prior to surgery, and until the patient was fully ambulatory or discharge	92	43.7	79.8	51.7	213	5.67			

Table 1 (continued)

Reference	Study design	Country	Population	Intervention and comparator	No	Age, mean ± SD	Female Sex, %	BMI mean ± SD	Operative time (mins), mean ± SD	Length of stay (days), mean ± SD	Procedure type	Follow up (days)	If exclued previous VTE
Steib 2015	RCT	France	Patients undergoing laparoscopic RYGB	I: Enoxaparin, 4000 IU b.i.d., given at 6 p.m. the day before surgery, for ≥ 10 days	47	39.5 ± 1.7	72.3	47 ± 1	173 ±	NR	Laparoscopic RYGB	d9, d30	No
				C: Enoxaparin: 4000 IU q.d., given at 6 p.m. the day before surgery, for ≥ 10 days§	44	39 ± 1.5	75.0	49 ± 1	172 ± 9	NR			
				C: Enoxaparin, 6000 UI q.d., given at 6 p.m. the day before surgery, for ≥ 10 days§	44	40 ± 1.5	90.9	48 ± 1	173 ± 9	NR			
Extended prophylaxis vs Restricted prophylaxis													
Fennern 2020	Retrospective cohort	USA	Patients undergoing open or laparoscopic gastric bypass or a laparoscopic SG	I: Post-discharge heparin (including both UFH and LMWH, dose or duration of heparin unspecific) for less than 35 days	2587	46 (37–54) †	73.6	NR	NR	2 (1–2) †	Laparoscopic SG, laparoscopic or open RYGB	90	Yes
				C: No post-discharge heparin	40,906	45 (38–53) †	78.0	NR	NR	2 (1–2) † remained in hospital for a mean stay of 4 days			

Table 1 (continued)

Reference	Study design	Country	Population	Intervention and comparator	No	Age, mean ± SD	Female Sex, %	BMI mean ± SD	Operative time (mins), mean ± SD	Length of stay (days), mean ± SD	Procedure type	Follow up (days)	If exclued previous VTE
Leeman 2020	Retrospective cohort	Netherlands	Patients undergoing a primary RYGB or SG	I: Dalteparin 5000 IU, 12 h pre-operatively, for 14 days	2599	40.5 ± 11.0	82.5	43.4 ± 4.8	53 ± 19 for RYGB, 36 ± 13 min for SG	1.17 (0.18) †	RYGB, SG	90 days for VTE, 30 days for bleeding	No
				C: Dalteparin 5000 IU, starting postoperatively until discharge (High-risk patients receive extended prophylaxis according to the intervention group)	720	40.1 ± 11.4	82.2	42.8 ± 4.9					
Raftopoulos 2008	Retrospective cohort	USA	Patients undergoing bariatric surgery	I: Enoxaparin 30 mg b.i.d. starting 12 h after surgery until discharge, followed by a 10-day course of enoxaparin 40 mg q.d. after hospital discharge	176	44.1 (18–73) ‡	81.3	46.1 (26–75) ‡	215	2.2	Open or laparoscopic primary bariatric procedures and laparoscopic revision of bariatric procedures	30	No
				C: Enoxaparin 30 mg 1 h prior to surgery, 30 mg b.i.d. starting 12 h after surgery until discharge	132	42.6 (19–63) ‡	84.8	47.8 (27–70.9) ‡	232	3			

Table 1 (continued)

Reference	Study design	Country	Population	Intervention and comparator	No	Age, mean ± SD	Female Sex, %	BMI mean ± SD	Operative time (mins), mean ± SD	Length of stay (days), mean ± SD	Procedure type	Follow up (days)	If exclued previous VTE
Rodríguez 2020	Retrospective analysis of prospectively collected data	Chile	Patients undergoing laparoscopic SG by a single surgeon	I: Enoxaparin 40 mg q.d., the same day of operation and during the whole hospital stay, and received additional post-discharge thromboprophylaxis with rivaroxaban 10 mg once daily for 10 days	223	34.5 ± 10	63.2	35.7 ± 3.39	NR	NR	Laparoscopic SG	30	Yes
				C: Enoxaparin 40 mg q.d., the same day of operation and during the whole hospital stay	198	36.3 ± 11	68.2	36.2 ± 2.67	NR	NR			
Trivedi 2017*	Retrospective cohort	NR	Patients undergoing laparoscopic primary bariatric surgery	I: The same pre-operative and in hospital prophylaxis in addition to extended prophylaxis for 10 or 28-day	1150	NR	NR	NR	NR	NR	NR	30	NR
				C: Restricted prophylaxis	1106	NR	NR	NR	NR	NR	NR		

*Abstract

†Median (IQR)

‡Mean (range)

§Number of events in these dosing groups in each study were added

BPD/DS, biliopancreatic diversion/duodenal switch; *LMWH*, low molecular-weight heparin; *NR*, not reported; *RCT*, randomized controlled trial; *RYGB*, Roux-en Y gastric bypass; *SD*, standard deviation; *SG*, sleeve gastrectomy; *UFH*, unfractionated heparin

Table 2 GRADE summary of findings for different pharmacologic agents for VTE prophylaxis in patients undergoing bariatric surgery

Outcomes	Relative effect (95% CI), source of evidence	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group,* %	Difference (95% CI), † %		
LMWH vs UFH					
VTE (Birkmeyer 2012)	OR 0.34 (0.19 to 0.62) 20,293 patients in 1 observational study	Not applicable	−0.4 (−0.7 to −0.2)	Low	LMWH may reduce VTE more than UFH
VTE (Kothari 2007)	OR 0.33 (0.01 to 8.19) 476 patients in 1 observational study	Not applicable	−0.4 (−1.6 to 0.7)	Very low (serious imprecision)	Whether there is an important difference or not is very uncertain
Major bleeding (Birkmeyer 2012)	OR 0.94 (0.63 to 1.41) 20,293 patients in 1 observational study	Not applicable	−0.1 (−0.3 to 0.1)	Very low (serious imprecision)	Whether there is an important difference or not is very uncertain
Major bleeding (Kothari 2007)	OR 4.90 (1.39 to 17.27) 476 patients in 1 observational study	Not applicable	4.6 (1.3 to 7.9)	Low	Augmented LMWH dosing may increase major bleeding more than UFH
Mortality (Kothari 2007)	OR not estimable (no event in either group) 476 patients in 1 observational study	Not applicable	0 (−0.8 to 0.8)	Very low (serious imprecision)	Whether there is an important difference or not is very uncertain
LMWH vs Fondaparinux					
VTE	OR 1.02 (0.14 to 7.39) 198 patients in 1 RCT	Not applicable	0 (−3.9 to 4.0)	Low (serious risk of bias and imprecision)	There may be no important difference
Major bleeding	OR not estimable (no event in either group) 198 patients in 1 RCT	Not applicable	0 (−2.0 to 2.0)	Low (serious risk of bias and imprecision)	There may be no important difference
Mortality	OR not estimable (no event in either group) 198 patients in 1 RCT	Not applicable	0 (−2.0 to 2.0)	Low (serious risk of bias and imprecision)	There may be no important difference

*Differences were calculated directly from absolute estimates

†We calculated the risk difference directly in Stata

CI, confidence interval; *LMWH*, low molecular-weight heparin; *OR*, odds ratios; *RCT*, randomized controlled trial; *UFH*, unfractionated heparin; *VTE*, venous thromboembolism

Bleeding: Seven studies reported major bleeding, including two RCTs (195 patients) [17, 39] and five observational studies (1976 patients) [15, 16, 18, 19, 40] (Table 1). We conducted a meta-analysis of RCTs and observational studies on bleeding events separately. Pooled estimates from RCTs suggested that augmented LMWH dosing may increase major bleeding compared with standard dosing, but the confidence intervals were wide and included a benefit of standard dosing (OR 3.03, 95% CI 0.38 to 23.96, RD 2.1% higher, low-quality evidence, Table 3, Fig. 2B). Due to very low-quality evidence, pooled estimates from observational studies suggested uncertain effects of augmented LMWH dosing compared with standard dosing on major bleeding (OR 2.06, 95% CI 1.10 to 3.87, RD 1.0% higher, Table 3, Fig. 2C). The sensitivity analysis that took into account risk of bias did not appreciably change the results.

With regard to any bleeding events, pooled estimates from RCTs suggested that augmented dosing increased more compared with standard dosing (Appendix 8).

Extended Prophylaxis vs. Restricted Prophylaxis

VTE: Five observational studies that involved 49,797 patients reported on VTE outcomes [22, 41–44]. Pooled estimates showed uncertain effects of extended prophylaxis on VTE, with wide confidence intervals (OR 0.54, 95% CI 0.15 to 1.90, very low-quality evidence, Table 4). The sensitivity analysis that took into account risk of bias did not appreciably change the results. Two of these

Table 3 GRADE summary of findings for LWMH augmented vs standard dosing for VTE prophylaxis in patients undergoing bariatric surgery

Outcomes	Relative effect (95% CI), source of evidence	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group,* %	Difference (95% CI), † %		
Evidence from RCTs					
VTE	OR not estimable (no event in either group) Based on data from 195 patients in 2 RCTs	Not applicable	0 (−2.9 to 2.9)	Low (serious risk of bias and imprecision)	There may be no important difference
Major bleeding	OR 3.03 (0.38 to 23.96) 195 patients in 2 RCTs	Not applicable	2.1 (−2.7 to 7.0)	Low (serious risk of bias and imprecision)	Augmented LMWH dosing may increase major bleeding more than standard dosing
Evidence from observational studies					
VTE	OR 0.57 (0.07 to 4.39) 1966 patients in 5 observational studies	Not applicable	−0.1 (−1.2 to 1.1)	Very low (serious risk of bias, imprecision, and inconsistency)	Whether there is an important difference or not is very uncertain
Major bleeding	OR 2.06 (1.10 to 3.87) 1976 patients in 5 observational studies	Not applicable	1.0 (−1.1 to 3.1)	Very Low (serious risk of bias and imprecision)	Whether there is an important difference or not is very uncertain

*Differences were calculated directly from absolute estimates

†We calculated the risk difference directly in Stata

CI, confidence interval; *LMWH*, low molecular-weight heparin; *OR*, odds ratios; *RCT*, randomized controlled trial; *VTE*, venous thromboembolism

Table 4 GRADE summary of findings for extended vs restricted duration for VTE prophylaxis in patients undergoing bariatric surgery

Outcomes	Relative effect (95% CI), source of evidence	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group,* %	Difference (95% CI), † %		
VTE	OR 0.54 (0.15 to 1.90) 49,797 patients in 5 observational studies	Not applicable	−0.1 (−0.5 to 0.3)	Very low (serious risk of bias and imprecision)	Whether there is an important difference or not is very uncertain
Major bleeding	OR 1.24 (0.92 to 1.68) 44,222 patients in 3 observational studies	Not applicable	0.3 (−0.1 to 0.7)	Very low (serious risk of bias and imprecision)	Whether there is an important difference or not is very uncertain
Mortality	OR 0.96 (0.06 to 15.39) 2564 patients in 2 observational studies	Not applicable	0 (−0.2 to 0.2)	Very low (serious risk of bias and imprecision) Very low	Whether there is an important difference or not is very uncertain

*Differences were calculated directly from absolute estimates

†We calculated the risk difference directly in Stata

CI, confidence interval; *LMWH*, low molecular-weight heparin; *OR*, odds ratios; *VTE*, venous thromboembolism

studies also reported uncertain results of extended prophylaxis on DVT [42, 44]. One study reported an incidence of PE in extended prophylaxis group of 2.3%, with none of these events in the control group [42]. One study reported that four cases of PMVT occurred and no cases were reported in extended prophylaxis group [43] (Appendix 9). The Forest plot for VTE outcomes was shown in Fig. 3A.

Bleeding: Three observational studies that involved 44,222 patients reported on major bleeding [22, 35, 36]. Very low-quality evidence raised the possibility that suggested that extended prophylaxis increases major bleeding compared with restricted prophylaxis (OR 1.24, 95% CI 0.92 to 1.68, RD 0.3% higher, Table 4). The sensitivity analysis that took into account risk of bias did not appreciably change the results. For any bleeding and minor events, pooled estimates did observe a similar result (Appendix 9). The Forest plot for bleeding outcomes was shown in Fig. 3B.

Mortality: Evidence from two observational studies [42, 44] suggested that extended-duration prophylaxis have little to no effect on mortality (very low-quality evidence, Table 4, Fig. 3C).

Discussion

In this systematic review, we summarized the evidence for different pharmacological agents, dosing, and duration for VTE prophylaxis in patients undergoing bariatric surgery. Low- or very low-quality evidence demonstrated that LMWH might be more effective than UFH in preventing VTEs without increasing major bleeding based on an large-scale observational study [37]. LMWH and fondaparinux regimens were equally effective at reducing DVT without increasing the risk of major bleeding or mortality; however, the available data were limited and the evidence level was rated as low. We did not find any evidence demonstrating oral anticoagulants in perioperative VTE prophylaxis in patients undergoing bariatric surgery.

Our review showed standard dosing may be both effective and safe based on our predefined dosing regimens. Based on pooled estimates of observational studies with very low-quality evidence, augmented LMWH dosing did not show benefit in reducing the incidence of VTEs, but may increase major bleeding compared to standard dosing. This was consistent with ACCP guidelines [14], in which prophylaxis doing was not stratified by risk level of VTE and types of surgery, while opposite to recommendations of European

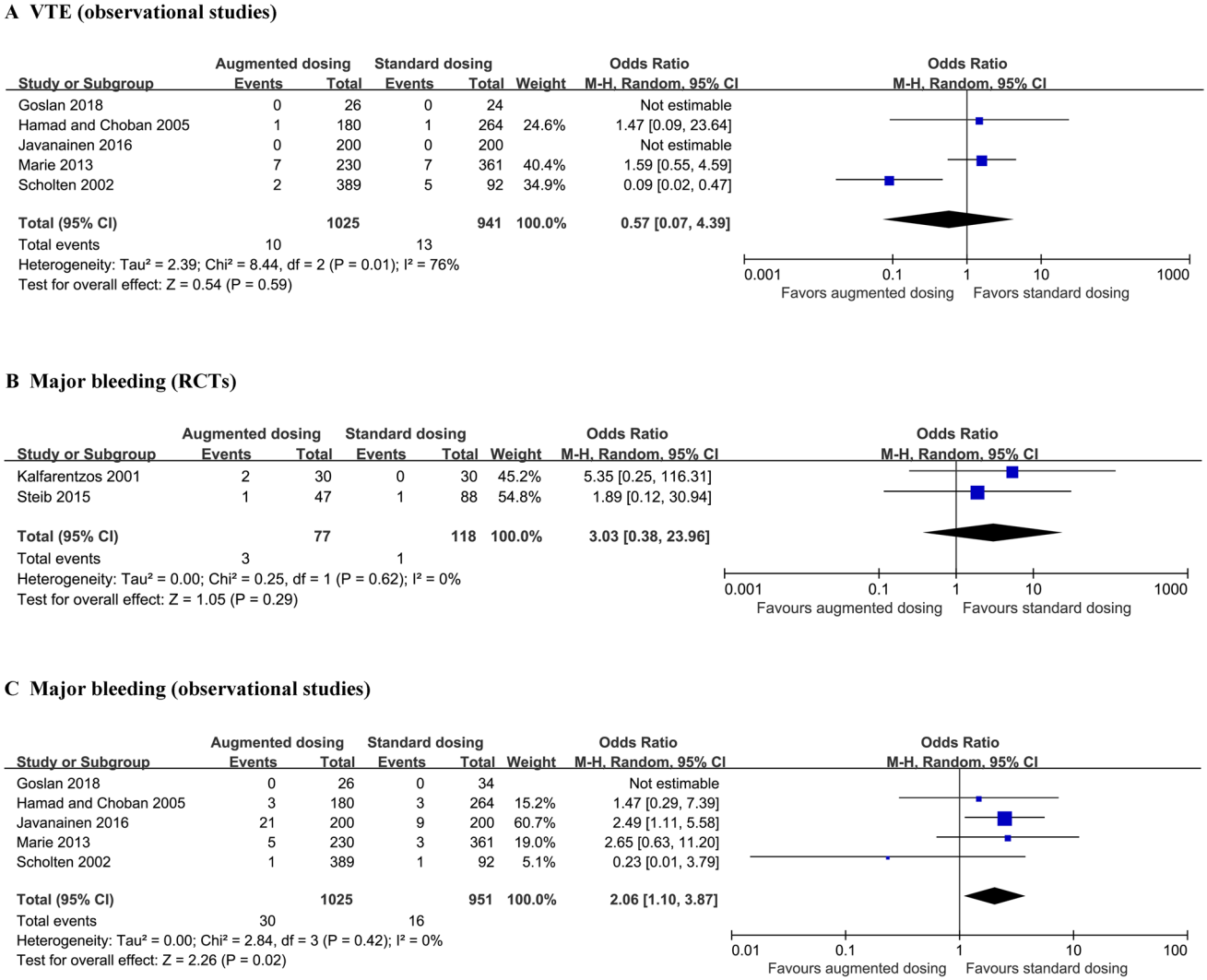

Fig. 2 Meta-analysis of the effects of LMWH augmented dosing vs standard dosing for VTE prophylaxis. (**A**) Effect of LMWH augmented dosing vs standard dosing on VTE (based on observational studies), (**B**) Effect of LMWH augmented dosing vs standard dosing on major bleeding (based on observational studies), (**C**) Effect of LMWH augmented dosing vs standard dosing on major bleeding (based on RCTs). Abbreviations: LMWH, low molecular-weight heparin; RCT, randomized controlled trial; VTE, venous thromboembolism

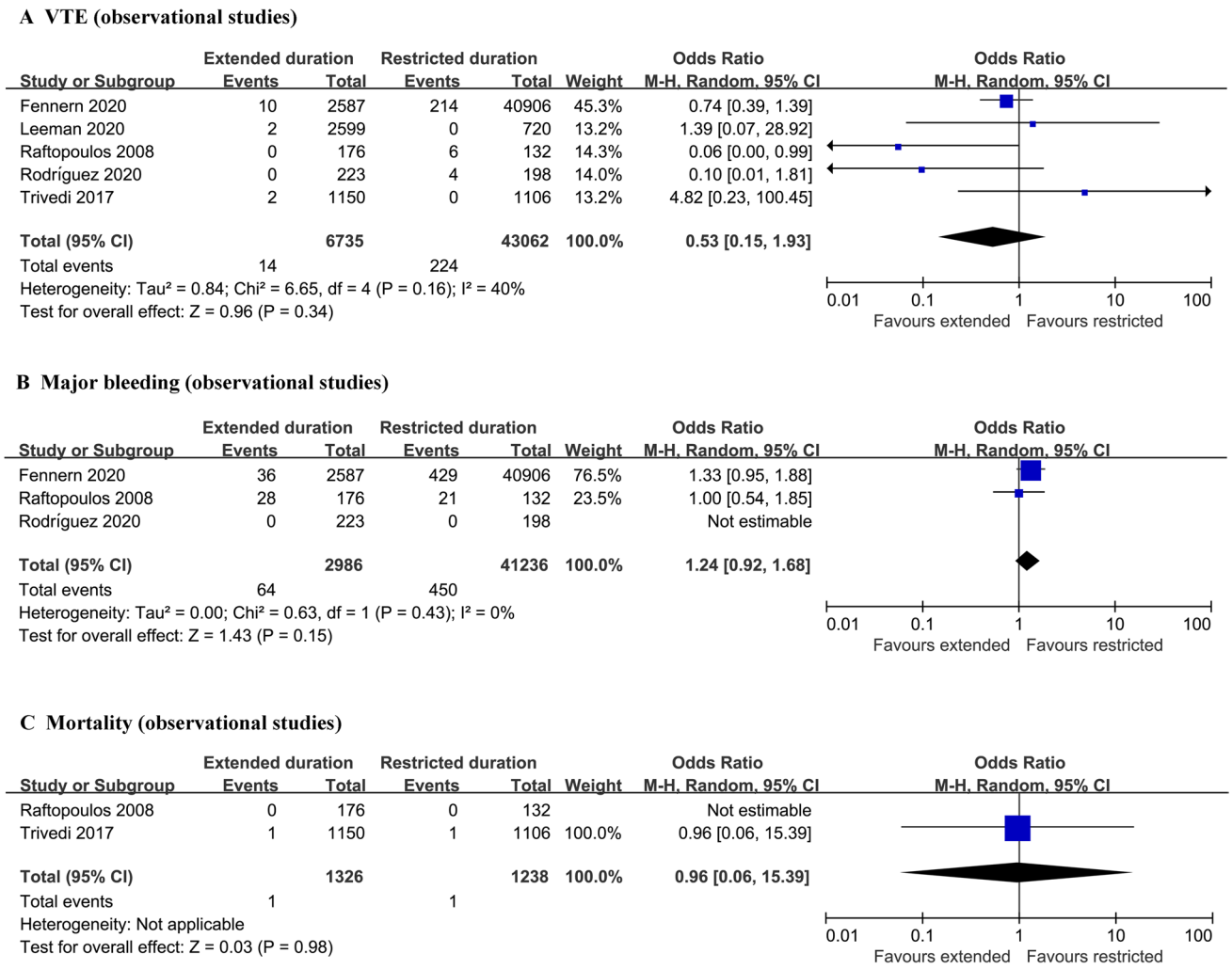

Fig. 3 Meta-analysis of the effects of extended duration vs restricted duration for VTE prophylaxis. (**A**) Effect of extended duration vs restricted duration on VTE (based on observational studies), (**B**) Effect of extended duration vs restricted duration on on major bleeding (based on observational studies), (**C**) Effect of extended duration vs restricted duration on mortality (based on observational studies). Abbreviations: VTE, venous thromboembolism

Society of Anesthesiology Guidelines 2018 that augmented dosing should be administered to bariatric patients with high risk of VTE [13]. All studies we included in our review did not distinguish dosing regimen between different VTE risks. Although some studies suggested that weight or BMI-based dosing may be both safe and effective with low rates of postoperative VTE and major bleeding, there is no clear evidence to reach a consensus. Further study regarding VTE risk-adjusted prophylaxis dosing regimen for patients undergoing bariatric might thus be warranted.

Our review did not identify evidence of the benefit of extended prophylaxis on reducing VTE and major bleeding risk compared to restricted prophylaxis. However, we could not make conclusions regarding duration of prophylaxis due to very low-quality evidence from observational studies until further higher level of evidence is available to determine the optimal prophylaxis duration. In light of the majority of post-bariatric surgery VTE events occurred post-discharge [6, 8, 20, 21], the benefit of extended prophylaxis may be greater in subgroups of bariatric surgery patients at higher VTE risk, and extended prophylaxis after discharge in this population of patients thus may be considered recommended in recent clinical guidelines and studies [13, 20].

To date, two reviews have investigated the efficacy and safety of pharmacoprophylaxis including pharmacological agents, dosing, and duration for the prevention of VTE after bariatric surgery [26, 45]. Our findings regarding pharmacological agents and prophylactic dosing are similar to a review conducted by Brotman et al. [26], which suggested that LMWH is more effective than UFH and the evidence of the benefits of the augmented than standard dosing of enoxaparin is insufficient. However, their results supported

extended prophylaxis based mainly on limited evidence from a retrospective cohort, which is inconsistent with our results. Besides, our review included more studies and conducted a meta-analysis. In addition, our review added additional information to the evidence of fondaparinux prophylaxis. Although another review on pharmacoprophylaxis regimens to prevent VTE in bariatric patients summarized the available evidence regarding different pharmacological agents, dosing, and duration of different regimens [45], they did not assess risk of bias for each study. Moreover, they did not use a formal system such as GRADE for rating the certainty of the evidence, which is crucial to evidence credibility.

Limitations

Our review has several limitations. First, low or very low-quality evidence from observational studies contributes to inconclusive results. Second, both studies and sample size in some comparison groups are not enough, resulting in very wide CIs for outcomes. Third, all included studies enrolled bariatric patients with different pre-existing risk of VTE and major bleeding and procedure type, causing clinical heterogeneity. Last, we could not assess the quality of the included abstracts in our review.

Conclusion

The present systematic review and meta-analysis suggest that LMWH could be equally effective as fondaparinux, and more effective than UFH, for VTE prophylaxis in patients undergoing bariatric surgery. Standard dosing may be effective in VTE prophylaxis without increasing major bleeding risk compared with augmented dosing. Current evidence is insufficient to support routine application of extended prophylaxis regimen. Because the available studies did not stratify the risk level of VTE events, we could not conclude the benefit of extended prophylaxis in higher VTE risk patient.

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Declarations

Ethical Approval For this type of study, formal consent is not required.

Informed Consent Informed consent does not apply.

Conflict of Interest The authors declare no competing interests.

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