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► **To cite this version:**

Ingrid M Bistervels, Andrea Buchmüller, Hanke M G Wiegers, Fionnuala Ní Áinle, Bernard Tardy, et al.. Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (Highlow study): an open-label, multicentre, randomised, controlled trial. *The Lancet*, 2022, 400, pp.1777 - 1787. 10.1016/s0140-6736(22)02128-6 . hal-04817534

HAL Id: hal-04817534

<https://hal.science/hal-04817534v1>

Submitted on 3 Dec 2024

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Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (Highlow study): an open-label, multicentre, randomised, controlled trial

Ingrid M Bistervels*, Andrea Buchmüller*, Hanke M G Wieggers*, Fionnuala Ní Áinle, Bernard Tardy, Jennifer Donnelly, Peter Verhamme, Anne F Jacobsen, Anette T Hansen, Marc A Rodger, Maria T DeSancho, Roman G Shmakov, Nick van Es, Martin H Prins, Céline Chauleur, Saskia Middeldorp, for the Highlow Block writing committee† and Highlow Investigators‡

Summary

Background Pregnancy-related venous thromboembolism is a leading cause of maternal morbidity and mortality, and thromboprophylaxis is indicated in pregnant and post-partum women with a history of venous thromboembolism. The optimal dose of low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy and the post-partum period is uncertain.

Methods In this open-label, randomised, controlled trial (Highlow), pregnant women with a history of venous thromboembolism were recruited from 70 hospitals in nine countries (the Netherlands, France, Ireland, Belgium, Norway, Denmark, Canada, the USA, and Russia). Women were eligible if they were aged 18 years or older with a history of objectively confirmed venous thromboembolism, and with a gestational age of 14 weeks or less. Eligible women were randomly assigned (1:1), before 14 weeks of gestational age, using a web-based system and permuted block randomisation (block size of six), stratified by centre, to either weight-adjusted intermediate-dose or fixed low-dose low-molecular-weight heparin subcutaneously once daily until 6 weeks post partum. The primary efficacy outcome was objectively confirmed venous thromboembolism (ie, deep-vein thrombosis, pulmonary embolism, or unusual site venous thrombosis), as determined by an independent central adjudication committee, in the intention-to-treat (ITT) population (ie, all women randomly assigned to treatment). The primary safety outcome was major bleeding which included antepartum, early post-partum (within 24 h after delivery), and late post-partum major bleeding (24 h or longer after delivery until 6 weeks post partum), assessed in all women who received at least one dose of assigned treatment and had a known end of treatment date. This study is registered with ClinicalTrials.gov, NCT01828697, and is now complete.

Findings Between April 24, 2013, and Oct 31, 2020, 1339 pregnant women were screened for eligibility, of whom 1110 were randomly assigned to weight-adjusted intermediate-dose (n=555) or fixed low-dose (n=555) low-molecular-weight heparin (ITT population). Venous thromboembolism occurred in 11 (2%) of 555 women in the weight-adjusted intermediate-dose group and in 16 (3%) of 555 in the fixed low-dose group (relative risk [RR] 0.69 [95% CI 0.32–1.47]; p=0.33). Venous thromboembolism occurred antepartum in five (1%) women in the intermediate-dose group and in five (1%) women in the low-dose group, and post partum in six (1%) women and 11 (2%) women. On-treatment major bleeding in the safety population (N=1045) occurred in 23 (4%) of 520 women in the intermediate-dose group and in 20 (4%) of 525 in the low-dose group (RR 1.16 [95% CI 0.65–2.09]).

Interpretation In women with a history of venous thromboembolism, weight-adjusted intermediate-dose low-molecular-weight heparin during the combined antepartum and post-partum periods was not associated with a lower risk of recurrence than fixed low-dose low-molecular-weight heparin. These results indicate that low-dose low-molecular-weight heparin for thromboprophylaxis during pregnancy is the appropriate dose for the prevention of pregnancy-related recurrent venous thromboembolism.

Funding French Ministry of Health, Health Research Board Ireland, GSK/Aspen, and Pfizer.

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Introduction

Deep-vein thrombosis and pulmonary embolism during pregnancy or the post-partum period are the leading causes of maternal morbidity and mortality.^{1,2} Conversely, thromboprophylaxis can contribute to major bleeding,³

which is also a major cause of maternal morbidity and mortality. Despite these known risks, there is a paucity of evidence-based thromboprophylaxis strategies. Without thromboprophylaxis, women with a history of venous thromboembolism have a 2–10% risk of developing

Published Online
October 28, 2022
[https://doi.org/10.1016/S0140-6736\(22\)02128-6](https://doi.org/10.1016/S0140-6736(22)02128-6)

See Online/Comment
[https://doi.org/10.1016/S0140-6736\(22\)02030-X](https://doi.org/10.1016/S0140-6736(22)02030-X)

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for randomised trials and meta-analyses of randomised trials, published in English, that assessed the effectiveness of heparin or low-molecular-weight heparin in pregnant women with a history of venous thromboembolism, published between database inception and June 29, 2022, using the terms (“venous thrombosis” OR “pulmonary embolism” OR “venous thromboembolism”) AND (“heparin” OR “low-molecular-weight heparin” OR “thromboprophylaxis”) AND “pregnancy”. We identified two small randomised controlled trials that assessed the use of heparin in pregnant women with a history of venous thromboembolism. One was a randomised trial focusing on the safety of heparin during pregnancy, that included 40 women. Participants were randomly assigned to either unfractionated heparin at 10 000 international units (IU) twice daily antepartum followed by unfractionated heparin 8000 IU twice daily for 6 weeks post partum (n=20), or to no antepartum prophylaxis and unfractionated heparin 8000 IU twice daily for 6 weeks post partum only (n=20). One (5%) woman in the group not receiving antenatal heparin developed deep-vein thrombosis at a gestational age of 28 weeks. The other trial was a UK-based placebo-controlled randomised pilot trial of enoxaparin 40 mg that included women with a history of previous thromboembolic events, with the main aim to discover whether a sufficient number of women could be recruited to make large-scale randomised controlled trials feasible. Only

16 women were recruited, and one (13%) of eight women in the placebo group had a pulmonary embolism 29 days after delivery. These trials have also been summarised in a systematic review and an evidence-based guideline.

Added value of this study

To our knowledge, the international Highlow study is the first large, randomised, controlled thromboprophylaxis trial in pregnant and post-partum women with a history of venous thromboembolism, comparing two doses of low-molecular-weight heparin to prevent recurrence. We found no difference between weight-adjusted intermediate-dose low-molecular-weight heparin and fixed low-dose low-molecular-weight heparin on the risk of venous thromboembolism during the combined antepartum and post-partum periods.

Implications of all the available evidence

In women with a history of venous thromboembolism, post-hoc analyses suggest that low-dose low-molecular-weight heparin for thromboprophylaxis is the appropriate dose to prevent antepartum venous thromboembolism. Furthermore, we found potential higher efficacy of intermediate-dose low-molecular-weight heparin than low-dose low-molecular-weight heparin during the post-partum period in post-hoc analyses. This finding should be further investigated in future randomised controlled studies, and could help clinicians and patients to make an informed decision about increasing the dose after delivery.

pregnancy-associated recurrent venous thromboembolism.^{4–8} Hence, for pregnant women with a history of venous thromboembolism who are not using long-term anticoagulation medication, guidelines recommend post-partum thromboprophylaxis with subcutaneous low-molecular-weight heparin in all women, and antepartum thromboprophylaxis in those who have a moderate or high risk of recurrent venous thromboembolism.^{9–12}

The optimal dose of low-molecular-weight heparin for antepartum and post-partum thromboprophylaxis in women with a history of venous thromboembolism is uncertain. Because only two small, randomised studies in pregnant women have been done, dosing has been extrapolated from non-pregnant populations.^{13–15} However, physiological changes during pregnancy, including weight gain, increase in glomerular filtration rate, and plasma volume expansion, might affect the pharmacokinetics of low-molecular-weight heparin and reduce efficacy.^{16,17} Indeed, the proportion of women with pregnancy-related recurrent venous thromboembolism despite prophylaxis has been high in some observational studies.^{18–20} Guidelines from several professional societies indicate that there is no evidence to base the suggested thromboprophylactic dose on,¹² and provide no clear guidance. For instance, in their 2012 guidelines, the American College of Chest Physicians suggested the use

of either a prophylactic low or intermediate dose of low-molecular-weight heparin antepartum and post partum;⁹ in their 2018 guidelines, the American Society of Hematology suggested prophylactic use of low-dose rather than intermediate-dose low-molecular-weight heparin antepartum, and either dose post partum;¹¹ and in their 2018 guidelines, the American Society of Obstetrics and Gynecologists stated that intermediate-dose low-molecular-weight heparin could be considered at extremes of bodyweight or as pregnancy progresses.¹⁰

In this study, we aimed to investigate the efficacy and safety of intermediate-dose versus low-dose low-molecular-weight heparin in pregnant women with a history of venous thromboembolism.

Methods

Study design and participants

The Highlow study was an investigator-initiated, open-label, randomised, controlled study conducted at 70 hospitals in the Netherlands (n=34), France (n=26), Ireland (n=3), Belgium (n=1), Norway (n=1), Denmark (n=2), Canada (n=1), the USA (n=1), and Russia (n=1; some sites merged over the course of the study; a list is provided in the appendix [pp 9–15]). The trial rationale and design have been reported previously.²¹ Pregnant women aged 18 years or older with a history of

objectively confirmed venous thromboembolism (ie, a thromboembolism diagnosed by compression ultrasound examination, venography, CT, perfusion scintigraphy, or pulmonary angiography) either unprovoked or provoked by hormonal or minor risk factors, and a gestational age of 14 weeks or less, were eligible for inclusion. Exclusion criteria were a previous venous thromboembolism related to a major risk factor only (ie, surgery, major trauma, or plaster cast immobilisation in the 3 months before venous thromboembolism, in the absence of concomitant use of hormones), an indication for therapeutic-dose anticoagulants, or a contraindication to low-molecular-weight heparin. Use of low-molecular-weight heparin according to local standard of care before randomisation was allowed and recorded. Women were allowed to participate more than once and were randomly assigned with each new pregnancy.

The protocol was approved by the institutional review board or ethics committee of all participating centres. The protocol is available online. Written informed consent was obtained from all patients before randomisation.

Randomisation and masking

Eligible women were randomly assigned (1:1), using a web-based system and permuted block randomisation with a block size of six, stratified by centre, to weight-adjusted intermediate-dose or fixed low-dose low-molecular-weight heparin once daily. Physicians and participants were unmasked to treatment allocation because medication was supplied by local pharmacies in usual patient care settings or as study drug in accordance with national regulatory requirements. An independent central adjudication committee, whose members were masked to treatment allocation, adjudicated all suspected episodes of venous thromboembolism, superficial thrombophlebitis, major bleeding, clinically relevant non-major bleeding, minor bleeding, suspected type I allergy to low-molecular-weight heparin, and suspected heparin-induced thrombocytopenia, using prespecified criteria. The members of the independent adjudication committee are listed in the appendix (p 20).

Procedures

Participants were instructed to self-administer their allocated dose of low-molecular-weight heparin once daily from pre-filled syringes subcutaneously. The intermediate-dose low-molecular-weight heparin regimen was approximately half of a therapeutic dose, categorised by actual bodyweight and adjusted if needed during pregnancy or post partum, with cutoffs of less than 50 kg, 50 kg to less than 70 kg, 70 kg to less than 100 kg, and 100 kg or more. Once-daily doses ranged from 3800 to 9500 international units (IU) for nadroparin, 6000 to 12 000 IU for enoxaparin, 7500 to 15 000 IU for dalteparin, or 4500 to 12 000 IU for

tinzaparin (table 1). The fixed low-dose regimen was based on bodyweight at randomisation (<100 kg or ≥100 kg), per clinical practice in many centres and suggested by the Royal College of Obstetricians and Gynaecologists' Green-top guideline (table 1),¹² and the dose was not changed throughout pregnancy or post partum. The preferred type of low-molecular-weight heparin varied per centre. Women were instructed to stop treatment at first signs of labour. If delivery was planned, the last dose was given at least 24 h before delivery. Required time intervals between last dose and neuraxial anaesthesia were according to local guidelines—ie, 24 h for the intermediate dose, and 10–12 h for the low dose. Heparin was continued until 6 weeks post partum, even if a pregnancy ended in miscarriage, abortion, or stillbirth.

In-person or telephone contacts were scheduled 2 weeks after randomisation, at 20 and 30 weeks of gestation, and 1 week, 6 weeks, and 3 months post partum. At each contact, suspected outcome events, adverse events, compliance with low-molecular-weight heparin use, and concomitant medications were recorded. In the intermediate-dose group, dose adjustments of low-molecular-weight heparin were made if required on the basis of change in bodyweight at these visits. Women were instructed to contact the study team in case of signs or symptoms of venous thromboembolism or bleeding, upon which clinical assessment and diagnostic imaging were performed.

Outcomes

The primary efficacy outcome was symptomatic, objectively confirmed, venous thromboembolism (ie, a thromboembolism that is diagnosed by compression ultrasound examination, venography, CT or pulmonary angiography, or obduction and confirmed by the independent central adjudication committee) at any time from

For the Highlow study protocol
see www.highlowstudie.nl

	Nadroparin dose, IU	Enoxaparin dose, IU	Dalteparin dose, IU	Tinzaparin dose, IU
Weight-adjusted intermediate dose group				
<50 kg bodyweight	3800	6000	7500	4500
50 to <70 kg bodyweight	5700	8000	10 000	7000
70 to <100 kg bodyweight	7600	10 000	12 500	10 000
≥100 kg bodyweight	9500	12 000	15 000	12 000
Fixed low-dose group				
<100 kg bodyweight	2850	4000	5000	3500
≥100 kg bodyweight	3800	6000	7500	4500
All doses are administered once daily. IU=international unit.				
Table 1: Dosing schemes for each low-molecular-weight heparin type, by treatment group				

randomisation up to 6 weeks post partum, which was defined as an occurrence of new deep-vein thrombosis, pulmonary embolism, or unusual site venous thrombosis (eg, splanchnic vein or cerebral sinus thrombosis). After a diagnosis of recurrent thrombosis, patients were censored from the study. Secondary efficacy outcomes were the three components of the primary outcome, objectively confirmed superficial thrombophlebitis, and a composite of venous thromboembolism or superficial thrombophlebitis, at any time from randomisation until 6 weeks post partum, and until 3 months post partum.

The primary safety outcome was major bleeding, which included antepartum, early post-partum (within 24 h after delivery), and late post-partum major bleeding (24 h or longer after delivery until 6 weeks post partum), based on population-specific definitions proposed by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH).²² Antepartum and late post-partum major bleeding included placenta praevia requiring delivery, placental abruption, fetal or neonatal death due to bleeding, or acute clinically overt maternal bleeding associated with one or more of the following: occurring in a critical organ, associated with a decrease in haemoglobin concentration of 2 g/dL or more, requiring transfusion of two or more units of whole blood or red blood cells to maintain a haemoglobin concentration of more than 7–9 g/dL, or leading to maternal death. Early post-partum major bleeding was defined as bleeding within 24 h after delivery requiring transfusion of two or more units of whole blood or red blood cells or an estimated blood loss of 1000 mL or more necessitating a second line of uterotonics, or the occurrence of a uterine intervention for haemostasis, balloon tamponade, embolisation, conservative surgery, hysterectomy, or maternal death. Secondary safety outcomes were a composite of major or clinically relevant non-major bleeding, clinically relevant non-major bleeding and minor bleeding using population-specific definitions, maternal mortality, bruises, skin reactions around the injection site (type IV allergy), type I allergic reaction to low-molecular-weight heparin, heparin-induced thrombocytopenia, and congenital anomalies or birth defects.²²

The list of outcomes, including the primary safety outcome, was revised during the conduct of the trial. In the first version of the protocol, we defined major bleeding according to the standard ISTH definitions for the evaluation of anticoagulants,²³ and definitions of post-partum haemorrhage with a cutoff for more than 500 mL within 24 h of delivery. However, after start of the central adjudication by the multidisciplinary committee, its members judged that these definitions did not reflect clinical relevance of peri-partum haemorrhage, ultimately leading to a pregnancy-specific classification of major bleeding that was endorsed by the ISTH Scientific and Standardization Committee. The final protocol amendment occurred on June 9, 2017, before the data were unblinded.

Statistical analysis

The study hypothesis was that weight-adjusted intermediate-dose low-molecular-weight heparin would be superior to fixed low-dose low-molecular-weight heparin for the prevention of pregnancy-associated venous thromboembolism. The sample size was event driven, with a targeted number of primary outcome events of 29, assuming a 65% relative risk reduction with intermediate-dose versus low-dose low-molecular-weight heparin, a power of 80%, and a two-sided significance level of 0.05. On the basis of an expected incidence of venous thromboembolism of 4–5% in the low-dose group,¹⁸ the expected sample size was determined to be 859–1074.

We did the primary efficacy analysis in the intention-to-treat (ITT) population, defined as all women randomly assigned to treatment, and included all data and adjudicated outcomes from randomisation up to 6 weeks post partum. Secondary efficacy analyses were also assessed in the ITT population. We also did prespecified analyses of the primary efficacy outcome from randomisation until 3 months post partum. In post-hoc exploratory analyses, we also assessed efficacy outcomes during the antepartum and post-partum periods. We did prespecified analyses of the primary and secondary efficacy outcomes up to 6 weeks post partum in the per-protocol population and included outcomes occurring during the on-treatment period (defined as the time from randomisation to the last day of allocated low-molecular-weight heparin dose plus 2 days). Women were considered off-treatment in case of deviation from the allocated dose for more than 2 consecutive weeks. The per-protocol population included women without major protocol deviations, a self-reported adherence of 80% or higher, and who received at least one dose of allocated study treatment and had known date of end of on-treatment period.

We assessed safety in all women who received at least one dose of allocated study treatment and who had a known date of end of on-treatment period, and included in our analyses all data and adjudicated outcomes from randomisation up to 6 weeks post partum.

We did prespecified subgroup analyses of the primary efficacy and safety outcomes according to maternal age, location of previous venous thromboembolism, provoking factors of previous venous thromboembolism, BMI, thrombophilia, parity, low-molecular-weight heparin use before randomisation, and use of aspirin during pregnancy. We did sensitivity analyses of the primary efficacy and safety outcomes including the first pregnancy in this study only and excluding women who had a miscarriage before 14 weeks.

For all outcomes, we used the two-sided χ^2 test (or Fisher's exact test if fewer than five observations) to compare the intermediate-dose group with the low-dose group. We calculated relative risks (RR) with 95% CIs on the basis of normal approximation. We did time-to-event

analyses using Cox proportional hazards models to obtain hazard ratios with 95% CIs, censoring patients at loss to follow-up, withdrawal of informed consent, or end of study period. We checked the proportionality assumption by visual inspection of the log-minus-log plots and assessment of Schoenfeld residuals. We did not impute missing data and we only analysed observed data. Baseline data that were missing but that were then collected during follow-up visits were used to complete the table of baseline characteristics. For baseline variables such as bodyweight, we used the available bodyweight closest to the randomisation date. For primary and secondary outcomes, data from the visits after missed visits were used.

We did all analyses using R (version 4.0.3), particularly using the packages “survival” (version 3.2–7) and “epitools” (version 0.5–10.1). This study is registered with ClinicalTrials.gov, NCT01828697.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 24, 2013, and Oct 31, 2020, 1339 women were screened, of whom 1110 were enrolled and randomly assigned to either the intermediate-dose (n=555) or low-dose (n=555) low-molecular-weight heparin group (ITT population; figure 1). 516 (46%) women were recruited from the Netherlands, 388 (35%) from France, 99 (9%) from Ireland, 42 (4%) from Belgium, 28 (3%) from Norway, 15 (1%) from Denmark, 12 (1%) from Canada, seven (1%) from the USA, and three (<1%) from Russia. Characteristics at the time of randomisation (ie, baseline) are shown in table 2. The mean age was 32.0 years (SD 4.8), median BMI was 25.0 kg/m² (IQR 22.0–30.0), and 903 (81%) women had a history of venous thromboembolism related to hormone use, pregnancy, or the post-partum period. Data on race and ethnicity were not collected. Women were randomly assigned to treatment at a median gestational age of 9 weeks and 3 days (IQR 7 and 2 to 11 and 6). Median follow-up duration was 247 days (IQR 228–266), during which time 1017 women (92%) had a livebirth at a median gestational age of 38 weeks and 5 days (IQR 37 and 2 to 39 and 5). Of the remaining 93 women, one (1%) woman had a stillbirth, 71 (76%) had pregnancy loss before 24 weeks of gestational age, and 12 (13%) had a termination of pregnancy. For nine (1%) women, the outcome of pregnancy was unknown. 67 (6%) women participated in the study more than once.

The primary efficacy outcome of symptomatic venous thromboembolism from randomisation or up to 6 weeks post partum occurred in 11 (2%) of 555 women in the weight-adjusted intermediate-dose low-molecular-weight heparin group and in 16 (3%) of 555 in the fixed low-dose low-molecular-weight heparin group (RR 0.69 [95% CI

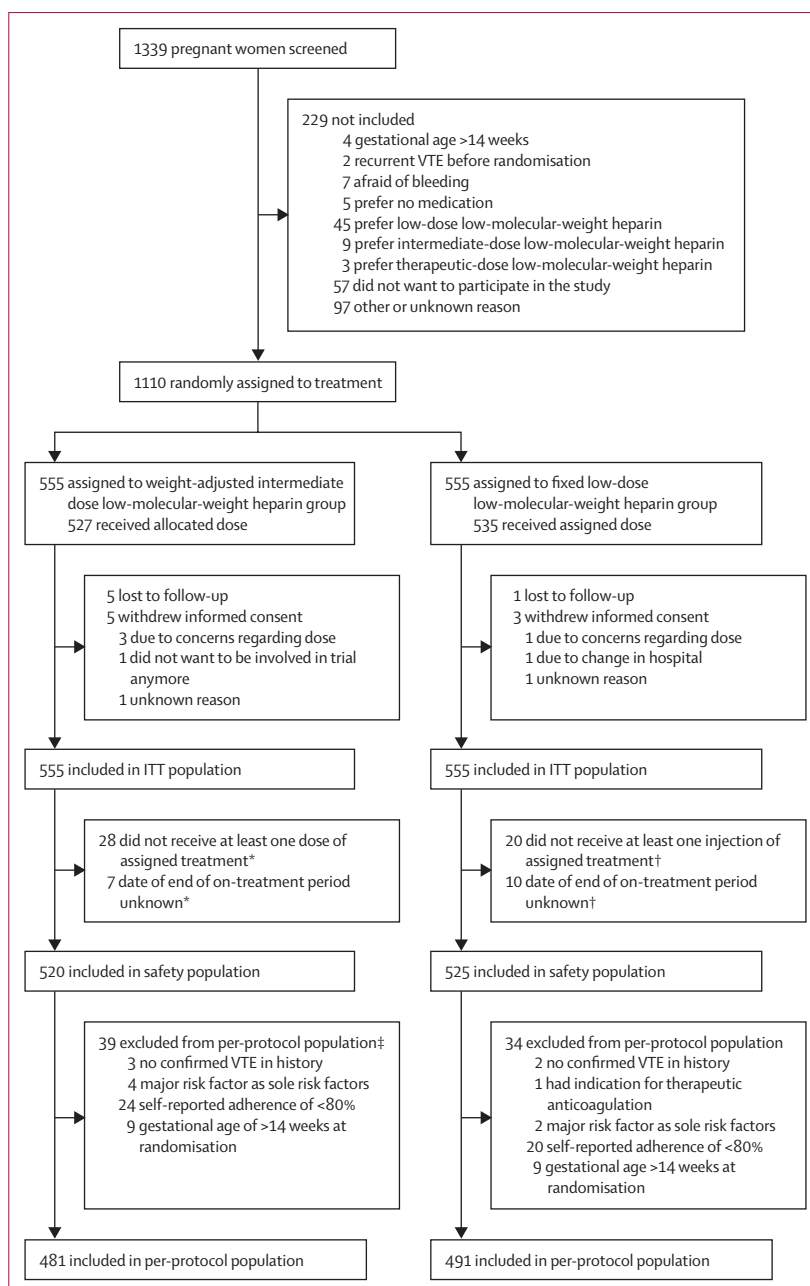


Figure 1: Trial profile

ITT=intention-to-treat. VTE=venous thromboembolism. *Two women excluded from the safety population also had protocol violations. †Five women excluded from the safety population also had protocol violation. ‡The number of women excluded from the per-protocol population is less than the sum of the reasons because one participant met two protocol deviations.

0.32 to 1.47]; $p=0.33$; table 3). The time to occurrence of the primary efficacy outcome is shown in figure 2A. Antepartum, five (1%) of 555 women had venous thromboembolism in each treatment group; and post partum, six (1%) of 555 women in the intermediate-dose group and 11 (2%) of 555 women in the low-dose group had venous thromboembolism (post hoc). The secondary efficacy endpoints up to 6 weeks post partum are shown

	Intermediate-dose low-molecular-weight heparin group (n=555)	Low-dose low-molecular-weight heparin group (n=555)
Baseline characteristics		
Age, years	32.0 (4.8)	32.0 (4.8)
Country of inclusion		
Netherlands	259 (46.7%)	257 (46.3%)
France	194 (35.0%)	194 (35.0%)
Ireland	49 (8.8%)	50 (9.0%)
Belgium	21 (3.8%)	21 (3.8%)
Norway	14 (2.5%)	14 (2.5%)
Denmark	8 (1.4%)	7 (1.3%)
Canada	6 (1.1%)	6 (1.1%)
USA	3 (0.5%)	4 (0.7%)
Russia	1 (0.2%)	2 (0.4%)
BMI, kg/m ²	25.0 (22.0–30.0)	25.0 (22.0–29.0)
Bodyweight		
<50 kg	9 (1.6%)	16 (2.9%)
50 to <70 kg	241 (43.4%)	237 (42.7%)
70 to <100 kg	250 (45.0%)	242 (43.6%)
≥100 kg	55 (9.9%)	58 (10.5%)
Primigravidity	141 (25.4%)	153 (27.6%)
Nulliparity	203 (36.6%)	214 (38.6%)
Gestational age at randomisation, in weeks and days	9 and 4 (7 and 3 to 11 and 6)	9 and 3 (7 and 1 to 12 and 0)
Clinical characteristics		
Use of low-molecular-weight heparin before randomisation*	267 (48.1%)	248 (44.7%)
Time since previous venous thromboembolism, years†	5.5 (2.6–8.9)	5.1 (2.2–9.0)
History of ≥2 episodes of venous thromboembolism	41 (7.4%)	46 (8.3%)
Location of previous venous thromboembolism‡		
Pulmonary embolism with or without DVT§	250 (45.0%)	222 (40.0%)
Upper or lower extremity DVT only¶	253 (45.6%)	283 (51.0%)
Unusual site venous thrombosis¶¶	48 (8.6%)	45 (8.1%)
No confirmed venous thromboembolism	4 (0.7%)	4 (0.7%)
Provoking factors of previous venous thromboembolism**		
Hormone therapy for contraception or assisted reproduction	320 (57.7%)	326 (58.7%)
During pregnancy	100 (18.0%)	80 (14.4%)
Unprovoked	73 (13.2%)	88 (15.9%)
Post-partum period	71 (12.8%)	69 (12.4%)
Air travel	30 (5.4%)	38 (6.8%)
Minor trauma	16 (2.9%)	14 (2.5%)
Major transient risk factor only	5 (0.9%)	3 (0.5%)

(Table 2 continues in next column)

	Intermediate-dose low-molecular-weight heparin group (n=555)	Low-dose low-molecular-weight heparin group (n=555)
(Continued from previous column)		
Known thrombophilia, n/N (%) previously tested	142/310 (25.6%)	149/315 (26.8%)
History of caesarean section	100 (18.0%)	85 (15.3%)
History of post-partum haemorrhage††	33 (5.9%)	30 (5.4%)
History of allergic skin reactions to low-molecular-weight heparin	37 (6.7%)	44 (7.9%)
Type of low-molecular-weight heparin after randomisation		
Enoxaparin	198 (35.7%)	215 (38.7%)
Nadroparin	205 (36.9%)	203 (36.6%)
Dalteparin	69 (12.4%)	76 (13.7%)
Tinzaparin	82 (15.0%)	58 (10.5%)
Aspirin use during pregnancy	38 (6.8%)	33 (5.9%)

Data are mean (SD), median (IQR), or n (%), unless otherwise stated. DVT=deep-vein thrombosis. *Data missing for 16 women in intermediate-dose group and 19 in low-dose group. †In case of multiple episodes of venous thromboembolism: the most recent event. ‡Some participants had venous thromboembolism at multiple sites at the same time. §Including extensive thrombophlebitis that was treated as DVT, muscle vein thrombosis close to popliteal vein treated as DVT, isolated calf vein thrombosis, and isolated pelvic vein thrombosis. ¶Including cerebral thrombosis, jugular vein thrombosis, abdominal vein thrombosis, and ovarian vein thrombosis. ||Includes participants without previous venous thromboembolism (one in intermediate-dose group and one in low-dose group), with arterial thrombosis (one in low-dose group), with superficial thrombophlebitis not treated as DVT (one in intermediate-dose group and one in low-dose group), and with retinal vein thrombosis (two in intermediate-dose group and one in low-dose group). **Some patients had more than one risk factor. ††Defined as loss of ≥500 mL of blood within 24 h after delivery.

Table 2: Demographic and clinical characteristics, intention-to-treat population

in table 3. None of the thrombotic events were fatal. Findings were consistent in the analyses up to 3 months post partum (table 3). In subgroup analyses of the primary efficacy outcome, we found no specific subgroups of women to experience venous thromboembolism; for example, no difference was found between those with and without a history of provoked or unprovoked venous thromboembolism, by bodyweight, or between those who had and had not used low-molecular-weight heparin before randomisation (appendix pp 22–23). Results of the sensitivity analysis of the primary outcome showed that exclusion of women who participated more than once, or those with a miscarriage or termination before 14 weeks' gestational age, did not materially affect our findings (appendix p 24).

In the on-treatment analysis of the per-protocol population, the primary efficacy outcome of symptomatic venous thromboembolism from randomisation up to 6 weeks post partum occurred in five (1%) of 481 women

in the intermediate-dose group and in 12 (2%) of 491 in the low-dose group (RR 0.43 [95% CI 0.15–1.20]; appendix pp 25–26, 29). Other secondary efficacy outcomes in the per-protocol population during the on-treatment period gave similar results as in the ITT population (appendix pp 25–26).

The primary safety outcome of major bleeding from randomisation up to 6 weeks post partum occurred in 23 (4%) of 520 women receiving intermediate-dose low-molecular-weight heparin and in 20 (4%) of 525 receiving low-dose low-molecular-weight heparin (RR 1.16 [95% CI 0.65–2.09]; $p=0.63$; table 4, figure 2B). Antepartum major bleeding occurred in two (<1%) women in the intermediate-dose group and in two (<1%) in the low-dose group. Early post-partum major bleeding occurred in 19 (4%) women in the intermediate-dose group and in 18 (3%) in the low-dose group. Late post-partum major bleeding occurred in two (<1%) women in the intermediate-dose group and in none in the low-dose group. There were no maternal deaths during the study. All safety outcomes are shown in table 4 and in the appendix (pp 30–31). The subgroup analysis and sensitivity analysis of the primary safety outcome are shown in the appendix (pp 24, 27–28), and did not differ materially from the main analyses.

Discussion

In the Highlow study, we found that antepartum and post-partum weight-adjusted intermediate-dose low-molecular-weight heparin did not reduce the risk of venous thromboembolism compared with fixed low-dose low-molecular-weight heparin in pregnant women with a history of venous thromboembolism. Despite thromboprophylaxis, in the ITT analysis including all women assigned to treatment (ie, including those with protocol deviations), we observed an absolute risk of venous thromboembolism during pregnancy or up to 6 weeks post partum of 2% in women receiving intermediate-dose low-molecular-weight heparin and 3% in those receiving low-dose low-molecular-weight heparin (RR 0.69 [95% CI 0.32 to 1.47]). In the on-treatment analysis in the per-protocol population, the risk difference between the treatment groups appeared larger, but this difference also was not significant (1% vs 2%; RR 0.43 [95% CI 0.15–1.20]). We found no difference in on-treatment major bleeding (4% in the intermediate-dose group vs 4% in the low-dose group; RR 1.16 [95% CI 0.65–2.09]).

Some observed differences between the treatment groups are noteworthy. First, the risk of pulmonary embolism, a component of the primary efficacy outcome, was substantially lower with intermediate-dose low-molecular-weight heparin than with fixed low-dose low-molecular-weight heparin (RR 0.11 [95% CI 0.01 to 0.87]). Second, venous thromboembolism or superficial thrombophlebitis up to 6 weeks post partum, a prespecified secondary efficacy outcome, occurred in 13 (2%) of 555 women in the intermediate-dose group and

	Intermediate-dose low-molecular-weight heparin group (n=555)	Low-dose low-molecular-weight heparin group (n=555)	Relative risk (95% CI)	Hazard ratio (95% CI)
From randomisation until 6 weeks post partum				
Venous thromboembolism (primary outcome)	11 (2%)	16 (3%)	0.69 (0.32–1.47)	0.68 (0.32–1.47)
Antepartum	5 (1%)	5 (1%)
Post partum	6 (1%)	11 (2%)
Pulmonary embolism	1 (<1%)	9 (2%)	0.11 (0.01–0.87)	..*
Antepartum	0	2 (<1%)
Post partum	1 (<1%)	7 (1%)
Deep-vein thrombosis	8 (1%)	6 (1%)	1.33 (0.47–3.82)	1.32 (0.46–3.81)
Antepartum	4 (1%)	3 (1%)
Post partum	4 (1%)	3 (1%)
Unusual site venous thrombosis†	2 (<1%)	1 (<1%)	2.00 (0.18–22.00)	1.99 (0.18–21.96)
Antepartum	1 (<1%)	0
Post partum	1 (<1%)	1 (<1%)
Superficial thrombophlebitis‡	3 (1%)	13 (2%)	0.23 (0.07–0.81)	0.22 (0.06–0.79)
Antepartum	3 (1%)	2 (<1%)
Post partum	0	11 (2%)
Venous thromboembolism or superficial thrombophlebitis	13 (2%)	29 (5%)	0.45 (0.24–0.85)	0.44 (0.23–0.85)
Antepartum	8 (1%)	7 (1%)
Post partum	5 (1%)	22 (4%)
From randomisation until 3 months post partum				
Venous thromboembolism	13 (2%)	18 (3%)	0.72 (0.36–1.46)	0.71 (0.35–1.45)
Pulmonary embolism	3 (1%)	9 (2%)	0.33 (0.09–1.22)	..*
Deep-vein thrombosis	8 (1%)	7 (1%)	1.14 (0.42–3.13)	1.14 (0.41–3.13)
Unusual site venous thrombosis§	2 (<1%)	2 (<1%)	1.00 (0.14–7.07)	0.99 (0.14–7.05)
Superficial thrombophlebitis	4 (1%)	13 (2%)	0.31 (0.10–0.94)	0.30 (0.10–0.93)
Venous thromboembolism or superficial thrombophlebitis	16 (3%)	31 (7%)	0.52 (0.29–0.93)	0.51 (0.28–0.92)

Data are n (%) or point estimate with 95% CI in parentheses. *Hazard ratio was not estimated due to violation of the proportionality assumption. †Including one cerebral venous thrombosis antepartum and one cerebral venous thrombosis post partum in the intermediate-dose group; and one abdominal venous thrombosis in the low-dose group. ‡Centrally adjudicated; after diagnosis, two participants in the intermediate-dose group and seven in the low-dose group were treated with therapeutic anticoagulant therapy; one of two participants in the intermediate-dose group continued with weight-adjusted intermediate-dose low-molecular-weight heparin, three of seven in the low-dose group were treated with intermediate-dose low-molecular-weight heparin, and another three in the low-dose group continued with low-dose low-molecular-weight heparin. §Including one additional cerebral venous thrombosis post partum in the low-dose group.

Table 3: Efficacy outcomes in the intention-to-treat population

in 29 (5%) of 555 in the low-dose group (RR 0.45 [95% CI 0.24–0.85]). This outcome is clinically relevant because superficial thrombophlebitis occurring while using

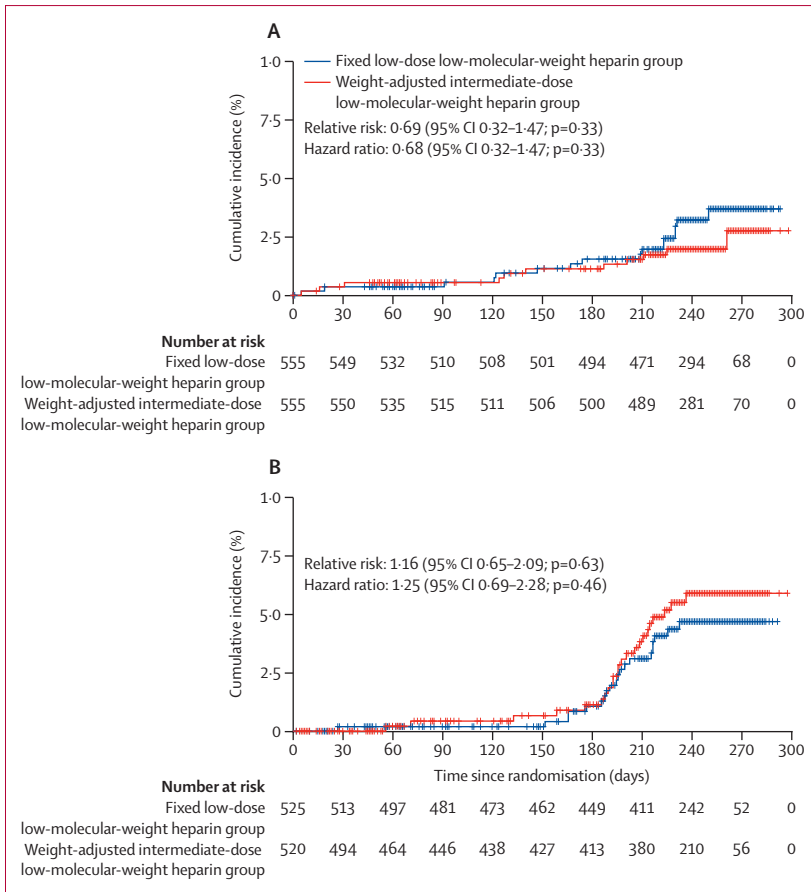


Figure 2: Kaplan-Meier cumulative event rates for venous thromboembolism in the intention-to-treat population (N=1110; A) and for major bleeding in the safety population (N=1045; B) from randomisation up to 6 weeks post partum. Ticks indicate number censored.

thromboprophylaxis often leads to increasing the dose of low-molecular-weight heparin.²⁴ Third, in post-hoc analyses, we observed a potential differential effect of the intervention in the antepartum versus the post-partum period. Women who were allocated to receive intermediate-dose low-molecular-weight heparin had a lower incidence of post-partum pulmonary embolism (one [$<1\%$] of 555 women vs seven [1%] of 555 women) and superficial thrombophlebitis (none vs 11 [2%]) than women allocated to low-dose low-molecular-weight heparin. Interestingly, we did not observe subgroups with a differential treatment effect, such as history of provoked or unprovoked venous thromboembolism or based on bodyweight. Although the absolute risk of venous thromboembolism might be increased in women with increased bodyweight or age,¹⁶ our study was not designed to draw conclusions about such differences between subgroups.

The results of the Highlow study provide an evidence base for guidelines and show that low-dose low-molecular-weight heparin for thromboprophylaxis during pregnancy is the appropriate dose to prevent pregnancy-related recurrence.⁹⁻¹² Higher doses of low-molecular-weight

heparin complicate peripartum management because of a longer required interval for neuraxial anaesthesia and are associated with increased costs and a potential for more side-effects, such as bruising and bleeding. The suggestion of greater efficacy of intermediate-dose low-molecular-weight heparin versus low-dose low-molecular-weight heparin during the post-partum period is to be regarded as hypothesis generating and would ideally be ascertained in a future randomised controlled trial. Additionally, finding ways to increase adherence to low-molecular-weight heparin during pregnancy and post partum and assessment of its effect on venous thromboembolism risk would be extremely valuable.

To date, only two small randomised controlled trials (one included 16 women,¹⁴ and the other included 40 women¹⁵) have assessed the efficacy of thromboprophylaxis in pregnant women with a history of venous thromboembolism. This paucity of studies is probably the result of substantial funding, regulatory, ethical, and structural barriers challenging the conduct of randomised trials in pregnant women. In the Highlow study, a large number of women were prospectively followed up with careful documentation of outcomes and adverse events. Loss to follow-up was very low, as was the rate of withdrawal of consent. Because the trial was run in nine countries with use of different types of low-molecular-weight heparin, the findings of this study are generalisable.

Our study has several limitations. The trial did not include a placebo group because the standard of care according to various guidelines is to provide pharmacological thromboprophylaxis with low-molecular-weight heparin to women with history of venous thromboembolism. For pragmatic reasons, we used an open-label design which might increase the risk of diagnostic suspicion bias. We also judged masking of clinicians to the assigned low-molecular-weight heparin dose to be unethical due to the requirement for different peripartum management strategies required for each group. However, the main efficacy and safety outcomes were adjudicated by a central committee who was unaware of treatment allocation. For the intermediate-dose low-molecular-weight heparin group, we chose to increase the dose with increasing bodyweight. We did not increase the dose in the low-dose group during the course of pregnancy, as is suggested by the American College of Obstetricians and Gynecologists and might be considered to be rational on the basis of pharmacokinetic studies.^{10,16,17} We found a considerable number of protocol deviations (146 deviations in 138 women), such as non-adherence to required weight adjustments in the intermediate-dose group, differences in peripartum low-molecular-weight heparin management due to concerns about post-partum bleeding or inaccessibility to neuraxial anaesthesia, and premature discontinuation of assigned treatment during the post-partum period. The effect of these deviations might be reflected in the greater observed efficacy of intermediate-dose low-molecular-weight heparin in the on-treatment

analysis in the per-protocol population. We relied on self-reported adherence rather than on a syringe count during each visit. Selection bias might have been introduced by allowing use of low-molecular-weight heparin before randomisation, multiple enrolments for the same women, and not restricting inclusion to the first pregnancy after the previous venous thromboembolism, potentially resulting in a population with a reduced risk of recurrence. We allowed inclusion of women up to 14 weeks of gestational age who had started thromboprophylaxis before inclusion in the study because a history of venous thromboembolism sometimes only becomes apparent at the first prenatal visit. In the subgroup analyses based on low-molecular-weight heparin use before randomisation, the relative effect of the intervention was similar between the treatment groups, with absolute risks that varied between 2% with previous low-molecular-weight heparin use and 3% without previous low-molecular-weight use in the intermediate-dose group, and 2% with previous use to 3% without previous use in the low-dose group. Although this finding suggests risk modification by previous use of low-molecular-weight heparin, this was a subgroup analysis, and so was not sufficiently powered to enable us to draw firm conclusions. Sensitivity analyses in which we excluded 67 women who participated more than once did not materially affect the results. In the absence of previous data, we assumed a relative risk reduction of 65% in an event-driven sample size calculation, but the observed relative risk reduction was smaller. Because of multiple reports^{18–20} of so-called breakthrough recurrences of venous thromboembolism on low-dose low-molecular-weight heparin, we hypothesised that intermediate dose would be superior to low dose, such that the low dose would be as ineffective as placebo and we assumed a relative risk reduction of the intermediate dose versus the low dose of 65% in the sample size calculation, but the observed absolute risk and the relative risk reduction were smaller. Finally, we did not meet the targeted number of centrally adjudicated and confirmed venous thromboembolism events, with only 27 adjudicated events. However, if we had reached 29 adjudicated events, this greater number of events would not have changed our power to show a difference between the treatment groups. The absence of race and ethnicity data might affect the generalisability of our findings, because the incidence of venous thromboembolism differs between ethnic groups.²⁵

The knowledge gap regarding optimal dosing of low-molecular-weight heparin in pregnancy and during the post-partum period has been explicitly identified by major organisations and societies.^{2,11} Hence, we are confident that the results of our study will affect international and national guidelines and that recommendations will be rapidly taken up by clinicians, knowledge users, and policy makers globally. For individual clinicians, counselling of pregnant women

	Intermediate-dose low-molecular-weight heparin group (n=520)	Low-dose low-molecular-weight heparin group (n=525)	Relative risk (95% CI)	Hazard ratio (95% CI)
Primary safety outcome				
Major bleeding	23 (4%)	20 (4%)	1.16 (0.65–2.09)	1.25 (0.69–2.28)
Antepartum	2 (<1%)	2 (<1%)
Early post partum	19 (4%)	18 (3%)
Late post partum	2 (<1%)	0
Secondary safety outcomes				
Major or clinically relevant non-major bleeding	50 (10%)	45 (9%)	1.12 (0.76–1.65)	1.21 (0.81–1.81)
Antepartum	23 (4%)	10 (2%)
Early post partum	25 (5%)	35 (7%)
Late post partum	2 (<1%)	0
Clinically relevant non-major bleeding	27 (5%)	25 (5%)	1.09 (0.64–1.85)	..*
Antepartum	21 (4%)	8 (2%)
Early post partum	6 (1%)	17 (3%)
Late post partum	0	0
Minor bleeding	76 (15%)	66 (13%)	1.16 (0.86–1.58)	1.27 (0.91–1.77)
Antepartum	17 (3%)	18 (3%)
Early post partum	55 (11%)	46 (9%)
Late post partum	4 (1%)	2 (<1%)
Any bleeding	123 (24%)	110 (21%)	1.13 (0.90–1.42)	1.23 (0.95–1.59)
Antepartum	39 (8%)	28 (5%)
Early post partum	78 (15%)	80 (15%)
Late post partum	6 (1%)	2 (<1%)
Heparin-induced thrombocytopenia	0	0
Type I allergic reaction to heparin	8 (2%)	2 (<1%)
Congenital abnormality or birth defect	9 (2%)	5 (1%)
Bruising	248 (48%)	184 (35%)
Type IV allergic skin reaction	180 (35%)	115 (22%)

Data are n (%) or point estimate with 95% CI in parentheses. *Hazard ratio was not estimated due to violation of the proportionality assumption.

Table 4: Safety outcomes in the safety population, from randomisation up to 6 weeks post partum

who are challenged by a history of venous thromboembolism will, for the first time, be supported by high-quality data.

In summary, among women with a history of venous thromboembolism, weight-adjusted intermediate-dose low-molecular-weight heparin during the combined antepartum and post-partum periods was not associated with a lower risk of recurrence than fixed low-dose low-molecular-weight heparin. Post-hoc analyses suggest intermediate-dose low-molecular-weight heparin might be more effective than low-dose low-molecular-weight heparin in the post-partum period, but this finding will need confirmation in future randomised controlled studies.

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Contributors

SM designed the trial. SM, AB, FNÁ, PV, AFJ, ATH, MAR, MTD, and RGS were national coordinators of the study. SMB, IMB, and HMGW were international coordinators. IMB, AB, HMGW, FNÁ, JD, PV, AFJ, ATH, MAR, MTD, RGS, CC, SM, and all Highlow investigators (listed in the appendix [pp 9–15]) recruited participants. SM, IMB, HMGW, NvE, and MHP designed the statistical analysis plan, HMGW and NvE did the analyses, and data were interpreted by all authors. All authors had full access to the data. IMB, HMGW, NvE, and SM had access to and verified the underlying study data. IMB, HMGW, NvE, and SM wrote the first draft of the manuscript, which was critically reviewed and revised by all authors. The executive writing committee (IMB, AB, HMGW, FNÁ, BT, JD, PV, AFJ, ATH, MAR, MTD, RGS, NvE, MHP, CC, and SM) was responsible for the decision to submit the manuscript. All authors approved the final version of the manuscript. The members of the executive writing committee and the block writing committee assume responsibility for the overall content and integrity of this Article. PWK, LB, BT, M-NV, and AM were members of the Independent Central Adjudication Committee, and MHP was the study statistician.

Declaration of interests

FNÁ reports grants as principal investigator from the Irish Health Research Board during the conduct of the study, and grants as principal investigator from Daiichi-Sankyo, Bayer, and Sanofi (investigator-initiated studies, fees paid to university) outside of the submitted work. AB reports grants from the French Ministry of Health, during the conduct of the study. JD reports grants as principal investigator from the Irish Health Research Board during the conduct of the study. NvE reports fees for scientific presentation from Bristol-Meyers Squibb (fee transferred to institution) and advisory board fees from LEO Pharma and Bayer (fees transferred to institution), outside of the submitted work. AFJ reports personal fees from Sanofi-Aventis outside of the submitted work. SM reports grants from GSK, Aspen, and Pfizer during the conduct of the study; grants and personal fees from Daiichi-Sankyo, Bayer, Pfizer, and Boehringer Ingelheim; and personal fees from Portola/Alexion, AbbVie, Pfizer/Bristol-Meyers Squibb, Norgine, Viatrix, and Sanofi, outside of the submitted work. MTD reports personal fees from Sanofi Genzyme and Bioproducts Laboratory outside of the submitted work. PV reports grants and personal fees from LEO Pharma, Boehringer Ingelheim, Daiichi-Sankyo, Bayer, and Pfizer/Bristol-Meyers Squibb and personal fees from Anthos and Portola/Alexion, outside of the submitted work. All other authors declare no competing interests

Data sharing

Requests for data sharing can be sent to saskia.middeldorp@radboudumc.nl. Only deidentified data will be made available to academic researchers upon reasonable request. Data will be available once all planned analyses have been completed and published or presented. Non-Highlow investigators will be asked to sign a Data Sharing Agreement before data sharing. The study protocol, statistical analysis plan, independent central adjudication committee charter, and

informed consent form have been available without restrictions to others from the start of the study.

Acknowledgments

The Highlow study was partially supported by a grant from the French Ministry of Health (2014, Programme Hospitalier de Recherche Clinique national, number 1408211); the Health Research Board Ireland (Definitive Interventions and Feasibility Awards [DIFA] 2017, number DIFA-2017-040); an unrestricted grant from GSK (2012), which was taken over by Aspen (2016); and Pfizer. Neither the grant agencies nor GSK, Aspen, or Pfizer had any role in the design, data collection, analysis, or interpretation of the study results. No funding for this specific analysis was obtained. We thank all women who participated in the study and all clinicians who referred potential participants to us. We also thank Jan Beyer-Westendorf, Andra H James, Michael Greaves, Ida Martinelli, Ingrid Pabinger, and Stavros V Konstantinides for their support during the initial design of the trial. The Highlow study was endorsed and infrastructurally supported by the Dutch Thrombosis Network, Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology (Consortium 2.0), two French gynaecological networks (Gynécologie-Obstétrique, Centres d'Investigation Clinique and Groupe de Recherche en Obstétrique et Gynécologie), the French network on thrombosis (Investigation Network on Venous Thromboembolism [INNOVTE]), the Irish Network for VTE Research (INViTE), the Irish HRB Mother and Baby Clinical Trials Network, and by the International Network of Venous Thrombosis Networks (Invent VTE). We thank these networks for their collaboration and support.

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