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

Authors:

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

**Ingrid M. Bistervels, Andrea Buchmüller and Hanke M.G. Wiegers contributed equally to this article.*

**The members of the executive writing committee and the block writing committee assume responsibility for the overall content and integrity of this article. The full names, academic degrees, and affiliations of the members of the executive writing committee and the block writing committee are listed in the Supplementary Appendix. A complete list of the Highlow Investigators is provided in the Supplementary Appendix.

Address reprint requests to Prof. dr. Saskia Middeldorp at Department of Internal Medicine & Radboud Institute of Health Sciences (RIHS), Radboud university medical center, Nijmegen, the Netherlands, or at saskia.middeldorp@radboudumc.nl.

Corresponding author:

Prof. dr. Saskia Middeldorp, Department of Internal Medicine, Radboud university medical center, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, the Netherlands

saskia.middeldorp@radboudumc.nl, telephone: +31 24 3614763; mobile number +31610630300

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Abstract

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

Methods: In this international, open-label, randomised trial, pregnant women with a history of venous thromboembolism were randomised before 14 weeks of gestational age to weight-adjusted intermediate-dose or fixed low-dose low-molecular-weight heparin until 6 weeks postpartum. The primary efficacy outcome was objectively confirmed venous thromboembolism. The primary safety outcome was major bleeding.

Findings: A total of 1,110 pregnant women were randomised and included in the intention-to-treat population. Venous thromboembolism occurred in 11 of 555 (2·0%) women assigned to weight-adjusted intermediate-dose low-molecular-weight heparin and in 16 of 555 (2·9%) assigned to fixed low-dose low-molecular-weight heparin (relative risk, 0·69; 95% confidence interval [CI], 0·32-1·47; P=0·33). Venous thromboembolism occurred antepartum in five (0·9%) and five (0·9%) women, and postpartum in six (1·1%) and 11 women (2·0%) in the intermediate-dose and low-dose groups, respectively. On-treatment venous thromboembolism in the per-protocol population (N=972) occurred in 1·0% and 2·4% (relative risk, 0·43; 95% CI, 0·15-1·20). On-treatment major bleeding in the safety population (N=1,045) occurred in 4·4% and in 3·8% receiving intermediate-dose or low-dose low-molecular-weight heparin, respectively (relative risk, 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 postpartum 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. Postpartum, intermediate-dose low-molecular-weight heparin may be more effective than low dose low-molecular-weight heparin. (ClinicalTrials.gov number, NCT01828697)

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Key words (MeSH terms)

venous thromboembolism; venous thrombosis; pulmonary embolism; pregnancy; postpartum period; postpartum haemorrhage; heparin; heparin, low-molecular-weight

Research in context

Evidence before this study

We searched PubMed for studies published between the inception of the database and June 29, 2022, using the search terms ("venous thrombosis" OR "pulmonary embolism" OR "venous thromboembolism") AND ("heparin" OR "low-molecular-weight heparin" OR "thromboprophylaxis") AND "pregnancy" to find randomised trials and meta-analyses of randomised trials, published in English, that evaluated the effectiveness of heparin or low-molecular-weight heparin in pregnant women with a history of venous thromboembolism. We found two small randomised, controlled trials that evaluated 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 with a history of venous thromboembolism. Women were randomised between unfractionated heparin 10,000 international units (IU) twice daily antepartum followed by unfractionated heparin 8,000 IU twice daily for 6 weeks postpartum, or to unfractionated heparin 8,000 IU twice daily for 6 weeks postpartum alone. One woman in the control group developed deep-vein thrombosis at a gestational age of 28 weeks. The other trial was a placebo-controlled randomised pilot trial of enoxaparin 40 mg that included women with a history of previous thromboembolic events, women with a known congenital thrombophilia, and women with other accepted risk factors for which clinicians would consider the use of antenatal heparin. The primary outcome was the number of recruited women. The recruitment period was 22 months in which 16 women were recruited in 11 centres; one woman in the placebo group had pulmonary embolism 29 days after delivery. We also identified one randomised, controlled trial in 292 women with thrombophilia and various clinical manifestations that investigated antepartum prophylactic dose dalteparin of 5,000 IU once daily, doubled at 20 weeks gestational age, versus no antenatal dalteparin; all women received dalteparin 5,000 IU once daily postpartum for 6 weeks. The trial included 36 women with a history of venous thromboembolism. Of 21 women allocated to antenatal dalteparin, one patient had antenatal venous thromboembolism and two

postpartum venous thromboembolism, whereas none of 9 women in the control group had venous thromboembolism. The abovementioned randomised trials have also been summarised in a systematic review and an evidence-based guideline.

Added value of this study

The international Highlow study is the first large, randomised, controlled thromboprophylaxis trial in pregnant and postpartum women with a history of venous thromboembolism, comparing two doses of low-molecular-weight heparin to prevent recurrence. There was no statistically significant difference between antepartum and postpartum 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 postpartum periods. Our study showed that despite thromboprophylaxis, the absolute risk of venous thromboembolism (deep-vein thrombosis and/or pulmonary embolism) during pregnancy or up to 6 weeks postpartum was 2·0% in women receiving intermediate-dose low-molecular-weight heparin and 2·9% in those receiving low-dose low-molecular-weight heparin (RR 0·69, 95% CI 0·32 to 1·47). Postpartum, intermediate-dose low-molecular-weight heparin appeared to be more effective than low dose low-molecular-weight heparin, with risks of venous thromboembolism of 1·1% and 2·0% respectively.

Implications of all the available evidence

In women with a history of venous thromboembolism, low-dose low-molecular-weight heparin for thromboprophylaxis during pregnancy is the appropriate dose. The suggestion of a higher efficacy of intermediate-dose low-molecular-weight heparin than low-dose low-molecular weight heparin during the postpartum period is an important finding that calls for confirmation in a future randomised, controlled trial.

Introduction

Deep-vein thrombosis and pulmonary embolism during pregnancy or the postpartum period are the leading cause of maternal morbidity and mortality.[1,2] Conversely, thromboprophylaxis can contribute to major bleeding[3], which also is a major cause of maternal morbidity and mortality. Despite these high stakes, evidence-based thromboprophylaxis strategies are lacking. Without thromboprophylaxis, women with a history of venous thromboembolism have a 2 to 10% risk of developing pregnancy-associated recurrent venous thromboembolism.[4-8] Hence, for pregnant women with a history of venous thromboembolism who are not using long-term anticoagulation, guidelines recommend postpartum thromboprophylaxis with subcutaneous low-molecular-weight heparin in all, 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 postpartum thromboprophylaxis in women with a history of venous thromboembolism is uncertain. Due to a lack of randomised studies in pregnancy, dosing is extrapolated from non-pregnant populations.[13-15] However, physiological changes during pregnancy including weight gain, increase in glomerular filtration rate, and plasma volume expansion may influence low-molecular-weight heparin pharmacokinetics and reduce efficacy.[16,17] Indeed, pregnancy-related recurrent venous thromboembolism despite prophylaxis was 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: the American College of Chest Physicians (ACCP, 2012) suggests the use of either a prophylactic low or intermediate-dose of low-molecular-weight heparin antepartum and postpartum;[9] the American Society of Hematology (ASH, 2018) suggests prophylactic low-dose over intermediate-dose low-molecular-weight heparin antepartum, and either dose postpartum;[11] and the American Society of Obstetrics and Gynecologists (ACOG, 2018) states that intermediate-dose low-molecular-weight heparin may be considered at extremes of body weight or as pregnancy progresses.[10]

We performed a randomised, controlled trial comparing the efficacy and safety of intermediate 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, multicentre, international, open-label, randomised, controlled trial (ClinicalTrials.gov number, NCT01828697), of which the rationale and design have been reported previously.[21] The study was conducted at 70 hospitals in The Netherlands, France, Ireland, Belgium, Norway, Denmark, Canada, United States, and Russia. The protocol was approved by the institutional review board or ethics committee of all participating centres. Written informed consent was obtained from all patients prior to randomisation.

Pregnant women aged 18 years or older with a history of objectively confirmed venous thromboembolism, either unprovoked or provoked by hormonal or minor risk factors, and gestational age of 14 weeks or less, were eligible. Exclusion criteria were a previous venous thromboembolism related to a major risk factor only (i.e. surgery, major trauma or plaster cast immobilization 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 protocol prior to randomisation was allowed and recorded. Women were allowed to participate more than once and were randomised per pregnancy.

Randomisation and masking

Women were randomly assigned to weight-adjusted intermediate-dose low-molecular-weight heparin or fixed low-dose low-molecular-weight heparin once-daily using a web-based system, balanced in permuted blocks of six and stratified by centre. Hence, physicians and patients could not foresee the outcome of

randomisation (i.e. concealment of allocation). After randomisation, there was no masking to assigned study group for physicians or patients, as medication was supplied by pharmacies in usual patient care settings or as study drug in accordance with national regulatory requirements. A central independent adjudication committee, whose members were unaware of the treatment allocation, adjudicated all suspected episodes of venous thromboembolism, superficial thrombophlebitis, major bleeding, clinically relevant non-major bleeding, suspected type 1 allergy to low-molecular-weight heparin, and suspected heparin-induced thrombocytopenia, using pre-specified criteria.

Procedures

Participants were instructed to administer the allocated dose of low-molecular-weight heparin from pre-filled syringes subcutaneously. The intermediate-dose low-molecular-weight heparin regimen was approximately half of a therapeutic dose, categorised by actual body weight and adjusted if needed during pregnancy or postpartum, with cut-offs of <50 kilograms (kg), 50 to 70 kg, 70 to 100 kg, and ≥100 kg. Once daily doses ranged from 3,800 to 9,500 international units (IU) for nadroparin, 6,000 to 12,000 IU for enoxaparin, 7,500 to 15,000 IU for dalteparin, or 4,500 to 12,000 IU for tinzaparin (**Panel**). The fixed low-dose regimen was based on weight at randomisation (<100 kg or ≥100 kg) as per clinical practice in many centres and suggested by the Royal College of Obstetricians and Gynaecologists' Green-top Guideline [12], and consisted of nadroparin 2,850 or 3,800 IU, enoxaparin 4,000 or 6,000 IU, dalteparin 5,000 or 7,500 IU, or tinzaparin 3,500 or 4,500 IU, and was not changed throughout pregnancy or postpartum. The preferred type of low-molecular-weight heparin varied per centre. Women were instructed to stop low-molecular-weight heparin at first signs of labour. If delivery was planned, the last dose was given at least 24 hours prior to delivery. Required time intervals between last dose of low-molecular-weight heparin and neuraxial anaesthesia were according to local guidelines, i.e. 24 hours for the intermediate-dose, and 10 to 12 hours

for the low-dose. Low-molecular-weight heparin was continued until 6 weeks postpartum, also 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 postpartum. 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 based on change in body weight. 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 up to 6 weeks postpartum, including deep-vein thrombosis, pulmonary embolism, or unusual site venous thrombosis, e.g. splanchnic vein or cerebral sinus thrombosis. Secondary efficacy outcomes were the three components of the primary outcome, objectively confirmed superficial thrombophlebitis, and a composite of venous thromboembolism or superficial thrombophlebitis.

The primary safety outcome was major bleeding, which included antepartum, early postpartum (within 24 hours after delivery), and late postpartum major bleeding (after 24 hours of delivery until 6 weeks postpartum) based on population-specific definitions proposed by a subcommittee of the International Society on Thrombosis and Haemostasis (ISTH).[22] Antepartum and late postpartum 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 fall in haemoglobin level of 2 g/dL or more, requiring transfusion of two or more units of whole blood or red cells to maintain a haemoglobin level of more than 7-9 g/dL, or leading to maternal

death. Early postpartum major bleeding was defined as bleeding within 24 hours after delivery requiring transfusion of two or more units of whole blood or red cells, or an estimated blood loss of ≥1,000 mL necessitating a second line of uterotonics, a uterine intervention for haemostasis, balloon tamponade, embolisation, conservative surgery, hysterectomy, or maternal death. Secondary safety outcomes were clinically relevant non-major bleeding and minor bleeding using population-specific definitions.[22]

The list of outcomes, including the primary safety outcome, was revised during 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 postpartum haemorrhage with a cut-off for >500 mL within 24 hours 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 peripartum haemorrhage, ultimately leading to a pregnancy-specific classification of major bleeding that was endorsed by the ISTH Scientific and Standardization Committee. The final revision took place in June 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 29 primary outcome events, assuming a 65% relative risk reduction with intermediate-dose as compared with low-dose low-molecular-weight heparin, a power of 80%, and a two-sided significance level of 0·05. Based on an expected incidence of venous thromboembolism of 4 to 5% in the low-dose group,[18] the expected sample size was determined to be 859 to 1,074.

The primary efficacy analysis was performed in the intention-to-treat population and included all data and adjudicated outcomes from randomisation up to 6 weeks postpartum in all randomised women. A secondary analysis of the efficacy outcomes was performed with outcomes from randomisation up to 3

months postpartum. The primary efficacy outcome up to 6 weeks postpartum was also evaluated 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 more, and who received at least one dose of allocated study treatment.

The analysis of safety outcomes was performed in the safety population and included all data and adjudicated outcomes from randomisation up to 6 weeks postpartum during the on-treatment period. The safety population included all women who received at least one dose of allocated study treatment.

Predefined subgroup analyses were performed according to maternal age, location of previous venous thromboembolism, provoking factors of previous venous thromboembolism, body mass index (BMI), thrombophilia, parity, low-molecular-weight heparin use before randomisation, and use of acetylsalicylic acid during pregnancy. Sensitivity analyses were performed including the first pregnancy in this study only and excluding women who experienced miscarriage before 14 weeks.

For all outcomes, a two-sided Chi-squared test (or a Fisher's exact test if fewer than 5 observations) was performed to compare the intermediate-dose with the low-dose group. Relative risks (RR) with 95% confidence intervals (CI) based on normal approximation were calculated. A time-to-event analysis using Cox proportional hazards models was performed to obtain hazard ratios (HR) with 95% CI, censoring patients at loss to follow-up, withdrawal of informed consent, or end of study period. The proportionality assumption was checked by visual inspection of the log-minus-log plots and assessment of Schoenfeld residuals. Missing data were not imputed and only observed data were analysed. Baseline data that were missing but were collected on follow-up visits were used to complete the baseline table. For baseline variables such as weight, the available weight closest to the randomisation date was used. For primary and secondary outcomes, data from the visits following the missed visit were used.

All analyses were conducted using R, version 4.0.3 (R Project for Statistical Computing, Vienna, Austria), particularly using the package 'survival' (version 3.2-7) and 'epitools' (version 0.5-10.1).

Role of the funding source

The Highlow study was partially supported by various grants; the French Ministry of Health (2014, PHRC national, number 1408211), the Health Research Board Ireland (Definitive Interventions and Feasibility Awards (DIFA) 2017, number DIFA-2017-040), GSK (2012), which was taken over by Aspen (2016), and Pfizer. None of the funders had a role in the design, data collection, data analysis, data interpretation or writing of the report.

Results

Between April 24, 2013 and October 31, 2020, 1,110 women were enrolled and randomised (**Figure 1**). The number of included women per country were as follows: The Netherlands (n=516), France (n=388), Ireland (n=99), Belgium (n=42), Norway (n=28), Denmark (n=15), Canada (n=12), United States (n=7), and Russia (n=3). Baseline characteristics are shown in **Table 1**. The mean age was 32·0 years (standard deviation [SD], 4·8), median BMI 25·0 kg/m^2 (interquartile range [IQR], 22·0 to 30·0), and 903 women (81·4%) had a history of venous thromboembolism related to hormone use, pregnancy, or postpartum period. Women were randomised at a median gestational age of 9 weeks and 3 days (IQR, 7+2 to 11+6). Median follow-up duration was 247 days (IQR, 228 to 266) during which 1,018 women (91·7%) had a live birth at a median gestational age of 38 weeks and 5 days (IQR, 37+2 to 39+5).

The primary efficacy outcome of symptomatic venous thromboembolism during pregnancy or up to 6 weeks postpartum occurred in 11 of 555 women (2·0%) in the weight-adjusted intermediate-dose low-molecular-weight heparin group and in 16 of 555 (2·9%) in the fixed low-dose low-molecular-weight heparin group (RR, 0·69; 95% CI, 0·32 to 1·47; P=0·33). The time to occurrence of the primary efficacy outcome is

shown in Figure 2A. During pregnancy, five of 555 women (0·9%) had venous thromboembolism in each treatment group. Postpartum, six of 555 women (1·1%) in the intermediate-dose, and 11 of 555 women (2·0%) in the low-dose group had venous thromboembolism. Pulmonary embolism, a component of the primary efficacy outcome, occurred in one patient in the intermediate-dose group and in nine patients in the low-dose group (RR, 0·11; 95% CI, 0·01 to 0·87). None of the thrombotic events were fatal. The composite of venous thromboembolism or superficial thrombophlebitis occurred in 13 patients (2·3%) in the intermediate-dose group and in 29 (5·2%) in the low-dose group (RR, 0·45; 95% CI, 0·24 to 0·85). Findings were consistent in the secondary analyses up to 3 months postpartum (Table 2). Efficacy outcomes in the intention-to-treat population are shown in Table 2, for subgroups in Table S2, and for the sensitivity analyses in Table S3. As shown in Table S2, there were no specific subgroups of women who experienced venous thromboembolism.

In the on-treatment analysis of the per-protocol population, the primary efficacy outcome of symptomatic venous thromboembolism during pregnancy or up to 6 weeks postpartum occurred in five of 481 women (1·0%) in the intermediate-dose group and in 12 of 491 (2·4%) in the low-dose group (RR, 0·43; 95% CI, 0·15 to 1·20; Table S4 and Figure S1). Other secondary efficacy outcomes in the per-protocol population during the on-treatment period are shown in Table S4.

Major bleeding during pregnancy or up to 6 weeks postpartum occurred in 23 of 520 women (4·4%) receiving intermediate-dose low-molecular-weight heparin and in 20 of 525 (3·8%) receiving low-dose low-molecular-weight heparin (RR, 1·16; 95% CI, 0·65-2·09; P=0·63). Antepartum major bleeding occurred in two of 520 women (0·4%) in the intermediate-dose, and in two of 525 women (0·4%) in the low-dose group. Early postpartum major bleeding occurred in 19 of 520 women (3·7%) in the intermediate-dose, and in 18 of 525 women (3·4%) in the low-dose group. Late postpartum major bleeding occurred in two of 520 (0·4%) in the intermediate-dose group and in none of 525 women (0·0%) in the low-dose group. The time to occurrence of on-treatment major bleeding is shown in Figure 2B. There were no maternal deaths during

the study. All safety outcomes are shown in Table 3 and Figures S2 and S3. The primary safety outcome for subgroups is shown in Table S5 and for the sensitivity analyses in Table S3.

Discussion

The Highlow study, which involved 1,110 pregnant women with a history of venous thromboembolism, showed that antepartum and postpartum weight-adjusted intermediate-dose low-molecular-weight heparin did not reduce the risk of venous thromboembolism compared to fixed low-dose low-molecular-weight heparin. Despite thromboprophylaxis, in the intention-to-treat analysis including all randomised women (i.e. also those with protocol deviations), we observed an absolute risk of venous thromboembolism during pregnancy or up to 6 weeks postpartum of 2·0% in women receiving intermediate-dose low-molecular-weight heparin and 2·9% 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 statistically significant (1·0% versus 2·4%; RR, 0·43; 95%CI, 0·15 to 1·20). There was no difference in on-treatment major bleeding (4·4% versus 3·8%, RR 1·16, 95% CI 0·65 to 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 markedly 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 postpartum, a pre-specified secondary efficacy outcome, occurred in 2·3% in the intermediate-dose group and in 5·2% in the low-dose group (RR, 0·45; 95% CI, 0·24 to 0·85). This outcome is clinically relevant, as superficial thrombophlebitis occurring while using thromboprophylaxis often leads to increasing the dose of low-molecular-weight heparin.[24] Third, there appeared to be a differential effect of the interventions in the antepartum versus the postpartum period. Women who were allocated to receive intermediate-dose low-

molecular-weight heparin had a lower incidence of postpartum pulmonary embolism (1 versus 7) and superficial thrombophlebitis (0 versus 11) 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 VTE or based on body weight (Table S2). Although the absolute risk of venous thromboembolism may be higher in women with increased body weight or age, our study was not designed to draw conclusions about such differences between subgroups.

What are the implications of our findings? 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.[9-12] Higher doses of low-molecular-weight heparin complicate peripartum management due to 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 postpartum period is to be regarded as hypothesis generating and would ideally be confirmed in a future randomised, controlled trial. In addition, finding ways to increase adherence to LMWH use during pregnancy and postpartum and assessment of its effect on VTE risk would be extremely valuable.

To date, only two small randomised, controlled trials (N=16 and N=40) evaluated the efficacy of thromboprophylaxis in pregnant women with a history of venous thromboembolism.[14,15] This is likely the result of major funding, regulatory, ethical and structural barriers challenging the conduct of randomised trials in pregnancy. In the Highlow study, a large number of women was prospectively followed with careful documentation of outcomes and adverse events. Loss to follow-up was very low, as was the rate of withdrawal of consent. As the trial was conducted in nine countries with use of different types of low-molecular-weight heparin, its findings are generalisable.

Our study has limitations. The Highlow trial did not include a placebo arm, as the standard of care according to various guidelines is to provide pharmacologic thromboprophylaxis with LMWH to women with history

of VTE. For pragmatic reasons, we used an open-label design which may increase the risk of diagnostic suspicion bias. It was also judged unethical to have clinicians blinded to the assigned low-molecular-weight heparin dose 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 unaware of treatment allocation. For the intermediate-dose LMWH, we chose to increase the dose with increasing body weight. We did not increase the low-dose during the course of pregnancy as is suggested by the ACOG and may be rational based on pharmacokinetic studies.[10,16,17] There was a considerable number of protocol deviations (n=146), such as nonadherence to required weight adjustments in the intermediate-dose group, differences in peripartum low-molecular-weight heparin management due to concerns about postpartum bleeding or inaccessibility to neuraxial anaesthesia, and premature discontinuation of low-molecular-weight heparin during the postpartum period. The impact of these deviations may 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 may have been introduced by allowing use of low-molecular-weight heparin prior to 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 lower risk of recurrence. We allowed inclusion until 14 weeks of gestational age of women who had started thromboprophylaxis prior to inclusion in the study, since a history of VTE sometimes only becomes apparent at the first prenatal visit. In the subgroup analyses based on LMWH use prior to randomisation (Table S2) the relative effect of the interventions is similar between the groups, with absolute risks that vary between 1.5% (with prior LMWH use) and 2.6% (without prior LMWH use) in the intermediate-dose group, and 2.0 to 3.1% respectively in the low-dose group. Although this suggests risk modification by prior use of LMWH, our data do not allow to draw this conclusion firmly. Sensitivity analyses with exclusion of 67 women who participated more than once did not materially alter the results. In absence of 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 "breakthrough recurrences" on low-dose LMWH, we hypothesized 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 as well as the relative risk reduction was smaller. Finally, we did not meet the targeted number of centrally adjudicated and confirmed venous thromboembolism.

The knowledge gap about optimal low-molecular-weight heparin dosing in pregnant and postpartum women has been explicitly identified by major guidelines. [2,11] Hence, we are confident that the results of our study will impact international and national guidelines and that recommendations will be rapidly taken up by clinicians, knowledge users and policymakers throughout the world. For individual clinicians, counselling of women facing a pregnancy challenged by a history of venous thromboembolism will, for the first time, be supported by high-quality data.

In conclusion, among women with a history of venous thromboembolism, weight-adjusted intermediate-dose low-molecular-weight heparin during the combined antepartum and postpartum periods was not associated with a lower risk of recurrence than fixed low-dose low-molecular-weight heparin. Secondary data analysis suggests intermediate dose low-molecular-weight heparin may be more effective than low dose low-molecular-weight heparin in the postpartum period.

Authorship Contributions

SM designed the trial. SM, AB, FNA, PV, AFJ, ATH, MAR, MTdS, and RGS were national coordinators. SMB, IMB and HMGW were international coordinators. IMB, AB, HMGW, FNA, JD, PV, AFJ, ATH, MAR, MTdS, RGS, CC, and all investigators listed in the supplementary appendix recruited patients. SM, IMB, HMGW, NvE and MHP designed the statistical analysis plan, HMGW and NvE performed the analyses and data were interpreted by all authors. All authors had full access to the 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, FNA, BT, JD, PV, AFJ, ATH, MAR, MTdS, RGS, NvE, MHP, CC, SM) was responsible for the decision to submit the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

Executive writing committee; the authors report the following unrelated support: FNA reports grants as principal investigator from the Irish Health Research Board during the conduct of the study, and grants as PI from Daiichi-Sankyo, Bayer and Sanofi (IIS paid to university) outside the submitted work; AB reports grants from 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 other fees from Bristol-Meyers Squibb, LEO Pharma, and Bayer, outside the submitted work; AFJ reports personal fees from Sanofi-Aventis, outside 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, personal fees from Portola/Alexion, Abbvie, Pfizer/ Bristol-Meyers Squibb, Norgine, Viatris, and Sanofi, outside the submitted work; MTdS reports personal fees from Sanofi Genzyme and Bioproducts Laboratory, outside the submitted work; PV reports grants and personal fees from LEO Pharma, Boehringer-

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Other authors declare no competing financial interests.

Data sharing

Requests for data sharing can be sent to saskia.middeldorp@radboudumc.nl. Only deindentified 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 prior to data sharing. The study protocol, statistical analysis plan, Central Adjudication Committee Charter, and informed consent form have been available without restrictions to others from the start of the study on.

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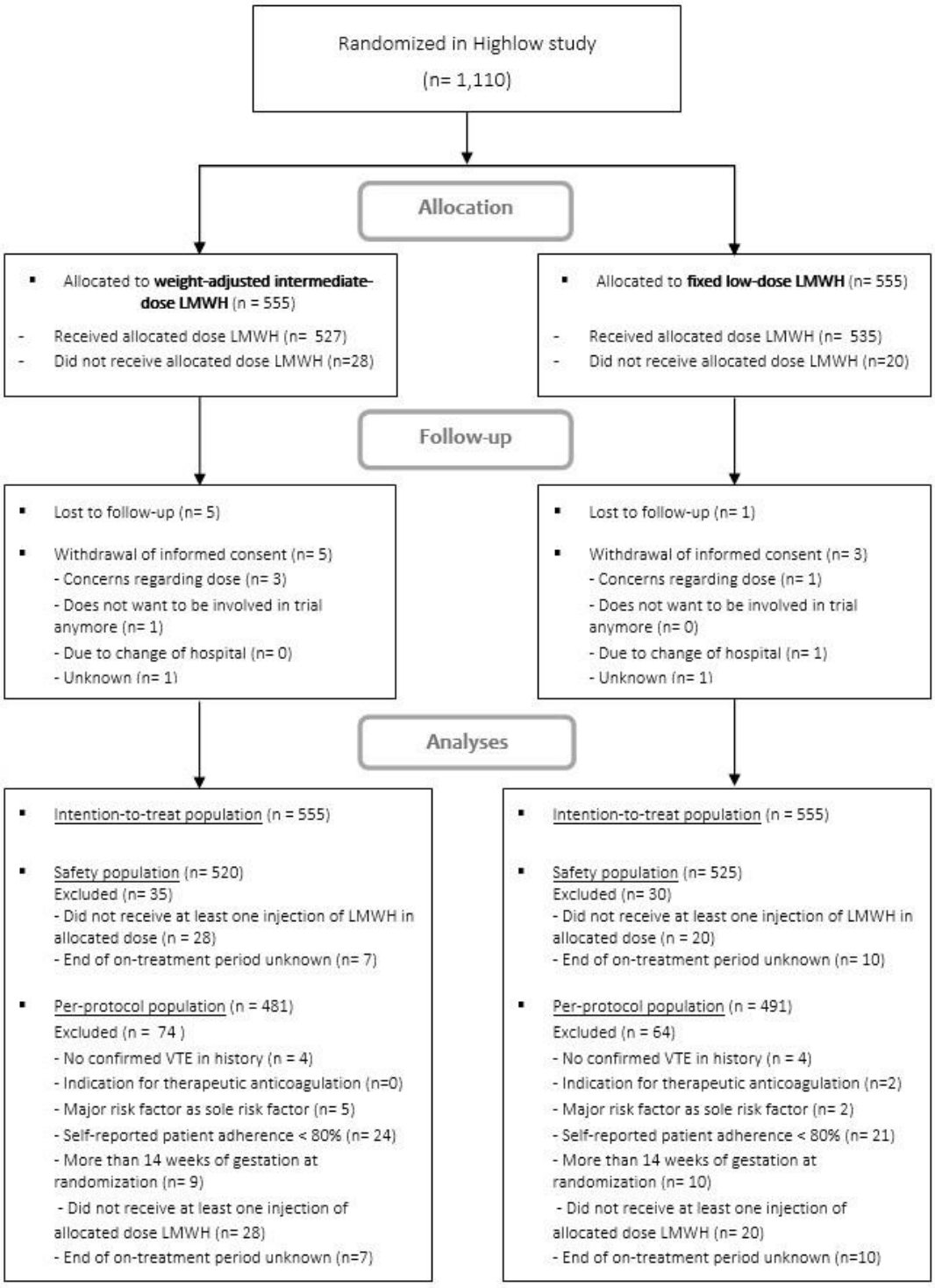
Figure 1. CONSORT Flow Diagram

Abbreviations: LMWH, low-molecular-weight heparin; VTE, venous thromboembolism
The number of women excluded from the per protocol population is less than the sum of the reasons, since some patients met more than one major protocol deviation.



Panel: Dosing schemes for all low-molecular-weight heparin types in the Highlow study

Weight-adjusted intermediate-dose						Fixed low-dose					
Weight		nadroparin	enoxaparin	dalteparin	tinzaparin	Weight		nadroparin	enoxaparin	dalteparin	tinzaparin
In kg	In lbs					In kg	In lbs				
< 50	< 110	3,800 IU	6,000 IU	7,500 IU	4,500 IU	< 100	< 220	2,850 IU	4,000 IU	5,000 IU	3,500 IU
50 to < 70	110 to < 154	5,700 IU	8,000 IU	10,000 IU	7,000 IU						
70 to < 100	154 to < 220	7,600 IU	10,000 IU	12,500 IU	10,000 IU	≥100	≥ 220	3,800 IU	6,000 IU	7,500 IU	4,500 IU
≥100	≥ 220	9,500 IU	12,000 IU	15,000 IU	12,000 IU						

All doses are administered once daily

Abbreviations: kg, kilograms; lbs, pounds; IU, International Units; mg, milligram

Table 1. Patient characteristics of the intention-to-treat population

	Intermediate-dose low-molecular-weight heparin (N=555)	Low-dose low-molecular-weight heparin (N=555)
Mean age - years (SD)	32·0 (4·8)	32·0 (4·8)
Median body mass index - kg/m2 (IQR)	25·0 (22·0-30·0)	25·0 (22·0-29·0)
Weight at randomisation - no. (%)		
<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 - no. (%)	141 (25·4)	153 (27·6)
Nulliparity - no. (%)	203 (36·6)	214 (38·6)
Median gestational age at randomisation –weeks and days (IQR)	9 and 4 (7 and 3 to 11 and 6)	9 and 3 (7 and 1 to 12 and 0)
Use of low-molecular-weight heparin prior to randomisation - no. (%)	267 (48·1)	248 (44·7)
Median time since previous venous thromboembolism † - years (IQR)	5·5 (2·6-8·9)	5·1 (2·2-9·0)
History of ≥2 episodes of venous thromboembolism - no. (%)	41 (7·4)	46 (8·3)
Location of previous venous thromboembolism ‡ - no. (%)		
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 **- no. (%)		

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)
Postpartum 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)
Known thrombophilia - no./no. previously tested. (%)	142/310 (25·6)	149/315 (26·8)
History of caesarean section - no. (%)	100 (18·0)	85 (15·3)
History of postpartum haemorrhage ¥ - no. (%)	33 (5·9)	30 (5·4)
Known allergic skin reactions to low-molecular-weight heparin - no. (%)	37 (6·7)	44 (7·9)
Type of low-molecular-weight heparin after randomisation - no. (%)		
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)
Acetylsalicylic acid use during pregnancy - no. (%)	38 (6·8)	33 (5·9)
Country of inclusion - no. (%)		
The 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)
United States of America	3 (0·5)	4 (0·7)
Russia	1 (0·2)	2 (0·4)

Abbreviations: DVT, deep-vein thrombosis; IQR, interquartile range; SD, standard deviation; kg/m^2, kilograms per square meter

¥ Defined as ≥ 500mL according to the criteria of the World Health Organization
† In case of multiple episodes of venous thromboembolism: the most recent event
‡ Some patients had venous thromboembolism at multiple sites at the same time
¶ Including: extensive thrombophlebitis that was treated as deep-vein thrombosis, muscle vein thrombosis close to popliteal vein treated as deep-vein thrombosis, isolated calf vein thrombosis, isolated pelvic vein thrombosis,
§ Including cerebral thrombosis, jugular vein thrombosis, abdominal vein thrombosis, and ovarian vein thrombosis.
*** Some patients had more than one risk factor*
¥¥ Includes patients without previous venous thromboembolism (one in intermediate-dose group and one in low-dose group), patient with arterial thrombosis (one in low-dose group), superficial thrombophlebitis not treated as deep-vein thrombosis (one in intermediate-dose group and one in low-dose group), and patients with retinal vein thrombosis (two in intermediate-dose group and one in low-dose group)

*Missing for '*Use of low-molecular-weight heparin prior to randomisation'*: 16 in intermediate-dose group and 19 in low-dose group.*

1 Table 2. Efficacy outcomes

	Intermediate-dose low-molecular-weight heparin	Low-dose low-molecular-weight heparin	Relative risk (95% CI)	Hazard ratio (95% CI)
Efficacy outcomes during pregnancy or until 6 weeks postpartum	no. of patients/total no. (%)			
Intention-to-treat population	*555*	*555*		
Primary efficacy outcome: venous thromboembolism	11 (2·0)	16 (2·9)	0·69 (0·32-1·47)	0·68 (0·32-1·47)
Antepartum	5 (0·9)	5 (0·9)		
Postpartum	6 (1·1)	11 (2·0)		
Pulmonary embolism	1(0·2)	9 (1·6)	0·11 (0·01-0·87)	**
Antepartum	0 (0·0)	2 (0·4)		
Postpartum	1 (0·2)	7 (1·3)		
Deep-vein thrombosis	8 (1·4)	6 (1·1)	1·33 (0·47-3·82)	1·32 (0·46-3·81)
Antepartum	4 (0·7)	3 (0·5)		
Postpartum	4 (0·7)	3 (0·5)		
Unusual site venous thrombosis*	2 (0·4)	1 (0·2)	2·00 (0·18-22·00)	1·99 (0·18-21·96)
Antepartum	1 (0·2)	0 (0·0)		
Postpartum	1 (0·2)	1 (0·2)		
Superficial thrombophlebitis ¥	3 (0·5)	13 (2·3)	0·23 (0·07-0·81)	0·22 (0·06-0·79)
Antepartum	3 (0·5)	2 (0·4)		
Postpartum	0 (0·0)	11 (2·0)		
Venous thromboembolism or superficial thrombophlebitis	13 (2·3)	29 (5·2)	0·45 (0·24-0·85)	0·44 (0·23-0·85)

Antepartum	8 (1·4)	7 (1·3)		
Postpartum	5 (0·9)	22 (4·0)		
Efficacy outcomes during pregnancy or until 3 months postpartum	no. of patients/total no. (%)			
Intention-to-treat population	*555*	*555*		
Venous thromboembolism	13 (2·3)	18 (3·2)	0·72 (0·36-1·46)	0·71 (0·35-1·45)
Pulmonary embolism	3 (0·5)	9 (1·6)	0·33 (0·09-1·22)	**
Deep-vein thrombosis	8 (1·4)	7 (1·3)	1·14 (0·42-3·13)	1·14 (0·41-3·13)
Unusual site venous thrombosis*	2 (0·4)	2 (0·4)	1·00 (0·14 -7·07)	0·99 (0·14 -7·05)
Superficial thrombophlebitis	4 (0·7)	13 (2·3)	0·31 (0·10-0·94)	0·30 (0·10-0·93)
Venous thromboembolism or superficial thrombophlebitis	16 (2·9)	31 (5·6)	0·52 (0·29-0·93)	0·51 (0·28-0·92)

Abbreviations: 95% CI, 95% confidence interval.

** Including: up to 6 weeks: one cerebral venous thrombosis antepartum and one cerebral venous thrombosis postpartum in the intermediate-dose group; one abdominal venous thrombosis in the low-dose group; up to 3 months: one additional cerebral venous thrombosis postpartum in the low-dose group.*

*** Hazard ratio was not estimated due to violation of the proportionality assumption.*

¥ Superficial thrombophlebitis was centrally adjudicated. After diagnosis, two patients in the intermediate-dose group and seven in the low-dose group were treated with therapeutic anticoagulant therapy; one patient in the intermediate-dose group continued with intermediate dose low-molecular-weight heparin, three patients in the low-dose group were treated with intermediate-dose low-molecular-weight heparin; three patients in the low-dose group continued with low-dose low-molecular-weight heparin.

1 Table 3. Safety outcomes

	Intermediate-dose low-molecular-weight heparin	Low-dose low-molecular-weight heparin	Relative risk (95% CI)	Hazard ratio (95% CI)
Safety outcomes during pregnancy or until 6 weeks postpartum	no. of patients/total no. (%)			
Safety population	*520*	*525*		
Primary safety outcome: major bleeding	23 (4·4)	20 (3·8)	1·16 (0·65-2·09)	1·25 (0·69-2·28)
Antepartum	2 (0·4)	2 (0·4)		
Early postpartum	19 (3·7)	18 (3·4)		
Late postpartum	2 (0·4)	0 (0·0)		
Secondary safety outcomes				
Major or clinically relevant non-major bleeding	50 (9·6)	45 (8·6)	1·12 (0·76-1·65)	1·21 (0·81-1·81)
Antepartum	23 (4·4)	10 (1·9)		
Early postpartum	25 (4·8)	35 (7·4)		
Late postpartum	2 (0·4)	0 (0·0)		
Clinically relevant non-major bleeding	27 (5·2)	25 (4·8)	1·09 (0·64-1·85)	**
Antepartum	21 (4·0)	8 (1·5)		
Early postpartum	6 (1·2)	17 (3·2)		
Late postpartum	0 (0·0)	0 (0·0)		
Minor bleeding	76 (14·6)	66 (12·6)	1·16 (0·86-1·58)	1·27 (0·91-1·77)
Antepartum	17 (3·3)	18 (3·4)		
Early postpartum	55 (10·6)	46 (8·7)		

Late postpartum	4 (0·8)	2 (0·4)		
Any bleeding	123 (23·7)	110 (21·0)	1·13 (0·90-1·42)	1·23 (0·95-1·59)
Antepartum	39 (7·5)	28 (5·3)		
Early postpartum	78 (15·0)	80 (15·2)		
Late postpartum	6 (1·2)	2 (0·04)		
Other AE				
Heparin-induced thrombocytopenia	0 (0·0)	0 (0·0)		
Type 1 allergy	8 (1·5)	2 (0·4)		
Congenital abnormality or birth defect	9 (1·7)	5 (1·0)		
Bruising	248 (47·7)	184 (35·0)		
Type IV allergic skin reaction	180 (34·6)	115 (21·9)		

Abbreviations: 95% CI, 95% confidence interval.

*** Hazard ratio was not estimated due to violation of the proportionality assumption.*

Figure 2A. Kaplan-Meier cumulative event rates for venous thromboembolism during pregnancy or up to 6 weeks postpartum in the intention-to-treat population

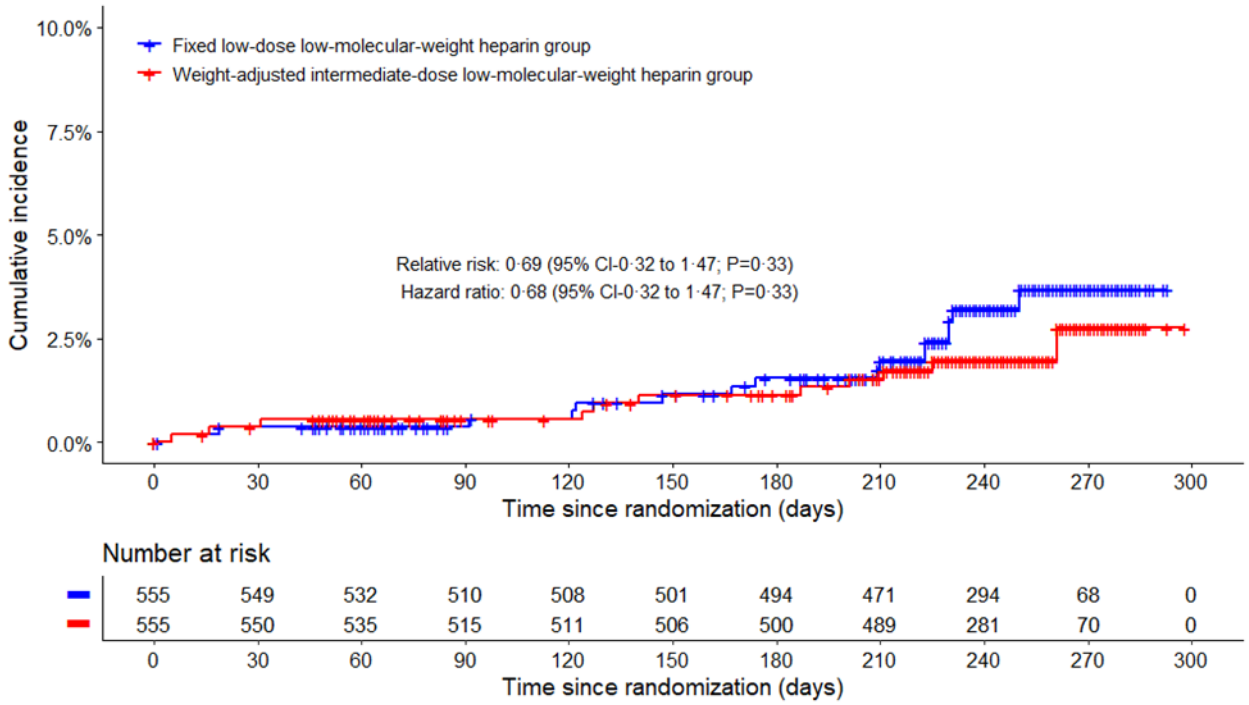
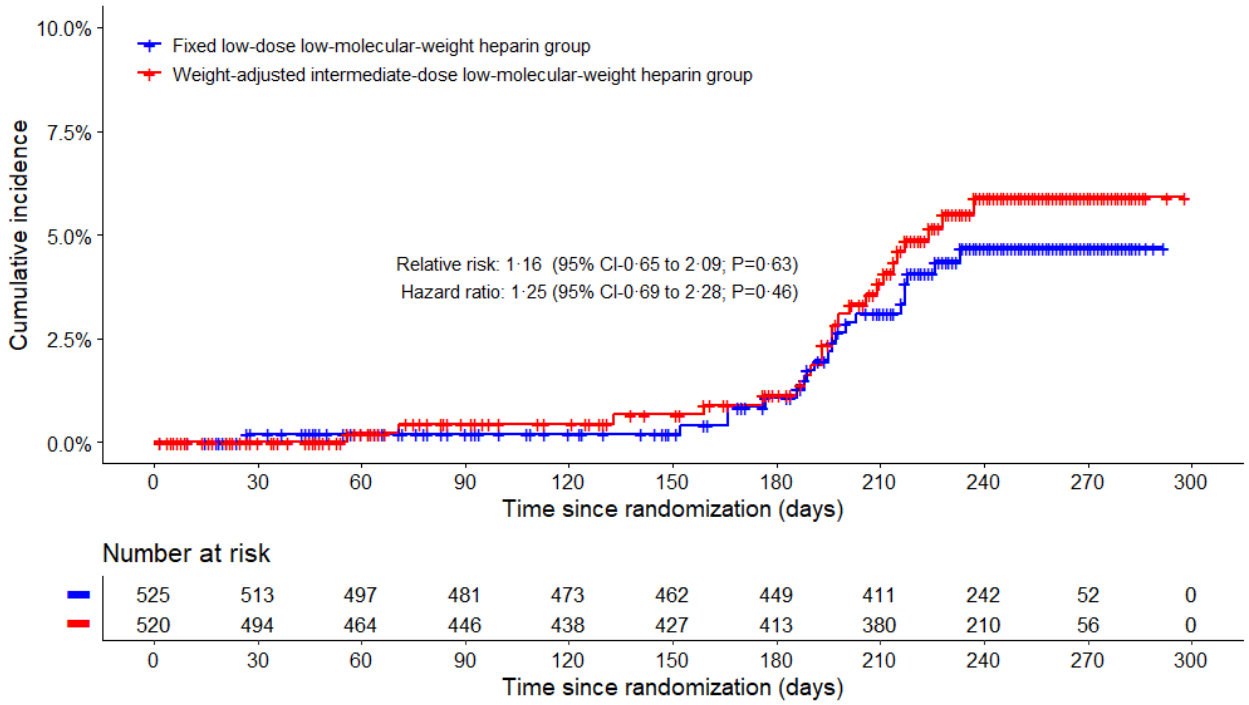


Figure 2B. Kaplan-Meier cumulative event rates for major bleeding during the on-treatment period in the safety population



Appendix (main manuscript)

The members of the executive writing committee are as follows:

Ingrid M. Bistervels, M.D., Andrea Buchmüller, M.D., Hanke M.G. Wiegers, M.D., Prof Fionnuala Ní Áinle, M.D., Prof Bernard Tardy, M.D., Jennifer Donnelly, M.D., Peter Verhamme, M.D., Prof Anne F. Jacobsen, M.D., Anette T. Hansen, M.D., Prof Marc A. Rodger, M.D., Prof Maria T. DeSancho, M.D., Prof Roman G. Shmakov, M.D., Nick van Es, M.D., Prof Martin H. Prins, M.D., Prof Céline Chauleur, M.D., Prof Saskia Middeldorp, M.D.

The members of the block writing committee are as follows:

Eline S. van den Akker, M.D., Prof Mireille N. Bekker, M.D., Thomas van Bemmel, M.D., Prof Laurent Bertoletti, M.D., Julie Blanc, M.D., Suzanne M. Bleker, M.D., Aude Bourtembourg-Matras, M.D., Prof Florence Bretelle, M.D., Bridgette Byrne, M.D., Prof Francis Couturaud, M.D., Pierre Delorme, M.D., Elise S. Eerenberg, M.D., Maureen T.M. Franssen, M.D., Jens Fuglsang, M.D., Wessel Ganzevoort, M.D., Prof François Goffinet, M.D., Jiska M. de Haan-Jebbink, M.D., Wieteke Heidema, M.D., Monique A. Hertzberg, MSc., Marcel M.C. Hovens, M.D., Prof Menno V. Huisman, M.D., Leonie de Jong-Speksnijder, M.D., Prof Pieter-Willem Kamphuisen, M.D., Denis J. O'Keeffe, M.D., Karine Lacut (*deceased)*, M.D., Josje Langenveld, M.D., M. Simone Lunshof, M.D., Caroline P. Martens, M.D., Adel Merah, M.D., Emmanuelle Le Moigne, M.D., Dimitri N.M. Papatsonis, M.D., Prof Gilles Pernod, M.D., Prof Franck Perrotin, M.D., Edith Peynaud-Debayle, M.D., Prof Fabrice Pierre, M.D., Prof Geneviève Plu Bureau, M.D., Tiphaine Raia-Barjat, M.D., Robbert J.P. Rijnders, M.D., Roger Rosario, M.D., Marc Ruivard, M.D., Prof Jeannot Schmidt, M.D., Marieke Sueters, M.D., Thomas Vanassche, M.D., Marie-Noëlle Varlet, M.D., Alexandre J. Vivanti, M.D., Matthieu Y. van der Vlist, M.D., Lucet F. van der Voet, M.D., Karlijn C. Vollebregt, M.D., Prof Johanna I.P. de Vries, M.D., Sabina de

Weerd, M.D., Peter E. Westerweel, M.D., Lia D.E. Wijnberger, M.D., Marije ten Wolde, M.D., Paula F. Ypma, M.D., Catherine Zuily-Lamy, M.D., Joost J. Zwart, M.D.

The authors' affiliations are as follows:

Amsterdam University Medical Center, University of Amsterdam, Amsterdam (I.M.B., H.M.G.W., S.M.B., N.v.E., W.G., S.M.), Albert Schweitzer Hospital, Dordrecht (P.E.W., S.d.W., M.Y.v.d.V.), Amphia Hospital, Breda (D.P., L.d.J.-S., M.S.L.), Deventer Hospital, Deventer (J.J.Z., L.F.v.d.V.), Leiden University Medical Center, Leiden (M.S., M.V.H.), Rijnstate Hospital, Arnhem (M.M.C.H., L.W.), OLVG Hospital, Amsterdam (E.S.v.d.A., J.M.d.H.-J.), Gelre Ziekenhuizen, Apeldoorn (T.v.B., E.S.E.), Jeroen Bosch Hospital, 's Hertogenbosch (R.J.P.R.), Haga Hospital, The Hagues (P.F.Y.), University Medical Center Utrecht, Utrecht (M.N.B.), Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam (J.I.P.d.V.), Spaarne Gasthuis, Haarlem (K.C.V.), Radboud university medical center, Nijmegen (W.H., S.M.), Flevoziekenhuis, Almere (M.t.W.), Zuyderland Medical Center, Heerlen (J.L.), and University Medical Center Groningen, Groningen (M.T.M.F.) — all in the Netherlands;

CIC 1408 Centre Hospitalier Universitaire de Saint-Etienne, Saint-Etienne (A.B., C.C., T.R.-B.), Centre Hospitalier Universitaire de Brest, Brest (E.L.M., F.C., K.L.), Assistance Publique Hôpitaux de Paris Port Royal, Paris Cité (P.D., F.G., G.P.B.), Hôpital Nord, Marseille (F.B., J.B.), Hôpital Saint Joseph, Marseille (R.R.), Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand (J.S., M.R.), Assistance Publique Hôpitaux de Paris Antoine Béclere, Clamart (A.J.V.), Assistance Publique Hôpitaux de Paris Louis-Mourier, Colombes (E.P.-D.), Centre Hospitalier Universitaire de Grenoble, La Tronche (G.P.), Centre Hospitalier Universitaire de Besançon, Besançon (A.B.M.), Centre Hospitalier Universitaire de Nancy, Nancy (C.Z.-L.), Centre

Hospitalier Universitaire de Poitiers, Poitiers (F. Pierre), Centre Hospitalier Universitaire de Tours, Tours (F. Perrotin), — all in France;

Rotunda Hospital, Dublin (F.N.A., J.D.), School of Medicine, University College Dublin, Dublin (F.N.A.) The Coombe Women & Infants University Hospital, Dublin (B.B.), University Hospital Limerick, Limerick (D.J.O'K.) – all in Ireland; University of Leuven, Leuven, Belgium (P.V., T.V., C.P.M.); Oslo University Hospital, Oslo (A.F.J., M.A.H.), and Faculty of Medicine, University of Oslo, Oslo, - both in Norway; Aalborg University Hospital, Aalborg (A.T.H.), and Aarhus University Hospital, Aarhus, (A.T.H. and J.F.) — both in Denmark; The Ottawa Hospital, Ottawa, Canada (M.A.R.); New York Presbyterian Hospital, Weill Cornell Medicine, New York, United States of America (M.T.d.S.); and Institute of Obstetrics, National Medical Research Center for Obstetrics, Gynecology and Perinatology, Ministry of Healthcare of the Russian Federation, Moscow, Russia (R.G.S.).

P.W.K., L.B., B.T., M.-N.V., and A.M. were members of the Independent Central Adjudication Committee. M.H.P. was the study statistician.

A complete list of the Highlow Investigators is provided in the Supplementary Appendix.