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Safety and efficacy of low-molecular-weight heparin in patients with acute venous thromboembolism postthrombolytic therapy as compared to unfractionated heparin: A systematic review and meta-analysis

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Abstract:

BACKGROUND: Low-molecular-weight heparin (LMWH) is a proven treatment for patients with venous thromboembolism (VTE) with a lower risk of VTE recurrence and lower rates of major hemorrhage compared to unfractionated heparin (UFH) and have largely replaced its use in many indications, but its use around thrombolysis remains controversial.

AIM: This study aims to evaluate the currently available evidence on LMWH use in postthrombolysis as compared to UFH.

MATERIALS AND METHODS: Embase and MEDLINE were searched between 1992 and 2022, in addition to other sources. We included experimental and observational studies that assessed the use of LMWH as compared to UFH in patients with massive and submissive pulmonary embolism (PE) in the acute postthrombolysis phase. Data were pooled to estimate odds ratios (ORs), with 95% confidence intervals for VTE recurrence, bleeding complications and 30-day mortality.

RESULTS: Three studies were included in this systematic review: one randomized controlled trial, one prospective, and one retrospective study. A total of 299 patients were treated with UFH, and 227 patients were treated with LMWH. Patients treated with LMWH had a statistically significant lower risk of major bleeding with OR 0.41 (0.17, 0.97) $P = 0.04$ and 30-day mortality with OR 0.44 (0.23, 0.85) $P = 0.01$. On the other hand, though the risk of VTE recurrence and clinically relevant non-major bleeding (CRNMB) were lower, this was not statistically significant with OR of 0.18 (0.03, 1.07) $P = 0.06$ for VTE recurrence, and OR of 0.75 (0.39, 1.42) $P = 0.38$ for CRNMB.

CONCLUSION: In patients with massive and submissive PE postthrombolysis, LMWH is a reasonable option for anticoagulation with lower risk of VTE recurrence, bleeding complications and 30-day mortality when compared to UFH. However, this conclusion is largely influenced by observational data and the very limited evidence available. Certainly, more studies are needed to evaluate this clinical question.

Keywords:

Anticoagulation, low-molecular-weight heparin, massive pulmonary embolism, postthrombolysis

Introduction

In patients presenting with pulmonary embolism (PE) associated with

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hemodynamic compromise or those with extensive/limb-threatening deep vein thrombosis (DVT), thrombolysis followed by anticoagulation is recommended.[1,2] PE with hemodynamic compromise, i.e. massive PE, is defined by the presence of systematic hypotension (systolic arterial pressure < 90 mmHg or a drop in systolic arterial pressure of at least 40 mmHg for at least 15 min which is not caused by new onset arrhythmias or the presence of shock).[3] Submassive PE is defined by the presence of right ventricular dysfunction or cardiac necrosis and thrombolysis in this patient group is debatable and is usually considered case by case depending on the patients overall assessment.[4] Thrombolysis can be administered either systematically through an intravenous (IV) infusion, usually preferred in massive PE patient due to its widespread availability,[1] or catheter directed, which allows slow and local infusion of fibrinolytics in low doses directly to the pulmonary arteries leading to an enhanced safety profile as compared to systematic thrombolysis.[5]

There is currently a knowledge gap in what the choice and timing of anticoagulation postthrombolysis should be. Commonly, these patients are started on an unfractionated heparin (UFH) infusion.[6] However, the use of UFH has many limitations including a narrow therapeutic window, unpredictable variation in anticoagulant effect, increased risk of heparin-induced thrombocytopenia and major bleeding, and the need for continuous infusion and laboratory monitoring.[7,8] Low-molecular-weight heparin (LMWH) is a proven treatment for patients with venous thromboembolism (VTE) and is more effective than the use of dose-adjusted IV UFH, with a lower risk of VTE recurrence (Peto odds ratio [OR] 0.69, 95% confidence intervals [CIs] 0.49–0.98) and lower rates of major hemorrhage (Peto OR 0.69, 95% CI 0.50–0.95).[8-11] It has largely replaced the use of UFH in many indications, but its use around thrombolysis remains controversial though used frequently. The main reason for its continued use around thrombolysis is its short half-life that allows rapid discontinuation if needed in the event of bleeding, and so it remains to be the suggested agent around thrombolysis.[7,12] Arguably, the benefit of a slightly shorter half-life with UFH should be contrasted with the more predictable response and reduced bleeding risk with LMWH. In patients receiving thrombolysis for ST elevation myocardial infarction, there is increasing evidence that LMWH is the preferred antithrombin agent adjunct to thrombolysis.[13]

The goal of this systematic review is to evaluate the currently available evidence on LMWH use in postthrombolysis in comparison to UFH.

Materials and methods

This systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines. The review is registered in Prospero (https://www.crd.york.ac.uk/PROSPERO) on February 2, 2022, with registration number: CRD42023394224.

Full-text articles published between 1992 and 2022 were eligible for inclusion. Randomized controlled trials (RCTs) and observational studies including cohort studies (prospective or retrospective), case–control studies, or case series that included adult patients with acute proximal VTE requiring thrombolysis (whether massive PE, submassive PE, or iliofemoral DVT) and were treated with fixed-dose LMWH compared with dose-adjusted UFH were included. Studies that looked at LMWH with no comparison to UFH or that looked at patients outside the acute phase were excluded. There was no language restriction in our search.

The search includes the electronic search of MEDLINE (Ovid) and Embase (Ovid) from 1992 to 2022, as LMWH was first approved in 1993 and the first study comparing LMWH to UFH dates back to 1992.[14] The search strategy combines keywords and MeSH terms of each of the PICO components, see complete details of the MEDLINE and Embase search in Appendix 1. The search strategy was overseen by librarian support. There was no language restriction, which allowed studies from all around the world to be included and, reduced selection bias.

Initially, broad screening was conducted according to the title. Subsequently, all relevant abstracts were reviewed. In the end, all potentially included articles were reviewed at full length. Data from included studies were abstracted on study characteristics, details of the population included, the intervention used including the type and dose of anticoagulation used, and study outcomes were extracted.

Two reviewers separately assessed articles for inclusion to verify eligibility (MA and AA). A discrepancy was resolved by consensus and/or in conjunction with a third reviewer (EM).

The review includes studies that looked at adult patients (> or = 18 years of age) who suffer a major proximal VTE event (whether massive PE, submassive PE, or massive iliofemoral DVT) documented on radiological imaging and underwent thrombolysis (mechanical, systematic, or catheter-directed) in the acute phase, and evaluated the use of any form of fixed-dose LMWH (e.g., dalteparin, enoxaparin, and tinzaparin) at full therapeutic or intermediate-dose anticoagulation against adjusted dose UFH (high- or low-nomogram dose) immediately postthrombolysis in the acute phase of VTE. We excluded studies that evaluated LMWHs with no comparison

to UFH, studies that looked at patients outside of the acute phase or studies in which patients were switched between UFH and LMWH or were crossed over and did not report results on each medication separately.

The primary outcome of this meta-analysis was VTE recurrence up to 30 days' postthrombolysis, secondary outcomes were incidence of major bleeding and clinically relevant nonmajor bleeding (CRNMB) as defined by the International Society on Thrombosis and Haemostasis (ISTH)[15] as well as the 30-day mortality.

Quality and risk of bias (ROB) of included observational studies were rated with The Newcastle–Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses.[16] For randomized trials, the ROB-2 tool was used.[17] Heterogeneity will be assessed using the I^2 statistic to measure the degree of inconsistency between studies.

Statistical analysis

To compare patients on LMWH versus UFH, meta-analysis using a random effects model was used given the heterogeneity between studies when it comes to the selected population type and different agents and methods of thrombolysis.

A traditional pairwise meta-analysis was planned by separately combining RCTs from observational studies due to methodological heterogeneity. However, given that there were not enough studies to separately analyze RCTs and observational studies, a combined analysis was done.

The meta-analysis was performed through the Dersimonian–Laird method, results are presented as pooled OR as an effect measure along with a 95% interval using Review Manager (RevMan) [Computer program]. Version 5.4.1. The Cochrane Collaboration, 2024. Available at revman.cochrane.org.[18]

Results

Literature search findings

The literature search of the databases yielded 8476 studies to screen; see the detailed search strategy in the Appendix. Four hundred and fifty-two studies were duplicates leaving 8024 studies. Using Covidence software[19] and starting with the most recent studies, after a title and abstract screening, a total of 12 articles were reviewed in full text. Of those, three studies fulfilled our eligibility criteria.

The nine studies that were excluded: three were due to wrong intervention, three were excluded for having the wrong patient population (as they included mostly patients with nonmassive PE), two excluded for having the wrong outcome, and one was excluded as it was a poster only with no clear definitions of the outcomes measures (mainly bleeding complication) and the possibility of cross over with same patients included in one of the included articles.[20] Details of the PRISMA flowchart are found in Figure 1, and details and references for the excluded studies with detailed reason of exclusion can be found in the Appendix.

Study characteristics

One RCT, one prospective cohort study, and one retrospective study were included in this review.[21,22] Interestingly, two studies are from Turkey with one author in common between the two studies and one study from the US. One is an RCT from a tertiary hospital, one is a prospective multicenter study and one is a retrospective single-center study. The three studies included a total of 526 patients with massive or submissive PE postthrombolysis, 227 patients on LMWH, and 299 treated with UFH. For full details on the included studies, please refer to Table 1. There were no studies on postthrombolysis in patients with extensive DVT found.

Two studies used twice-daily SC LMWH (enoxaparin), in one,[21] the first dose of enoxaparin was following thrombolytic therapy. The other study,[20] started anticoagulation at the time of PE diagnosis and continued throughout the catheter-directed thrombolysis (CDT) procedure. The last study[22] used LMWH without specifying type or dose. All studies compared to adjusted dose of IV UFH (18 U/kg/h) to maintain an activated partial thromboplastin time of 46–70 s. In two studies, patients were bridged to warfarin and continued anticoagulation for at least 3 months, the third study did not elaborate on what was the plan for anticoagulation after the acute phase.

Of patients that were evaluated for inclusion in the studies, the studies had a similar composite of severe PE events compared to nonmassive PE events (18%[22] and 20%[23]). Graif *et al*.[20] included consecutive patients who underwent CDT. Ucar *et al*.[21] included patients with cardiogenic shock or sustained hypotension while Senturk *et al*.[22] and Graif *et al*.[20] included patients with shock or hypotension as well as those with markers for myocardial injury or right ventricular dysfunction, in other words, submassive PE.

Although outcome definitions overall were similar, there was some variation especially when it comes to defining major bleeding. Ucar *et al*. defined major hemorrhage as stroke, hematoma (5 cm), oral or gastrointestinal bleeding, or bleeding with concomitant hypotension that required treatment with IV fluids, blood transfusion, surgical control, discontinuation of

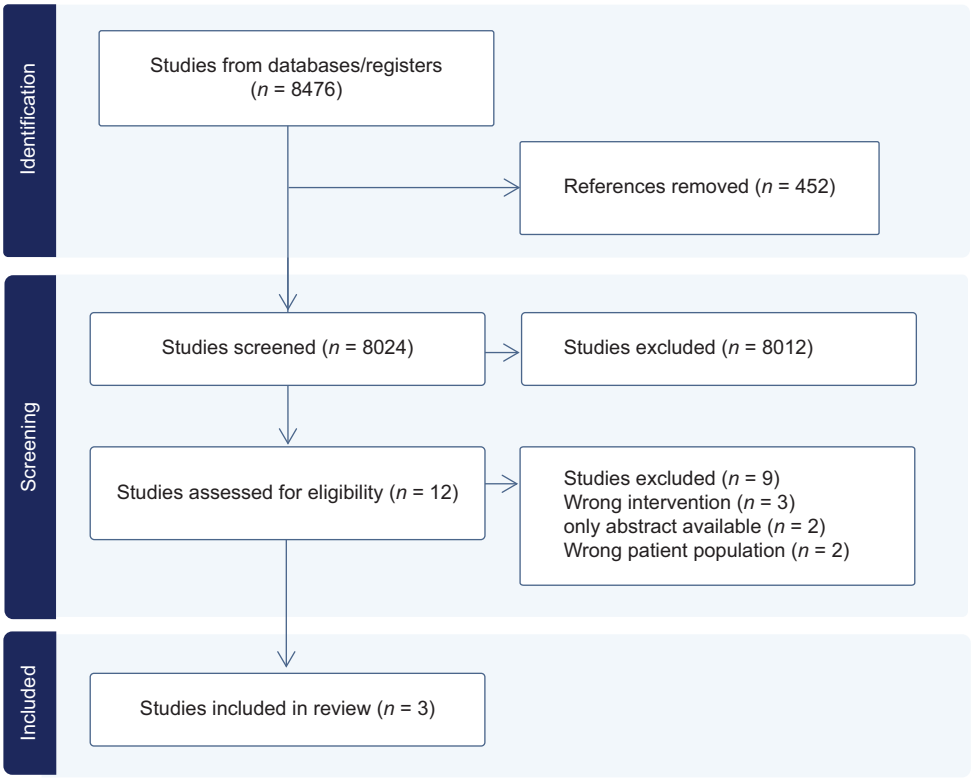

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis

thrombolytic treatment regimen, decrease 15% points in hematocrit or 5 g/dl reduction in hemoglobin. The definition overall is comparable to the ISTH definition used by this review except for the 5 g/dl drop which is more significant than the ISTH definition at 2 g/dl.[15] Senturk *et al*. defined major bleeding as bleeding in a critical organ or accompanied by a drop in hemoglobin of 2.0 g/dL or more or needing 2 units of blood transfusion or more. On the other hand, they excluded fatal bleeding. Graif *et al*. defined bleeding complications according to the Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO) classification.[24] In this review, major and moderate GUSTO complications in the study were considered as major bleeding episodes by ISTH definition, since moderate GUSTO complications required blood transfusion.

Of note, Ucar *et al*.[21] reported OR in a reverse fashion despite LMWH being the experimental arm, for example, they reported an OR of 1.4 for any adverse events, when this was recalculated based on the event rates reported it was found to be 0.72, and so for the purpose of this review, all ORs were recalculated using LMWH as the experimental group and UFH as the control group.

Risk of bias on included studies

This review was challenged by the limited studies found and the fact that the studies had very different designs (RCT, prospective cohort, and retrospective cohort). All studies demonstrated limitations and some risk of bias in their methods. However, they are reasonably representative of the average patient with massive and submassive PE and usual clinical practice. The RCT study naturally carries a better internal validity given its design, yet this is still not perfect given the lack of blinding of the treating physician raising a possibility of performance bias. On the other side, the prospective study likely carries a reasonable external validity and generalizability given the many centers involved. However, its interval validity is lacking due to many factors, most importantly the fact that it is observational with an unbalance between the two arms, which also apply to Graif *et al*.[20]

For details on the methodological quality of the included studies, see Figures 1 and Table 1 in the Appendix.

Synthesis of study results

Venous thromboembolism recurrence

Ucar *et al*.[21] reported four episodes of VTE recurrence in the UFH group compared to one recurrence in the LMWH group, all events resulting in mortality. Senturk *et al*.[22] also reported 4 VTE recurrences in the UFH group, all of them were patients with massive PE. Graif *et al*.[20] didn't report recurrence rates. Meta-analysis of the two studies that reported VTE recurrence showed a nonstatistically significant lower risk of VTE recurrence in patients on LMWH with OR of 0.18 (0.03, 1.07) and $P = 0.06$.

Table 1: Characteristics of included studies

Study	Type	Year	Center	Population	Methods	Follow-up	Outcomes
Ucer *et al*.[23] NCT01956955	Randomized controlled study	2014	Single tertiary center, Turkey	Adult patients with massive PE between January 2011 and October 2013 Patients who died before randomization or had contraindications for thrombolysis or anticoagulation were excluded	1:1 randomization with no stratification Data collectors and consent takers were blinded but treating physicians were not	Not reported	The primary outcome of the study was initially designed to be a major hemorrhage. However, due to the much lower rate of occurrence of this event than expected, it also assessed any hemorrhage, all-cause mortality (in-hospital), and a composite outcome defined as any hemorrhage (either major or minor) or in-hospital death
Senturk *et al*.[22]	A prospective, observational multicenter study	2016	25 centers in Turkey	Adults admitted with massive or submassive PE confirmed by CT and received thrombolytic therapy, between January and November 2013 Exclusion criteria were absolute contraindications for thrombolytic therapy or nonmassive PE	Massive and sub-massive PEs were categorized into two groups depending on whether they were treated with LMWH or UFH after thrombolytic treatment	30-day clinical follow-up data were obtained for all patients	The primary endpoint was all-cause mortality during the first 30 days; the secondary end point included all-cause mortality, nonfatal symptomatic recurrent PEs, or nonfatal major bleeding
Graif *et al*.[20]	Retrospective cohort study	2019	Single center in the United States	Adult patient with acute PE symptoms less than 14 days who received CDT with alteplase between December 2009 and July 2019. Excluded were patients with onset of symptoms>14 days before presentation or evidence of chronic PE as diagnosed on CT angio or died before receiving CDT	A retrospective review of 156 consecutive cases of CDT with alteplase for acute PE All patients received full-dose anticoagulation before, during, and after thrombolysis with LMWH or unfractionated heparin infusion	Not reported	Primary endpoints for the study included hemorrhagic complications according to the GUSTO. Secondary endpoints included change in invasive PAP as measured during the CDT procedures and change in the Miller pulmonary embolism severity index.[10] Also recorded were the tPA infusion rates (mg/h), tPA infusion duration (h), and total tPA dose infused (mg). A subgroup analysis comparing LMWH and heparin infusion was also performed for all of the aforementioned parameters

CDT=Catheter directed thrombolysis, CT=Computerized tomography, LMWH=Low-molecular-weight heparin, PE=Pulmonary embolism, tPA=Tissue plasminogen activator, UFH=Unfractionated heparin, PAP=Pulmonary artery pressure, GUSTO=Global use of strategies to open occluded arteries

Secondary outcomes

Major bleeding

The results of the three studies each suggested a lower risk of major bleeding in patients on LMWH, compared to UFH. The meta-analysis showed that patients on LMWH carried an OR of 0.41 (95% CI [0.17–0.97] and $P = 0.04$, $I^2 = 0\%$) compared to those anticoagulated with UFH. There is a major obstacle in this assessment given the difference in study designs and the variable definitions of major bleeding between studies with no full data to allow adjustment to the numbers according to the review's definition of major bleeding.

CRNMB

The rates of nonmajor bleeding were comparable between the two groups in the three studies. Both were not statistically significant. Meta-analysis resulted in an OR of 0.75 (95% CI of [0.39, 1.42] and $P = 0.38$,

Table 2: Study outcomes

Outcome	Anti-coagulant	Ucar 2014[23]		Senturk 2016[22]		Graif 2019[20]		Meta-analysis
		n/total (%)	Unadjusted OR (95% CI) *P*	*n*/total (%)	Unadjusted OR (95% CI) *P*	*n*/total (%)	Unadjusted OR (95% CI) *P*	*P*
VTE recurrence	LMWH	1/60	0.24 (0.03–2.22) 0.21	0/122	0.11 (0.01–2.10) 0.14	NR	NR	0.18 (0.03–1.07) 0.06
	UFH	4/61		4/127		NR		
Major bleeding	LMWH	2/60 (3.3)	0.34 (0.07–1.7)	5/122 (4)	0.50 (0.17–1.51)	0/45 (0)	0.21 (0.01–3.93)	0.41 (0.17–0.97)
	UFH	6/61 (9.8)	0.19	10/127 (7.9)	0.22	5/111 (4.5)	0.29	0.04
CRNMB	LMWH	7/60 (11.7)	1.21 (0.38–3.80)	11/122 (9)	0.64 (0.29–1.43)	0/45 (0)	0.26 (0.01–4.98)	0.75 (0.39–1.42)
	UFH	6/61 (9.8)	0.77	17/127 (13.4)	0.28	22/111 (20)	0.38	0.38
30-day mortality	LMWH	4/60 (6.7)[a]	0.52 (0.16–2.08)	10/122 (8.2)[b]	0.43 (0.19–0.94)	1/45 (2.2)	0.34 (0.04–2.83)	0.44 (0.23–0.85)
	UFH	7/61 (11.5)[a]	0.41	22/127 (17.3)[b]	0.035	7/45 (6.3)	0.32	0.01

[a]Cause of death in Ucar *et al*. were recurrent embolism (*n*=5), respiratory failure (*n*=4), and major hemorrhage (*n*=2), intracranial, and gastrointestinal, [b]Causes of death in Senturk *et al*. were recurrent emboli (*n*=4), respiratory failure (*n*=9), major hemorrhage (*n*=3), acute renal failure (*n*=1), acute cardiac failure (*n*=3), and multiple organ failure. CI=Confidence interval, OR=Odds ratio, VET=Venous thromboembolism, CRNMD=Clinically relevant nonmajor bleeding, LMWH=Low-molecular-weight heparin, UFH=Unfractionated heparin, NR=Not reported

I^2 = 0%); the CI crosses the null effect and is statistically nonsignificant. See Figure 3 in the appendix.

Thirty-day mortality

All studies argued a lower risk of mortality in the population on LMWH compared to UFH based on unadjusted OR. Senturk *et al*.[22] further explored the 30-day mortality rate by performing a logistic regression analysis putting confounders in context including comorbid conditions, major and minor bleeding complications, and severity of embolism. This found that the anticoagulation option was not associated with increased risk of 30-day mortality (adjusted OR 2.16 [0.91–5.14] *P* = 0.08).

Ideally, we would have liked to use the adjusted OR for the meta-analysis as it provides a better estimate in light of an uncontrolled observational study by incorporating the effects of unbalanced confounding factors between the compared groups. Unfortunately, this could not be done as studies did not provide any adjusted ORs for mortality rates. Another limitation is that Ucar *et al*. did not report the duration over which mortality was counted, and this might affect the estimate.

Meta-analysis of the three studies using unadjusted odds suggested a statistically significant difference between mortality rates in patients on LMWH versus UFH with an OR of 0.44 and 95% CI of (0.23, 0.85) *P* = 0.01, I^2 = 0%. For a summery of individual and pooled study outcomes please refer to Table 2.

Subgroup analysis and sensitivity analysis

A subgroup analysis for 30-day mortality in patients with massive PE only showed an OR of. 58 and 95% CI of (0.29, 1.17) *P* = 0.13. Due to the very limited number of studies identified in this systematic review, no further subgroup analysis (e.g., CDT vs. systematic thrombolysis) or sensitivity analysis was possible. Moreover, funnel plots are not very informative at this very low number of included studies.

For detailed forest plots for the results please refer to the Appendix Figures 2-5. Moreover, the detailed GRADE evidence profile of the study outcomes and summary of findings table pooling the included studies can be found in Tables 2 and 3, respectively, located in the appendix.

Discussion

Main findings

LMWH seems to be a reasonable option for anticoagulation in patients with massive or submassive pulmonary emboli postthrombolysis based on the results review. We found that fixed weight adjusted-dose LMWH carry a lower risk of VTE recurrence as well as for all the secondary outcomes including major bleeding, CRNMB, and 30-day mortality when compared to dose adjusted UFH. These estimates were statistically significant for major bleeding and 30-day mortality rates only.

For all outcomes comparing LMWH and UFH, the quality of evidence was very low due to multiple factors. First of all, we attempted a meta-analysis of studies with very different study designs (one RCT and two observational studies) which carry varied limitations that challenge the pooling of results. Moreover, the sample of patients is insufficient to reach the optimal information size and most of it is derived from an observational study and this should be kept in mind when interpreting the results of this analysis.

This review especially highlights the complete lack of high-quality evidence on the type and dose of preferred anticoagulation postthrombolysis with no inherent reason preventing high quality randomized trials to help establish evidence-based practice for this very relevant

clinical question. In clinical practice, many factors might influence the decision of choosing one anticoagulant over the other, including the ease of IV access and medication availability or cost. Certainly, more studies are needed in this area to guide practice.

Currently, the American Society of Hematology guidelines recommend the use of thrombolytics followed by anticoagulation over anticoagulation alone in patients with hemodynamic compromise (massive PE) and suggest anticoagulation alone over the routine use of thrombolysis followed by anticoagulation in patients with evidence of the right ventricular dysfunction but without hemodynamic compromise (submassive PE).[1] The guidelines do not specify what and when anticoagulation should be used postthrombolysis. However, the British Thoracic Society Guidelines mentions UFH as the agent that should be used in patients with massive PE or when rapid reversal of effect may be needed, with no specific recommendation around anticoagulation postthrombolysis otherwise.[25] This is likely related to the choice of anticoagulant being very dependent on many factors and should be addressed on a case by cases bases depending on renal function, venous access, bleeding risk, etc.

The practice around thrombolysis of patients with massive and submassive PE is an area with so many yet unanswered questions, this includes questions around timing and dosing of anticoagulation; whether anticoagulation should be started before thrombolysis or only after, which recent systematic review attempted to answer and suggests that systematic thrombolysis followed by anticoagulation had a better advantage in all-cause mortality and major bleeding than the systemic thrombolysis before anticoagulation in patients with PE.[26] It is also unclear if thrombolytic therapy combined with parenteral anticoagulation increased the risk of bleeding. A recent retrospective study suggests no significant difference in major bleeding in patients who received anticoagulation within 1 h of thrombolysis compared to those in which anticoagulation was delayed more than 1 h postthrombolysis.[6]

The review also highlights the constant challenge of adjudicating bleeding events between different trials using different definitions, making reaching an accurate pooled estimate a problem. There have been many efforts to mitigate this including the ISTH standardized definitions,[15,27] but those are still not necessarily always used by authors.

Comparison with existing literature

There are no available prior reviews to assess this question. There are many studies comparing LMWH to UFH in the acute treatment of VTE that demonstrate LMWH treatment to be as effective and safe as dose-adjusted IV UFH, but those studies included only patients with nonmassive VTE events.[8-10]

Strength and limitations

The strength of this review is that it is attempting to answer a question that is clinically very important and majorly affects patient care and hospital flow. However, it carries many limitations including the very low number of eligible studies, their risk of bias given the domination of cohort studies, and the relatively small patient population. There is also the limitation associated with trying to meta-analysis an RCT with an observational study as previously described.

Conclusion

In patients with massive and submissive PE postthrombolysis, this systematic review shows low certainty evidence to suggest that LMWH is a reasonable option for anticoagulation with lower risk of VTE recurrence, bleeding complications and 30-day mortality when compared to UFH. More studies with robust methodology are required to allow any definite conclusions to be drawn. There was no data to assess anticoagulation postthrombolysis in patients with DVT.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, *et al.* American Society of Hematology 2020 guidelines for management of venous thromboembolism: Treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020;4:4693-738.
2. Stevens SM, Woller SC, Baumann Kreuziger L, Bounameaux H, Doerschug K, Geersing GJ, *et al.* Executive summary: Antithrombotic therapy for VTE disease: Second update of the CHEST guideline and expert panel report. Chest 2021;160:2247-59.
3. Torbicki A, van Beek EJR, Charbonnier B, Meyer G, Morpurgo M, Palla A, *et al*. Guidelines on diagnosis and management of acute pulmonary embolism. Task Force on Pulmonary Embolism, European Society of Cardiology. Eur Heart J 2000;21:1301-36.
4. Nguyen PC, Stevens H, Peter K, McFadyen JD. Submassive pulmonary embolism: Current perspectives and future directions. J Clin Med 2021;10:3383.
5. Zhang RS, Maqsood MH, Sharp AS, Postelnicu R, Sethi SS, Greco A, *et al.* Efficacy and safety of anticoagulation, catheter-directed thrombolysis, or systemic thrombolysis in acute pulmonary embolism. JACC Cardiovasc Interv 2023;16:2644-51.
6. Schwab Daugherty EM, Peng MR, Caraccio EE, Stevens SM, Woller SC. Timing of parenteral anticoagulation after thrombolysis for the treatment of pulmonary embolism. Thromb Res 2020;195:58-61.
7. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ,

Harjola VP, *et al*. ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41:543-603. doi: 10.1093/eurheartj/ehz405. PMID: 31504429.

8. Robertson L, Jones LE. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. Cochrane Database Syst Rev 2017;2:CD001100.
9. Hull RD, Raskob GE, Brant RF, Pineo GF, Elliott G, Stein PD, *et al.* Low-molecular-weight heparin versus heparin in the treatment of patients with pulmonary embolism. American-Canadian thrombosis study group. Arch Intern Med 2000;160:229-36.
10. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: A meta-analysis of randomized, controlled trials. Ann Intern Med 2004;140:175-83.
11. Leentjens J, Peters M, Esselink AC, Smulders Y, Kramers C. Initial anticoagulation in patients with pulmonary embolism: Thrombolysis, unfractionated heparin, LMWH, fondaparinux, or DOACs? Br J Clin Pharmacol 2017;83:2356-66.
12. Todoran TM, Giri J, Barnes GD, Rosovsky RP, Chang Y, Jaff MR, *et al.* Treatment of submassive and massive pulmonary embolism: A clinical practice survey from the second annual meeting of the pulmonary embolism response team consortium. J Thromb Thrombolysis 2018;46:39-49.
13. Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: A meta-analysis of the randomized trials. Circulation 2005;112:3855-67.
14. Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott CG, *et al.* Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992;326:975-82.
15. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
16. Wells GA, Shea B, O'Connell Da, Peterson J, Welch V, Losos M, *et al.* The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Oxford; 2000. Available from https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Last accessed on 2024 Feb 30].
17. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al.* RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
18. Review Manager (RevMan) [Computer Program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre TCC; 2008.
19. Covidence Systematic Review Software, Veritas Health Innovation, Melbourne, Australia. Available from: https://www.covidence.org. [Last accessed on 2023 Dec 3].
20. Graif A, Kimbiris G, Grilli CJ, Agriantonis DJ, Putnam SG, Leung DA. Safety of therapeutic anticoagulation with low-molecular-weight heparin or unfractionated heparin infusion during catheter-directed thrombolysis for acute pulmonary embolism. J Vasc Interv Radiol 2020;31:537-43.
21. Ucar EY, Akgun M, Araz O, Tas H, Kerget B, Meral M, *et al.* Comparison of LMWH versus UFH for hemorrhage and hospital mortality in the treatment of acute massive pulmonary thromboembolism after thrombolytic treatment: Randomized controlled parallel group study. Lung 2015;193:121-7.
22. Senturk A, Ucar EY, Berk S, Ozlu T, Altınsoy B, Dabak G, *et al.* Should low-molecular-weight heparin be preferred over unfractionated heparin after thrombolysis for severity pulmonary embolism? Clin Appl Thromb Hemost 2016;22:395-9.
23. Ucar EY, Araz O, Akgun M, Meral M, Kalkan F, Saglam L, *et al.* Low-molecular-weight heparin use with thrombolysis: Is it effective and safe? Ten years' clinical experience. Respiration 2013;86:318-23.
24. GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.
25. British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thora×2003;58:470-83.
26. Tan JS, Liu N, Hu S, Wu Y, Gao X, Guo TT, *et al.* Association between the use of pre- and post-thrombolysis anticoagulation with all-cause mortality and major bleeding in patients with pulmonary embolism. Front Cardiovasc Med 2022;9:880189.
27. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: Communication from the SSC of the ISTH. J Thromb Haemost 2015;13:2119-26.

Appendix

Appendix 1: Supplementary Material

Table of Contents

References to studies included in this review:

1. Ucar EY, Akgun M, Araz O, Tas H, Kerget B, Meral M, *et al.* Comparison of LMWH versus UFH for hemorrhage and hospital mortality in the treatment of acute massive pulmonary thromboembolism after thrombolytic treatment: Randomized controlled parallel group study. Lung 2015;193:121-7.
2. Senturk A, Ucar EY, Berk S, Ozlu T, Altınsoy B, Dabak G, *et al.* Should low-molecular-weight heparin be preferred over unfractionated heparin after thrombolysis for severity pulmonary embolism? Clin Appl Thromb Hemost 2016;22:395-9.
3. Graif A, Kimbiris G, Grilli CJ, Agriantonis DJ, Putnam SG, Leung DA. Safety of therapeutic anticoagulation with low-molecular-weight heparin or unfractionated heparin infusion during catheter-directed thrombolysis for acute pulmonary embolism. J Vasc Interv Radiol 2020;31:537-43.

References to studies excluded from this review:

1. Bandarage D, Stanko K, DeVries J, Henkin S, Young M. Initial anticoagulation strategy in patients undergoing ultrasound assisted catheter-directed thrombolysis. J Am Coll Cardiol 2021;77 Suppl 1:1789. Available from: https://www.jacc.org/doi/10.1016/S0735-1097%2821%2903145-4. [Last accessed on 2024 Apr 29].
   Reason for exclusion: Only poster available with no definition of bleeding outcomes.
2. Ucar EY, Araz O, Akgun M, Meral M, Kalkan F, Saglam L, *et al.* Low-molecular-weight heparin use with thrombolysis: Is it effective and safe? Ten years' clinical experience. Respiration 2013;86:318-23.
   Reason for exclusion: wrong intervention (compared LMWH vs LMWH and thrombolytics, no comparison with UFH).
3. Graif A, Chedrawy C, Vance A, Kimbiris G, Grilli C, Agriantonis D, *et al*. Catheter-directed thrombolysis for acute pulmonary embolism in 132 patients: A single-center experience, Abstract No. 223, J Vasc Int Radiol 2018;29:S97. Available from: https://www.jvir.org/article/S1051-0443(18)30250-1/pdf. [Last accessed on 2024 Apr 29].
   Reason for exclusion: abstract only and wrong outcome (didn't compare outcomes based on anticoagulant used).
4. Senturk A, Ozsu S, Duru S, Cakır E, Ulaslı SS, Demirdogen E, *et al.* Prognostic importance of central thrombus in hemodynamically stable patients with pulmonary embolism. Cardiol J 2017;24:508-14.
   Reason for exclusion: wrong patient population, included patients with non-massive PE only.
5. Schwab Daugherty EM, Peng MR, Caraccio EE, Stevens SM, Woller SC. Timing of parenteral anticoagulation after thrombolysis for the treatment of pulmonary embolism. Thromb Res 2020;195:58-61.

Reason for exclusion: wrong intervention.

6. Charbonnier B, Pacouret G. Role of low molecular weight heparins for treating non-massive pulmonary embolism. Presse Med 1994;23:1821-5.
   Reason for exclusion: wrong patient population (non-massive PE patients).
7. Graif A, Chedrawy C, Vance A, Putnam S, Kimbiris G, Lie K, *et al*. The effect of catheter-directed thrombolysis for acute pulmonary embolism on serum fibrinogen levels. J Vasc Int Radiol 2018;29 Suppl 1:S98. Available from: https://www.jvir.org/article/S1051-0443(18)30252-5/fulltext. [Last accessed on 2024 Apr 29].
   Reason for exclusion: Wrong outcome.
8. Jerjes Sánchez C, Villarreal Umaña S, Ramírez Rivera A, Garcia Sosa A, Miguel Canseco L, Archondo T, *et al*. Improving adjunctive treatment in pulmonary embolism and fibrinolytic therapy. The role of enoxaparin and weight-adjusted unfractionated heparin. J Thromb Thrombolysis 2009;27:154-62.
   Reason for exclusion: wrong intervention.
9. Dangol G, Barreiro TJ, Gemmel D, Maharjan S. Saddle up. Clinical insignificance of saddle pulmonary embolism. Am J Resp Crit Care Med 2018;197:A3763. Available from: https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A3763. [Last accessed on 2024 Apr 29].
   Reason for exclusion: wrong patient population.

Database (s):

Ovid MEDLINE (R) and Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations, Daily and Versions 1992 to December 12, 2022

Search strategy		
#	Searches	Results
1	Low-Molecular-Weight/or LMWH.mp.	5690
2	(dalteparin or enoxaparin or tinzaparin or Fragmin or nadroparine).mp.	7813
3	Venous Thromboembolism/or Thromboembolism/or Venous Thrombosis/or Thrombosis/or venous thromboembolism.mp. or Pulmonary Embolism/or deep vein thrombosis.mp. or DVT.mp.	186,978
4	1 or 2	12132
5	3 and 4	6414
6	thrombolysis.mp. or exp Fibrinolytic Agents/or Mechanical Thrombolysis/or exp Thrombolytic Therapy/or thromboly*.mp.	213,258
7	Fibrinolysis/or fibrinoly*.mp.	75,905
8	(rt-PA or alteplase or recombinant tissue plasminogen activator or streptokinase or urokinase or Abbokinase or prourokinase).mp.	35,402
9	or/6-8	248,856
10	5 and 9	5106

Embase 1992 to 2023 January 20

Search strategy		
#	Searches	Results
1	exp low molecular weight heparin/	78,633
2	(dalteparin or enoxaparin or tinzaparin or Fragmin or nadroparine).mp. (mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word)	35,118
3	venous Thromboembolism/or Thromboembolism/or Venous Thrombosis/or Thrombosis/or venous thromboembolism.mp. or Pulmonary Embolism/or deep vein thrombosis.mp. or DVT.mp.	356,470
4	1 and 2	34,616
5	3 and 4	18,007
6	thrombolysis.mp. or exp Fibrinolytic Agents/or Mechanical Thrombolysis/or exp Thrombolytic Therapy/or thromboly*.mp. or blood clot lysis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	213,663
7	Fibrinolysis/or fibrinoly*.mp.	93,363
8	(rt-PA or alteplase or recombinant tissue plasminogen activator or streptokinase or urokinase or Abbokinase or prourokinase).mp.	66,970
9	Or/6-8	245,050
10	5 and 9	3391
11	Limit 20 to yr="1992 – 2022"	3362

Table 1: Risk of bias assessment for cohort study using Ottawa-Newcastle score

	Senturk *et al.*[22]	Notes	Graif *et al.*[20]	Notes
Selection	***	The selection of intervention (LMWH versus UFH) was not clear	***	The selection of LMWH versus UFH was entirely based on physician preferences
Comparability	*	The 2 groups were comparable when it comes to severity, the study also used logistic regression to control for many factors	-	The study doesn't report any form of controlling of confounding factors, neither in patient's selection nor in analysis
Outcome	**	There was no mention of whether there was any patient lost to follow up or not	**	The study doesn't mention specifically the duration of follow up

LMWH=Low molecular weight heparin, UFH=Unfractionated heparin. *, **, ***The stars are assigned as per the Newcastle-Ottawa scale for assessing the quality of nonrandomized studies in meta-analyses (see details at :Wells GA, Shea B, O'Connell Da, Peterson J, Welch V, Losos M, *et al*. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Oxford; 2000. Available from https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). [Last accessed on 2024 Feb 30]

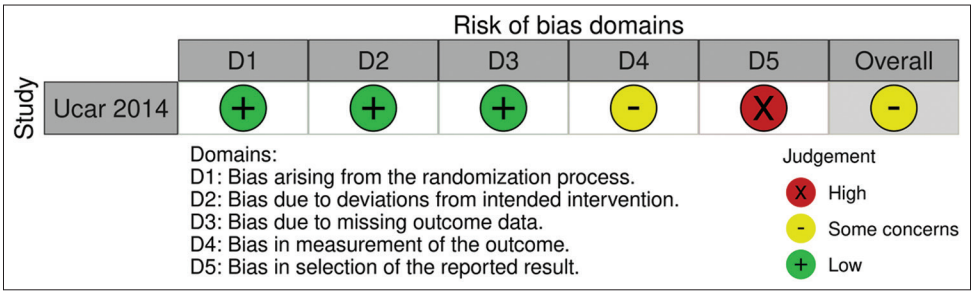

Figure 1: Risk of bias of included randomized controlled trial based on risk of bias-2 ratings

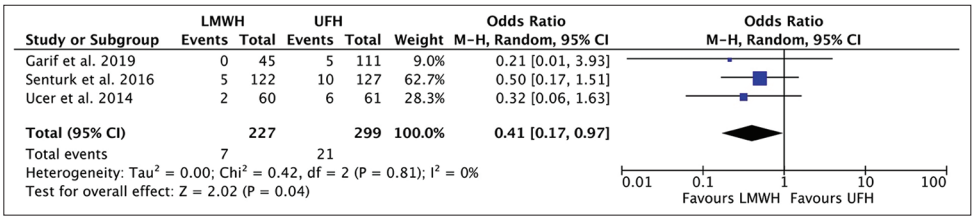

Figure 2: Forest plot for meta-analysis of the outcome of major hemorrhage. CI = Confidence interval, LMWH = Low-molecular-weight heparin, UFH = Unfractionated heparin

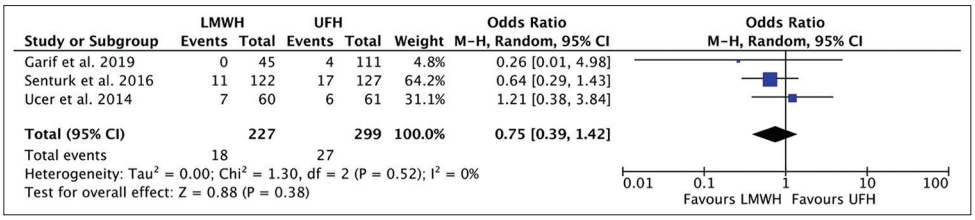

Figure 3: Forest plot of metanalysis for the outcome CRNMB. CI = Confidence interval, LMWH = Low-molecular-weight heparin, UFH = Unfractionated heparin

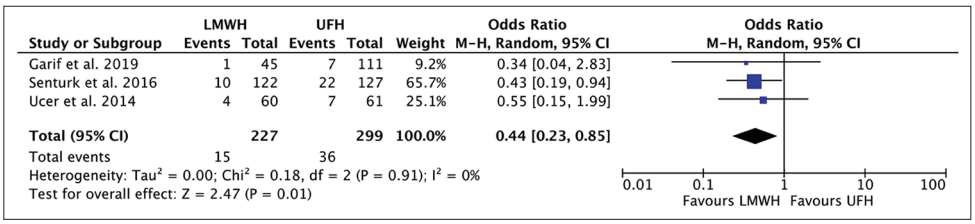

Figure 4: Forest plot of meta-analysis of the outcome 30-day mortality. CI = Confidence interval, LMWH = Low-molecular-weight heparin, UFH = Unfractionated heparin

Table 2: GRADE evidence profile table

Question: LMWH compared to UFH for VET postthrombolysis											
Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH, *n/n* (%)	UFH, *n/n* (%)	Relative (95% CI)	Absolute (95% CI)		
VTE recurrence												
2	1 RCT, 1 cohort	Serious[a]	Not serious	Not serious	Not serious	None	1/182 (0.5)	8/188 (4.3)	OR 0.18 (0.03–1.07)	35 fewer per 1000 (from 41 fewer to 3 more)	⊕◯◯◯ very low	Important
Major bleeding (assessed with: OR)												
3	1 RCT, 2 cohort	Very serious[a]	Not serious	Not serious	Serious[c]	None	7/227 (3.1)	21/299 (7.0)	OR 0.41 (0.17–0.97)	40 fewer per 1000 (from 58 fewer to 2 fewer)	⊕◯◯◯ very low	Important
CRNMB (assessed with: OR)												
3	1 RCT, 2 cohort	Serious[a]	Not serious	Not serious	Serious[a,b,c]	None	18/227 (7.9)	27/299 (9.0)	OR 0.75 (0.39–1.42)	21 fewer per 1000 (from 53 fewer to 33 more)	⊕◯◯◯ very low	Important
30-day mortality (assessed with: OR)												
3	1 RCT, 2 cohort	Very serious[a]	Serious[d]	Not serious	Serious[c]	None	15/227 (6.6)	36/299 (12.0)	OR 0.44 (0.23–0.85)	64 fewer per 1000 (from 90 fewer to 16 fewer)	⊕◯◯◯ very low	Critical

[a]Most of the data of this systematic review is generated from cohort studies which inherently carries a risk of bias. In addition, the patients in the cohort were chosen to receive LMWH versus Heparin based on an unclear mechanism, [b]The confidence interval of the effect estimate includes the null effect (OR of 1) and so there is insufficient evidence to conclude that the effect estimate is statistically significant, [c]Insufficient sample to reach the optimal information size, [d]The studies had different follow up (one was defined as 30 days, while the other 2 were not specified). CI=Confidence interval, OR=Odds ratio, RCT=Randomized controlled trial, LMWH=Low molecular weight heparin, UFH=Unfractionated heparin, VET=Venous thromboembolism, CRNMB=Clinically relevant nonmajor bleeding

Table 3: Summary of findings

LMWH compared to UFH for venous thromboembolism postthrombolysis Patient or population: VET postthrombolysis Intervention: LMWH Comparison: UFH						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with UFH	**Risk with LMWH**				
VTE recurrence	43 per 1000	8 per 1000 (1–45)	OR 0.18 (0.03–1.07)	370 (2 observational studies)	⊕◯◯◯ very low[a]	LMWH may carry a lower risk of VTE recurrence in patients post thrombolysis, though this did not reach statistical significance
Major bleeding assessed with: OR	92 per 1000	40 per 1000 (17–89)	OR 0.41 (0.17–0.97)	456 (3 observational studies)	⊕◯◯◯ very low[a,b,c]	LMWH was found to cause less major bleeding than UFH post thrombolysis, very low certainty evidence
CRNMB assessed with: OR	118 per 1000	91 per 1000 (50–160)	OR 0.75 (0.39–1.42)	456 (3 observational studies)	⊕◯◯◯ very low[a,b,c]	Lower rates of CRNMB in LMWH versus UFH, yet this is statistically insignificant and with very low certainty evidence
30-day mortality assessed with: OR	120 per 1000	57 per 1000 (31–104)	OR 0.44 (0.23–0.85)	526 (3 observational studies)	⊕◯◯◯ very low[a,c,d]	There is a signal indicating lower mortality with the use of LMWH in patients with massive and submassive PE post thrombolysis

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI), [a]Most of the data of this systematic review is generated from cohort studies which inherently carries a risk of bias. In addition, the patients in the cohort were chosen to receive LMWH vs Heparin based on an unclear mechanism, [b]The confidence interval of the effect estimate includes the null effect (OR of 1) and so there is insufficient evidence to conclude that the effect estimate is statistically significant, [c]Insufficient sample to reach the optimal information size, [d]The studies had different follow up (one was defined as 30 days, while in the other 2 it was not specified). GRADE Working group grades of evidence high certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. CI=Confidence interval, OR=Odds ratio, VET=Venous thromboembolism, CRNMB=Clinically relevant nonmajor bleeding, LMWH=Low-molecular-weight heparin, UFH=Unfractionated heparin, PE=Pulmonary embolism

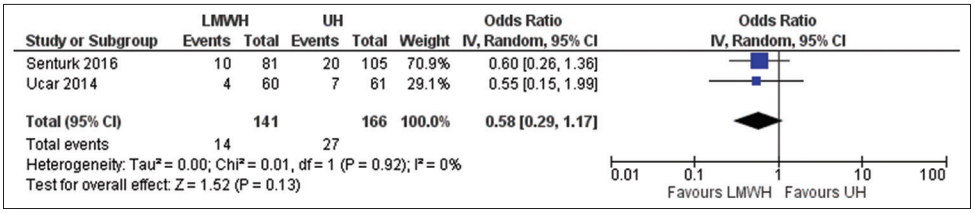

Figure 5: Forest plot of meta-analysis of the outcome 30-day mortality (patients with massive pulmonary embolism only). CI = Confidence interval, LMWH = Low-molecular-weight heparin, IV = Intravenous, UH = Unfractionated heparin