Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials

*Marc A Rodger, Jean-Christophe Gris, Johanna I P de Vries, Ida Martinelli, Évelyne Rey, Ekkehard Schleussner, Saskia Middeldorp, Risto Kaaja, Nicole J Langlois, Timothy Ramsay, Ranjeeta Mallick, Shannon M Bates, Carolien N H Abheiden, Annalisa Perna, David Petroff, Paulien de Jong, Marion E van Hoorn, P Dick Bezemer, Alain D Mayhew, for the Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study Group**

Summary

Background **Placenta-mediated pregnancy complications include pre-eclampsia, late pregnancy loss, placental abruption, and birth of a small-for-gestational-age (SGA) neonate. These complications are leading causes of maternal, fetal, and neonatal morbidity and mortality in high-income countries. Affected women are at high risk of recurrence in subsequent pregnancies; however, effective strategies to prevent recurrence are absent. Findings from our previous study-level meta-analysis suggested that low-molecular-weight heparin reduced the risk of recurrent placenta-mediated pregnancy complications. However, we identified significant heterogeneity in the results, possibly due to trial design or inclusion criteria. To identify which patients benefit from, and which outcomes are prevented by, low-molecular-weight heparin, we did an individual patient data meta-analysis.**

Methods **We did a systematic review in May, 2013, which identified eight eligible randomised trials done between 2000 and 2013 of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. We excluded studies on the basis of the wrong population, the study being ongoing, inability to confirm eligibility of participants, intervention stopped too early, and no response from the principal investigator. We requested individual patient data from the study authors for eligible women (women pregnant at the time of the study with a history of previous pregnancy that had been complicated by one or more of the following: pre-eclampsia, placental abruption, birth of an SGA neonate [<10th percentile], pregnancy loss after 16 weeks' gestation, or two losses after 12 weeks' gestation) and recoded, combined, and analysed the data for our meta-analysis. The primary outcome was a composite of early-onset (<34 weeks) or severe pre-eclampsia, birth of an SGA neonate (<5th percentile), late pregnancy loss (≥20 weeks' gestation), or placental abruption leading to delivery, assessed on an intention-to-treat basis. We assessed risk of bias with the Cochrane Risk of Bias tool. This study is registered with PROSPERO, number CRD42013006249.**

Findings **We analysed data from 963 eligible women in eight trials: 480 randomly assigned to low-molecular-weight heparin and 483 randomly assigned to no low-molecular-weight heparin. Overall, the risk of bias was not substantial enough to affect decisions regarding trial inclusion. Participants were mostly white (795/905; 88%) with a mean age of 30·9 years (SD 5·0) and 403/963 (42%) had thrombophilia. In the primary analysis, low-molecular-weight heparin did not significantly reduce the risk of recurrent placenta-mediated pregnancy complications (low-molecular-weight heparin 62/444 [14%] versus no low-molecular-weight heparin 95/443 (22%) absolute difference –8%, 95% CI –17·3 to 1·4, p=0·09; relative risk 0·64, 95% CI 0·36–1·11, p=0·11). We noted significant heterogeneity between single-centre and multicentre trials. In subgroup analyses, low-molecular-weight heparin in multicentre trials reduced the primary outcome in women with previous abruption (p=0·006) but not in any of the other subgroups of previous complications.**

Interpretation **Low-molecular-weight heparin does not seem to reduce the risk of recurrent placenta-mediated pregnancy complications in at-risk women. However, some decreases in event rates might have been too small for the power of our study to explore.**

Funding **Canadian Institutes of Health Research.**

Lancet 2016; 388: 2629–41

Published Online October 6, 2016 http://dx.doi.org/10.1016/S0140-6736(16)31139-4

See Comment page 2570

*Members listed at end of the report

Ottawa Blood Disease Center, (Prof M A Rodger MD) **and Centre for Practice-Changing Research** (N J Langlois MSc, T Ramsay PhD, R Mallick PhD, A D Mayhew MSc)**, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada; Consultations et Laboratoire d'Hématologie et Délégation à la Recherche Clinique et à l'Innovation, Nîmes cédex 09, France** (Prof J-C Gris MD)**; Department of Obstetrics and Gynaecology** (Prof J I P de Vries MD, M E van Hoorn MD, C N H Abheiden MD) **and Department of Epidemiology and Biostatistics** (P D Bezemer PhD)**, VU University Medical Center, Amsterdam, Netherlands; A. Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy** (I Martinelli MD)**; CHU Ste-Justine, Montreal, QC, Canada** (É Rey MD)**; Jena University Hospital, Department of Obstetrics and Gynaecology, Jena, Germany** (Prof E Schleussner MD)**; Academic Medical Center, Department of Vascular Medicine, Meibergdreef 9, Amsterdam, the Netherlands** (Prof S Middeldorp MD)**; Turku University, Turku University Hospital, Åbo, Finland** (Prof R Kaaja MD)**; Department of Medicine, McMaster University, Hamilton, ON, Canada** (Prof S M Bates MD)**; Laboratorio di Biostatistica,**

Introduction

Placenta-mediated pregnancy complications, including pre-eclampsia, birth of a small-for-gestational-age (SGA) neonate, placental abruption, or late pregnancy loss are common and lead to substantial maternal and fetal or neonatal morbidity and mortality.[1–3] The risk of recurrent placenta-mediated pregnancy complications in subsequent pregnancies is important,[4–6] and these complications might be multiple (for example, both pre-eclampsia and SGA), and not solely a repeat of the placenta-mediated complication in a previous pregnancy.[4–6]

No highly effective preventive strategies for use in subsequent pregnancies exist. Aspirin offers small risk reductions in patients with previous pre-eclampsia and SGA; however, it might be more effective at reducing risk

Centro di Ricerche Cliniche per le Malattie Rare Aldo e Cele Daccò, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Ranica, Italy (A Perna MSc)**; University of Leipzig, Clinical Trial Centre, Germany** (D Petroff PhD)**; and Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands** (P de Jong MD)

Correspondence to: Prof Marc Rodger, Ottawa Blood Disease Center, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON K1H 8 L6, Canada
mrodger@ohri.ca

Research in context

Evidence before this study

We previously published a systematic review and pooled summary-based study-level meta-analysis, the findings from which suggested that low-molecular-weight heparin might be a promising therapy for recurrent—especially severe—placenta-mediated pregnancy complications, but also suggested that further research was needed because significant heterogeneity limited the interpretation. For this study, in May, 2013, using the OVID platform, we searched OVID MEDLINE, OVID MEDLINE in-process and other non-indexed citations, and Embase classic (appendix), and also searched the Cochrane Library and ClinicalTrials.gov to identify relevant ongoing and completed trials. We used search terms such as "hypertension", "pregnancy-induced", "placental insufficiency", "heparin", and "low-molecular-weight" and keywords such as "pre-eclampsia", "abruption", and "LMWH". Vocabulary and syntax were adjusted across databases. Animal studies were excluded but there were no language or date restrictions for any of the searches. We extracted individual patient data from these studies to select women who met specific eligibility criteria. This individual patient data meta-analysis included women from three trials that were not included in the previous publication. We combined data from eight trials to do subgroup analyses that considered study design, patient characteristics, treatment differences, and specific outcomes.

Added value of this study

The results of our individual patient data meta-analysis showed that only women with previous placental abruption might benefit from antepartum low-molecular-weight heparin, and suggest strongly that antepartum low-molecular-weight heparin is of no benefit in women with previous pre-eclampsia, previous birth of a small-for-gestational-age neonate, or previous late pregnancy loss.

Implications of all the available evidence

Daily antepartum low-molecular-weight heparin injections do not seem to reduce the risk of recurrent placenta-mediated pregnancy complications in high-risk patients except in a small subgroup of women with previous abruption. The latter finding should be replicated in future multicentre trials.

(providing around 40% relative risk reduction) if started before 16 weeks' gestation.[7,8] There are no proven preventive strategies for the other complications. The cause(s) of placenta-mediated pregnancy complications remain controversial and are likely to be multifactorial. However, placental microvascular and macrovascular thrombosis is a frequent, overlapping, pathophysiological link in many pregnancies affected by placenta-mediated complications,[3] and anticoagulants could prevent recurrence of these complications.

Low-molecular-weight heparin is the anticoagulant of choice in pregnancy because it does not cross the placenta and has a favourable maternal safety profile with low risk of major bleeding, heparin-induced thrombocytopenia, or heparin-induced osteoporosis.[9] Nonetheless, low-molecular-weight heparin must be administered by burdensome daily or twice-daily subcutaneous injections, is costly, and might complicate regional anaesthetic options if not discontinued within 12–24 h of labour onset. Low-molecular-weight heparin might also play other roles, including promotion of placental angiogenesis during the first and second trimesters of pregnancy and promotion of soluble vascular endothelial growth factor receptor-1 expression during the first trimester,[10,11] that could also contribute to a reduced risk of placenta-mediated pregnancy complications.

Findings from some randomised controlled trials of whether low-molecular-weight heparin can prevent recurrent placenta-mediated pregnancy complications suggest an important treatment effect[12–16] but these findings have not been universal.[17–22] We previously published a pooled summary-based, study-level meta-analysis,[23] the findings from which strongly suggested that low-molecular-weight heparin reduces the risk of placenta-mediated complications in subsequent pregnancies (relative risk reduction 0·52, 95% CI 0·32–0·86). However, this meta-analysis, with aggregate data, was limited by substantial statistical (I^2 69%) and clinical heterogeneity. Results from single-centre trials, and trials that recruited women with severe previous placenta-mediated complications, showed a beneficial effect of low-molecular-weight heparin, raising the possibility that either single-centre bias was driving the summary effects, or that low-molecular-weight heparin was not effective in women with previous non-severe placenta-mediated pregnancy complications.[23] Additionally, many of the component studies recruited women with heterogeneous previous placenta-mediated pregnancy complications, and explored effects of low-molecular-weight heparin on composite outcomes that included a mix of these complications. These uncertainties lead to the questions of whether low-molecular-weight heparin is effective at all, whether it is only beneficial in subgroups of women with previous severe placenta-mediated pregnancy complications, and whether low-molecular-weight heparin prevents all or only some of these complications.

The trials of low-molecular-weight heparin to prevent placenta-mediated pregnancy complications were all academically sponsored and took many years to complete. To await results from future individual trials to address these questions would leave many patients without clear guidance in the interim. Therefore we did an individual patient data meta-analysis to account for study-centre effects, and to explore the effect of low-molecular-weight heparin in subgroups of women with previous placenta-mediated complications and on individual outcomes.

Methods

Search strategy and selection criteria

We did a systematic review to identify potentially eligible trials for meta-analysis. Detailed review methods, including the search strategy, search results in a PRISMA flow diagram, and a description of the trials identified are described in the published protocol.[24] Randomised controlled trials that used a low-molecular-weight heparin intervention for the prevention of recurrent placenta-mediated pregnancy complications were eligible. We developed electronic search strategies and tested them through an iterative process by an experienced medical information specialist in consultation with the review team. In May, 2013, using the OVID platform, we searched OVID MEDLINE, OVID MEDLINE in-process and other non-indexed citations, and Embase classic (appendix). We also searched the Cochrane Library and ClinicalTrials.gov to identify relevant ongoing and completed trials. We used search terms such as "hypertension", "pregnancy-induced", "placental insufficiency", "heparin", and "low-molecular-weight" and keywords such as "pre-eclampsia", "abruption", and "LMWH". Vocabulary and syntax were adjusted across databases. Animal studies were excluded but there were no language or date restrictions for any of the searches. We sought additional references through hand-searching the bibliographies of relevant items. The study population of interest included currently pregnant women who had previous pregnancies complicated by one or more of the following: pre-eclampsia, placental abruption, birth of an SGA neonate (less than the 10th percentile), pregnancy loss after 16 weeks' gestation, or two losses after 12 weeks' gestation.

Of the potentially eligible studies identified, we included eight trials in the primary and subgroup analyses, and excluded eight others for the following reasons: wrong population,[25,26] trial ongoing (EPPI, HEPEPE, HOPPE trials), inability to confirm eligibility of participants,[22] low-molecular-weight heparin intervention stopped too early in pregnancy,[21] and no response from the principal investigator.[27] Additional details about included and excluded studies are in the protocol.[24]

Data extraction

The lead investigators of eligible trials and statisticians who were familiar with the trial data met in person to reach consensus on the study outcomes and variables before data extraction. Detailed definitions and diagnostic criteria for all study outcomes are in the study protocol and we used a data dictionary that includes the definitions and coding for all individual patient data meta-analysis variables to enable standardisation across studies. We developed a Microsoft Excel 2010 template to ensure consistency of the anonymised and recoded individual patient data. Ethics approval was obtained for each included trial before data were recoded and combined for meta-analysis.

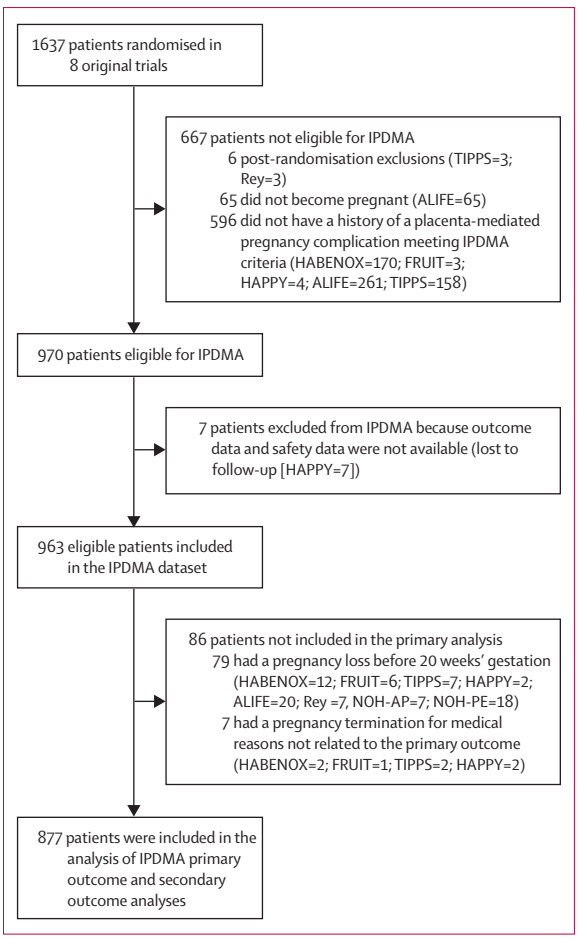

Figure: **Patient selection from the original studies**
IPDMA=individual patient data meta-analysis.

The primary outcome of our individual patient data meta-analysis was a composite outcome including four pregnancy complications: early-onset or severe pre-eclampsia, birth of an SGA neonate with a birthweight less than the 5th percentile, placental abruption, and late pregnancy loss. Early-onset pre-eclampsia was defined as being diagnosed at less than 34 weeks' gestation. Severe pre-eclampsia was characterised by at least one criterion indicative of severe disease, including systolic blood pressure at least 160 mm Hg or diastolic blood pressure at least 110 mm Hg, proteinuria of more than 0·5 g/24 h, raised liver enzymes (more than two times the local upper range of normal), platelets less than 100×10^9/L, pulmonary oedema, seizures (eclampsia), headache or other neurological manifestation (stroke, intracranial haemorrhage, cerebral oedema, hyper-reflexia, or visual impairment), coagulopathy, oliguria (<30 mL/h), or HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet count). Birth of an SGA neonate with a birthweight less than the 5th percentile was determined using local sex-specific and gestational age-specific birthweight charts. Placental abruption required a clinical diagnosis of

See Online for appendix

	Trial enrolment	Participants randomly assigned in original trial	Participants eligible for IPDMA by qualifying previous complications*	LMWH intervention and control
TIPPS[18] 2014	Multinational: 21 sites in Canada, US, Australia, and the UK	292 with thrombophilia and previous high-risk criteria	113 total 48 pre-eclampsia 47 SGA 18 placental abruption 36 ≥2 fetal losses after 12 weeks' GA 62 ≥1 fetal loss after 16 weeks' GA	Treatment: dalteparin 5000 IU to 20 weeks' GA then 10 000 IU to 36 weeks' GA Control: no dalteparin Aspirin use permitted
FRUIT[12] 2012	Multinational: 12 sites in the Netherlands, Sweden, and Australia	139 with heritable thrombophilia and previous early-onset pre-eclampsia or SGA <10th percentile (or both)	136 total 106 pre-eclampsia 47 SGA 11 placental abruption 41 ≥2 fetal losses after 12 weeks' GA 43 ≥1 fetal loss after 16 weeks' GA	Treatment: dalteparin 5000 IU plus aspirin Control: aspirin alone
HAPPY[17] 2012	Multicentre: 8 sites in Italy	135 with previous pre-eclampsia, loss >15 weeks' GA, SGA <10th percentile, or placental abruption	124 total 49 pre-eclampsia 53 SGA 20 placental abruption 41 ≥2 fetal losses after 12 weeks' GA 41 ≥1 fetal loss after 16 weeks' GA	Treatment: nadroparin 3800 IU Control: no nadroparin Aspirin use discouraged
HABENOX[19] 2011	Multinational: 4 sites in Finland, Sweden, and the Netherlands	207 with recurrent early or late miscarriage	37 total 0 pre-eclampsia 1 SGA 4 placental abruption 14 ≥2 fetal losses after 12 weeks' GA 29 ≥1 fetal loss after 16 weeks' GA	Treatment 1: enoxaparin 40 mg plus placebo Treatment 2: enoxaparin 40 mg plus aspirin Control: aspirin alone
NOH-PE[13] 2011	Single centre in France	224 with previous severe pre-eclampsia	224 total 224 pre-eclampsia 58 SGA	Treatment: enoxaparin 4000 IU plus aspirin Control: aspirin alone
NOH-AP[16] 2010	Single centre in France	160 with previous placental abruption	160 total 160 placental abruption 71 pre-eclampsia 44 SGA	Treatment: enoxaparin 4000 IU Control: no enoxaparin Aspirin use if clinically indicated
ALIFE[20] 2010	Multicentre: 8 sites in the Netherlands	364 (299 pregnant) with recurrent pregnancy loss	38 total 4 pre-eclampsia 5 SGA 3 placental abruption 32 ≥2 fetal losses after 12 weeks' GA 29 ≥1 fetal loss after 16 weeks' GA	Treatment: nadroparin 2850 IU plus aspirin Control 1: aspirin alone Control 2: placebo
Rey[15] 2009	Multicentre: 6 sites in Canada	116 with previous early pre-eclampsia, placental abruption, SGA<5th percentile, and pregnancy loss >12 weeks' GA	113 total 93 pre-eclampsia 62 SGA 36 placental abruption 69 ≥2 fetal losses after 12 weeks' GA 66 ≥1 fetal loss after 16 weeks' GA	Treatment: dalteparin 5000 IU Control: no dalteparin Aspirin use permitted

LMWH=low-molecular-weight heparin. SGA=small for gestational age. GA=gestational age. Loss=pregnancy loss. *Participants might have had a history of more than one qualifying placenta-mediated pregnancy complication.

***Table 1*: Trials included in the individual patient data meta-analysis (IPDMA)**

placental abruption leading to delivery. Late pregnancy loss was defined as occurring at or after 20 weeks' of gestation that could not be accounted for by other factors, including fetal chromosomal abnormalities, maternal infection, cervical insufficiency or incompetence, or an intentional termination of the pregnancy. We also did post-hoc analyses of data for birth of an SGA neonate with a birthweight less than the 3rd percentile. We had included birthweight less than the 10th and the 5th percentiles in the published protocol but neglected to include the more severe form of this outcome because of an oversight.

The data included participant characteristics (demographic characteristics, thrombophilia, and relevant medical history), pregnancy history and details of the current pregnancy and delivery, including infant data and pregnancy complications. Information about treatments during pregnancy, particularly related to low-molecular-weight heparin and aspirin, and associated adverse events were recorded. Analysis of osteoporotic fractures and maternal death were post-hoc because we had unintentionally not included these very rare events as secondary outcomes in our protocol.

Data synthesis and validation

Data from the original trials were recoded by local personnel who were familiar with the data. They populated the Excel template according to the criteria for each variable that had been agreed upon a priori by the group. The

eligibility of each participant was verified by the project coordinator (NJL) before data were included in the common dataset. Participants who were lost to follow-up or who did not have adequate primary outcome data were excluded. The recoded data from eligible women were imported to SAS version 9.3 and data verification scripts were run by the coordinating statistician (RM) to identify inconsistencies, outliers, and illogical data. The project coordinator (NJL) prepared data clarification requests and sent them via email to the investigators and personnel who had done the recoding. Data lock of the common dataset and analyses were done after resolution of all clarification requests. The primary analyses of the original trials were replicated before the meta-analysis to ensure that the results from each trial could be reproduced.

Risk of bias assessments

Assessments of study quality for included trials were done independently by two investigators (ADM and NJL) according to the seven criteria in the Cochrane Risk of Bias tool.[28] Funding was added as an additional criterion. The criteria were graded as low risk, high risk, or unclear risk of bias, and all disagreements were resolved by consensus. When the information was not available in the published paper or a public registry, the trial's lead author was contacted by email to request clarification or additional information.

Data analysis

The primary analysis included all eligible women with outcome data, and examined the risk of the primary composite outcome in the treatment (low-molecular-weight heparin) and control arms based on intention-to-treat analysis. Secondary univariate analyses were done for each of the pregnancy complications included in the composite outcome and other pregnancy complications of different severity, as outlined in the analysis plan. We calculated risk differences using generalised estimating equations to adjust for clustering at the study level. If expected counts were less than five, an adjustment was considered unfeasible and no formal test was done. Subgroup analyses were planned a priori based on clinical plausibility and existing evidence that the subgroups might be relevant.[24] We used SAS version 9.3 for all statistical analyses. This study is registered with PROSPERO, number CRD42013006249.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MAR, TR, RM, and NJL had complete access to the data, and all authors had final responsibility for the decision to submit for publication.

Results

The dataset included a total of 963 eligible women from eight published trials that were done between 2000 and 2013 (figure). The ALIFE[20] and HABENOX[19] trials enrolled women with a history of pregnancy loss, NOH-PE[13] included women with previous pre-eclampsia, and NOH-AP[16] enrolled women with previous placental abruption that led to delivery. HAPPY,[17] FRUIT,[12] TIPPS,[18] and the trial by Rey and colleagues[15] included women with various previous placenta-mediated pregnancy complications, although pre-eclampsia was the most common complication (table 1). Trial participants might have had more than one previous complication.

Overall, the eight studies were consistent in the risk of bias (full results of study quality assessments are available in the appendix). All trials included open-label low-molecular-weight heparin and, as such, masking of patients was graded as high risk for six of the eight studies; the primary outcome of livebirth was considered to be objective and unlikely to be influenced by the absence of masking for the other two studies.[19,20] Two studies were graded as unclear risk for selective outcome reporting because trial registration or a protocol was not available.[13,16] All studies had funding but the involvement of the supporting agency was clearly described in all papers as not influencing the results. Overall, the risk of bias was not substantial enough to affect decisions regarding trial inclusion.

	All participants (n=963)	LMWH (n=480)	No LMWH (n=483)
Maternal age (years; missing=1)	30·9 (5·0)	30·9 (4·8)	30·8 (5·1)
Race			
White	795/905 (88%)	409/457 (89%)	386/448 (86%)
Black	58/905 (6%)	23/457 (5%)	35/448 (8%)
Asian	31/905 (3%)	16/457 (4%)	15/448 (3%)
Other	21/905 (2%)	9/457 (2%)	12/448 (3%)
Body-mass index (kg/m²; missing=38)	25·0 (22·4–27·8)	25·1 (22·5–27·7)	24·9 (22·3–28·0)
Thrombophilia			
FVL mutation, heterozygous	187/951 (20%)	94/475 (20%)	93/476 (20%)
FVL mutation, homozygous	5/951 (1%)	2/475 (<1%)	3/476 (1%)
Prothrombin mutation, heterozygous	78/943 (8%)	43/470 (9%)	35/473 (7%)
Prothrombin mutation, homozygous	1/943 (<1%)	0/470 (0%)	1/473 (<1%)
Antithrombin deficiency	6/939 (1%)	2/471 (<1%)	4/468 (1%)
Protein C deficiency	18/945 (2%)	8/476 (2%)	10/469 (2%)
Protein S deficiency	106/943 (11%)	52/475 (11%)	54/468 (12%)
Antiphospholipid antibodies	31/882 (4%)	20/436 (5%)	11/446 (2%)
Smoker	74/912 (8%)	36/453 (8%)	38/459 (8%)
Chronic hypertension	154/757 (20%)	80/378 (21%)	74/379 (20%)
Type 1 or 2 diabetes outside of pregnancy	0/832 (0%)	0/415 (0%)	0/417 (0%)
Venous thromboembolism			
Maternal history	10/958 (1%)	5/478 (1%)	5/480 (1%)
Family history	34/840 (4%)	19/418 (5%)	15/422 (4%)
Arterial vascular disease (family history)	152/643 (24%)	84/320 (26%)	68/323 (21%)

Data are mean (SD), n/N (%), or median (lowest quartile and highest quartile). LMWH=low-molecular-weight heparin. FVL=Factor V Leiden.

***Table 2*: Characteristics of study participants**

	All participants (n=963)	LMWH (n=480)	No LMWH (n=483)
Gravida (includes current pregnancy)*			
2	633/963 (66%)	318/480 (66%)	315/483 (65%)
≥3	330/963 (34%)	162/480 (34%)	168/483 (35%)
Previous livebirths			
0	147/963 (15%)	81/480 (17%)	66/483 (14%)
1	724/963 (75%)	355/480 (74%)	369/483 (76%)
2	66/963 (7%)	30/480 (6%)	36/483 (7%)
≥3	26/963 (3%)	14/480 (3%)	12/483 (2%)
Previous pregnancy losses			
0	602/963 (63%)	304/480 (63%)	298/483 (62%)
1	163/963 (17%)	79/480 (16%)	84/483 (17%)
2	72/963 (7%)	36/480 (8%)	36/483 (7%)
≥3	126/963 (13%)	61/480 (13%)	65/483 (13%)
Previous late-pregnancy losses			
After 12 weeks' GA (2 or more losses)	233/919 (25%)	114/461 (25%)	119/458 (26%)
After 16 weeks' GA (1 or more losses)	270/930 (29%)	136/466 (29%)	134/464 (29%)
After 20 weeks' GA (1 or more losses)	177/903 (20%)	90/457 (20%)	87/446 (20%)
Previous SGA neonates			
SGA <10th percentile	317/906 (35%)	161/453 (36%)	156/453 (34%)
SGA <5th percentile	166/793 (21%)	82/403 (20%)	84/390 (22%)
SGA <3rd percentile	70/680 (10%)	31/346 (9%)	39/334 (12%)
Previous placental abruption	286/886 (32%)	143/441 (32%)	143/445 (32%)
Previous pre-eclampsia			
Pre-eclampsia	595/963 (62%)	293/480 (61%)	302/483 (63%)
Severe pre-eclampsia	441/851 (52%)	225/434 (52%)	216/417 (52%)
Early-onset pre-eclampsia	307/801 (38%)	160/407 (39%)	147/394 (37%)
Previous preterm delivery			
<37 weeks' GA	751/960 (78%)	378/480 (79%)	373/480 (78%)
<34 weeks' GA	605/960 (63%)	307/480 (64%)	298/480 (62%)

Data are n/N (%). LMWH=low-molecular-weight heparin. GA=gestational age. SGA=small for gestational age.
*Seven study participants had multiple gestations (twins) in the current pregnancy.

***Table 3*: Pregnancy history of study participants**

We noted no important imbalances between the treatment groups for demographic and clinical characteristics (table 2) or previous pregnancy history (table 3). The mean age of participants was 30·9 years (SD 5·0) and most were white. Most were enrolled in Europe (712/963; 74%), followed by North America (206/963; 21%) and Australia (45/963; 5%). Around a fifth had chronic hypertension and 8% (74/912) smoked. By design, all participants had had a previous pregnancy and most were in their second pregnancy. The most frequent previous placenta-mediated complication was pre-eclampsia and many women had severe or early-onset disease. About a third had given birth to an SGA neonate in less than the 10th percentile of birthweight, and about a third had previous placental abruption. Preterm delivery before 34 weeks' gestation was also common, and 361/963 (37·5%) had had at least one previous pregnancy loss.

The prevalence of thrombophilia varied substantially between trials, since in some cases this was stipulated by the protocol: the TIPPS[18] and FRUIT[12] trials required a diagnosis of thrombophilia for inclusion, whereas Rey and colleagues[15] excluded women with thrombophilia. Overall, 403/963 (42%) of the individual patient data meta-analysis sample was diagnosed with thrombophilia. In the eight trials, women allocated to the low-molecular-weight heparin treatment groups received dalteparin, enoxaparin, or nadroparin (drug, dose, and schedule of administration for each trial are in table 1). The use of aspirin also differed by trial: in some, it was provided to women in both the intervention and control groups;[12,13,19,20] in others, the daily use of aspirin was at the discretion of the investigator and its use was recorded[15,18] or was given to women meeting specific clinical criteria.[16] In one trial regular aspirin use was discouraged.[17] Two trials included a placebo control, matching the aspirin intervention.[19,20] The two trials that enrolled women with a history of pregnancy loss started the intervention very early, before 7 weeks' gestation;[19,20] most of the other trials required randomisation before 12 weeks' gestation, whereas two allowed randomisation to occur later, but before 17 weeks'[15] or 20 weeks' gestation.[18] All trials continued the intervention until at least 36 weeks' gestation or, in some cases, the onset of labour. Subgroup analyses enabled us to explore differences between participants and interventions.

In our primary outcome analysis, low-molecular-weight heparin did not significantly reduce the risk of recurrent placenta-mediated pregnancy complications (low-molecular-weight heparin 62/444 (14%) versus no low-molecular-weight heparin 95/443 (22%), absolute difference –8%, 95% CI –17·3 to 1·4, p=0·09; relative risk (RR) 0·64, 95% CI 0·36–1·11; p=0·11). We noted significant heterogeneity between single-centre and multicentre trials (table 4). In multicentre trials, no effect of low-molecular-weight heparin was shown in the primary composite outcome, its component outcomes, and almost all secondary outcomes. However, in single-centre trials, low-molecular-weight heparin seemed to prevent the composite primary outcome, the individual components of the composite outcome, and almost all secondary outcomes.

In subgroup analyses, we noted similar heterogeneity between multicentre and single-centre studies. In the multicentre trials, low-molecular-weight heparin did not prevent the composite primary outcome in women with previous pre-eclampsia, previous pregnancy loss, or previous birth of SGA neonates, irrespective of the severity of these previous complications (table 5). However, in single-centre trials, we noted a beneficial effect of low-molecular-weight heparin in women with previous pre-eclampsia, pregnancy loss, and previous birth of an SGA child, regardless of the severity of any previous complications. A beneficial effect of low-molecular-weight heparin was noted in women with previous placental abruption in both single-centre and multicentre trials.

In women with inherited or acquired thrombophilia and previous placenta-mediated pregnancy complications we noted no differences between the low-molecular-weight heparin groups and the groups

	All trials			Multicentre trials			Single-centre trials		
	LMWH (n=480)	No LMWH (n=483)	Absolute difference (95% CI), p value	LMWH (n=288)	No LMWH (n=291)	Absolute difference (95% CI), p value	LMWH (n=192)	No LMWH (n=192)	Absolute difference (95% CI), p value
Primary composite outcome of early-onset or severe pre-eclampsia, or SGA <5th percentile, or placental abruption, or pregnancy loss ≥ 20 weeks' gestation*	62/444 (14%)	95/433 (22%)	−8·0% (−17·3 to 1·4), p=0·09	47/263 (18%)	47/255 (18%)	−0·6% (−10·4 to 9·2), p=0·91	15/181 (8%)	48/178 (27%)	−18·7% (95% CI −21·6 to −15·7), p<0·0001
Secondary outcomes									
Placental abruption	15/469 (3%)	31/474 (7%)	−3·3% (−6·7 to −0·1), p=0·0491	5/277 (2%)	7/282 (2%)	−0·7% (−4·0 to 2·6), p=0·69	10/192 (5%)	24/192 (13%)	−7·3% (−9·0 to −5·6), p<0·0001
Placental abruption leading to delivery	5/469 (1%)	10/474 (2%)	−1·0% (−2·4 to 0·3), p=0·14	3/277 (1%)	5/282 (2%)	†	2/192 (1%)	5/192 (3%)	†
Any pregnancy loss*	46/477 (10%)	64/478 (13%)	−3·8% (−9·5 to 2·0), p=0·20	30/285 (11%)	37/286 (13%)	−2·4% (−11·3 to 6·5), p=0·60	16/192 (8%)	27/192 (14%)	−5·7% (−7·8 to −3·7), p<0·0001
Pre-eclampsia§	41/444 (9%)	67/433 (15%)	−6·2% (−13·1 to 0·6), p=0·08	29/263 (11%)	32/255 (13%)	−1·5% (−10·0 to 7·0), p=0·73	12/181 (7%)	35/178 (20%)	−13·0% (−16·4 to −9·6), p<0·0001
Severe pre-eclampsia§	22/442 (5%)	43/433 (10%)	−5·0% (−11·2 to 1·3), p=0·12	19/261 (7%)	19/255 (7%)	−0·2% (−6·4 to 6·0), p=0·96	3/181 (2%)	24/178 (13%)	−11·8% (−16·6 to −7·1), p<0·0001
Early-onset pre-eclampsia§	18/444 (4%)	32/433 (7%)	−3·3% (−7·9 to 1·2), p=0·15	11/263 (4%)	14/255 (5%)	−1·3% (−7·5 to 4·9), p=0·68	7/181 (4%)	18/178 (10%)	−6·2% (−10·5 to −2·0), p=0·0037
Severe or early-onset pre-eclampsia§	31/444 (7%)	51/433 (12%)	−4·8% (−11·6 to 2·0), p=0·17	24/263 (9%)	22/255 (9%)	0·5% (−6·8 to 7·8), p=0·89	7/181 (4%)	29/178 (16%)	−12·4% (−16·5 to −8·4), p<0·0001
HELLP syndrome§	2/384 (1%)	11/370 (3%)	−2·5% (−4·4 to −0·6)(p=0·0112)	1/203 (<1%)	3/192 (2%)	†	1/181 (1%)	8/178 (4%)	†
SGA <10th percentile§	61/444 (14%)	94/429 (22%)	−8·2% (−14·3 to −2·0), p=0·0094	47/263 (18%)	53/251 (21%)	−3·2% (−9·6 to 3·1), p=0·32	14/181 (8%)	41/178 (23%)	−15·3% (−19·1 to −11·5), p<0·0001
SGA <5th percentile§	27/443 (6%)	38/429 (9%)	−2·8% (−5·4 to −0·1), p=0·0417	22/262 (8%)	23/251 (9%)	−0·8% (−3·7 to 0·2), p=0·61	5/181 (3%)	15/178 (8%)	−5·7% (−6·1 to −5·2), p<0·0001
SGA <3rd percentile§	13/443 (3%)	12/429 (3%)	−0·1% (−1·9 to 2·2, p=0·89	13/262 (5%)	9/251 (4%)	1·4% (−1·3 to 4·1), p=0·32	0/181	3/178 (2%)	†
Pregnancy loss ≥20 weeks' gestation§	13/444 (3%)	18/432 (4%)	−1·2% (−4·2 to 1·8), p=0·42	8/263 (3%)	5/254 (2%)	1·1% (−2·1 to 4·2), p=0·50	5/181 (3%)	13/178 (7%)	−4·5% (−7·0 to −2·1), p=0·0003
Preterm delivery <37 weeks' gestation§	131/431 (30%)	136/414 (33%)	−2·5% (−9·7 to 4·5), p=0·49	58/255 (23%)	48/249 (19%)	3·5% (−1·3 to 8·2), p=0·15	73/176 (41%)	88/165 (53%)	−11·9% (−13·5 to −10·3), p<0·0001
Preterm delivery <34 weeks' gestation§	28/431 (6%)	45/414 (11%)	−4·4% (−9·0 to 0·3), p=0·07	17/255 (7%)	19/249 (8%)	−1·0% (−4·7 to 2·8), p=0·61	11/176 (6%)	26/165 (16%)	−10·0% (−14·6 to −4·4), p=0·0003
Neonatal death within 28 days of birth§	3/423 (1%)	9/406 (2%)	−1·5% (−3·1 to 0·1), p=0·07	1/247 (<1%)	2/241 (1%)	†	2/176 (1%)	7/165 (4%)	†
Safety outcomes									
Venous thromboembolism	1/468 (<1%)	2/457 (<1%)	†	1/276 (<1%)	2/265 (1%)	†	0/192	0/192	..
Allergic reaction to LMWH	9/480 (2%)	1/483 (<1%)	†	9/288 (3%)	1/291 (<1%)	†	0/192	0/192	..
Antepartum major bleeding‡	1/470 (<1%)	3/473 (1%)	†	0/278	0/281	..	1/192 (1%)	3/192 (2%)	†
Peripartum major bleeding	10/404 (2%)	12/395 (3%)	−0·3% (−1·6 to 1·0), p=0·30	10/212 (5%)	10/203 (5%)	0·2% (−2·0 to 2·6), p=0·80	0/192	2/192 (1%)	−1·0% (−2·5 to 0·4), p=0·50
Post-partum major bleeding	3/470 (1%)	4/473 (1%)	†	3/278 (1%)	4/281 (1%)	†	0/192	0/192	..
Thrombocytopenia	14/469 (3%)	6/476 (1%)	1·7% (−2·2 to 5·7), p=0·40	14/277 (5%)	6/284 (2%)	2·9% (−3·8 to 9·7), p=0·40	0/192	0/192	..
Heparin-induced thrombocytopenia	0	0	..	0	0	..	0	0	..
Osteoporotic fracture	0	0	..	0	0	..	0	0	..
Maternal death	0	0	..	0	0	..	0	0	..

Outcomes noted for study participants according to treatment allocation (intention to treat). Relative risk for the primary outcome difference for all trials 0·64, 95% CI 0·36–1·11; p=0·11. Data are n/N (%). LMWH=low-molecular-weight heparin. SGA=small for gestational age. ..=not applicable. *Excludes eight women with terminations for medical reasons other than the primary outcome. †Expected counts were less than five, therefore an adjustment was considered unfeasible and no formal test was done. §Excludes 86 women that had a pregnancy loss before 20 weeks' gestation or had a pregnancy termination for medical reasons other than the primary outcome. ‡All antepartum major bleeding was associated with the primary outcome event of placental abruption.

***Table 4*: Primary, secondary, and safety outcomes**

	All trials			Multicentre trials			Single-centre trials		
	LMWH (n=444)	No LMWH (n=433)	Absolute difference (95% CI), p value	LMWH (n=288)	No LMWH (n=291)	Absolute difference (95% CI), p value	LMWH (n=192)	No LMWH (n=192)	Absolute difference (95% CI), p value
Previous pregnancy complication									
Any pre-eclampsia	37/276 (13%)	73/285 (26%)	−12·2% (−20·2 to -4·3), p=0·0026	26/139 (19%)	36/146 (25%)	−6·0% (−18·2 to 6·3), p=0·34	11/137 (8%)	37/139 (27%)	−18·6% (−22·2 to −15·0), p<0·0001
Severe pre-eclampsia	26/212 (12%)	50/203 (25%)	−12·4% (−21·8 to −2·9), p=0·0104	18/94 (19%)	20/88 (23%)	−3·6% (−22·3 to 15·2), p=0·71	8/118 (7%)	30/115 (26%)	−19·3% (−25·4 to −13·2), p<0·0001
Early-onset pre-eclampsia	23/152 (15%)	36/141 (26%)	−10·4% (−22·2 to 1·4), p=0·08	22/103 (21%)	25/95 (26%)	−5·0% (−20·7 to 10·8), p=0·54	1/49 (2%)	11/46 (24%)	−21·9% (−27·5 to −16·2), p<0·0001
Severe or early-onset pre-eclampsia	33/239 (14%)	57/228 (25%)	−11·1% (−20·7 to −1·7), p=0·0207	25/121 (21%)	27/113 (24%)	−3·2% (−18·4 to 12·0), p=0·68	8/118 (7%)	30/115 (26%)	−19·3% (−25·4 to −13·2), p<0·0001
Any previous loss after 12 weeks' gestation	22/128 (17%)	19/114 (17%)	0·5% (−10·7 to 11·8), p=0·93	22/128 (17%)	19/114 (17%)	0·5% (−10·7 to 11·8), p=0·93	0	0	..
One or more late losses after 16 weeks' gestation	21/120 (18%)	19/109 (17%)	0·07% (− 11·9 to 12·2), p=0·99	21/120 (18%)	19/109 (17%)	0·07% (−11·9 to 12·2), p=0·99	0	0	..
Two or more late losses after 12 weeks' gestation	4/22 (18%)	2/14 (14%)	*	4/22 (18%)	2/14 (14%)	*	0	0	..
SGA <10th percentile	24/152 (16%)	40/145 (28%)	−11·8% (−25·3 to 1·7), p=0·09	21/105 (20%)	22/95 (23%)	−3·2% (−16·8 to 10·5), p=0·65	3/47 (6%)	18/50 (36%)	−30·0% (−40·0 to −19·3), p<0·0001
SGA <5th percentile	9/77 (12%)	20/77 (26%)	−14·3% (−27·1 to −0·7), p=0·04	8/59 (14%)	13/56 (23%)	−10·0% (−26·5 to 7·2), p=0·26	1/18 (6%)	7/21 (33%)	*
SGA <3rd percentile	6/31 (19%)	11/35 (31%)	−12·1% (−35·7 to 11·5), p=0·32	6/21 (29%)	6/25 (24%)	4·6% (−6·3 to 15·5), p=0·41	0/10	4/10 (40%)	*
Any pre-eclampsia and SGA <10th percentile	13/91 (14%)	30/97 (31%)	−16·6% (−28·5 to −4·8), p=0·0058	11/53 (21%)	16/55 (29%)	−8·3% (−26·5 to 9·9), p=0·37	2/38 (5%)	14/42 (33%)	−27·8% (− 37·5 to −18·7), p<0·0001
Any pre-eclampsia and SGA <5th percentile	6/53 (11%)	13/50 (26%)	−14·7% (−31·1 to 1·7), p=0·08	5/35 (14%)	8/33 (24%)	−10·0% (−36·8 to 16·9), p=0·47	1/18 (6%)	5/17 (29%)	*
Any pre-eclampsia and SGA <3rd percentile	3/15 (20%)	4/15 (27%)	*	3/5 (60%)	1/7 (14%)	*	0/10	3/8 (38%)	*
Any placental abruption	11/138 (8%)	33/134 (25%)	−16·7% (−23·0 to −10·4), p<0·0001	3/48 (6%)	9/47 (19%)	−12·9% (−22·1 to −3·7), p=0·006	8/90 (9%)	24/87 (28%)	−18·7% (−24·7 to −12·7), p<0·0001
Placental abruption leading to delivery	10/122 (8%)	32/118 (27%)	−18·9% (−22·8 to −15·1), p<0·0001	3/45 (7%)	9/42 (21%)	−14·8% (−23·3 to −6·3), p=0·0007	7/77 (9%)	23/76 (30%)	−21·2% (−33·3 to −9·0), p<0·0001
Any placental abruption with any pre-eclampsia	5/65 (8%)	20/69 (29%)	−21·3% (−29·7 to −12·9), p<0·0001	1/19 (5%)	7/21 (33%)	*	4/46 (9%)	13/48 (27%)	−18·4% (−29·0 to −7·7), p=0·0007

(Table 5 continues on next page)

allocated to receive no low-molecular-weight heparin in multicentre trials; however, we noted a beneficial low-molecular-weight heparin effect in women with inherited or acquired thrombophilia and previous placenta-mediated pregnancy complications in single-centre trials (table 5). This finding was replicated when subgroups of women with weak thrombophilia (ie, heterozygosity for the Factor V Leiden or prothrombin gene variants), moderate, and more potent thrombophilias were analysed separately.

	All trials			Multicentre trials			Single-centre trials		
	LMWH (n=444)	No LMWH (n=433)	Absolute difference (95% CI), p value	LMWH (n=288)	No LMWH (n=291)	Absolute difference (95% CI), p value	LMWH (n=192)	No LMWH (n=192)	Absolute difference (95% CI), p value
(Continued from previous page)									
Thrombophilia									
No thrombophilia	26/258 (10%)	58/246 (24%)	−13·5% (−18·1 to −8·9), p<0·0001	11/103 (11%)	19/94 (20%)	−9·5% (−22·0 to 2·9), p=0·13	15/155 (10%)	39/152 (26%)	−16·0% (−17·0 to −15·0), p<0·0001
Weak thrombophilia (heterozygous FVL or PGM)	21/112 (19%)	24/114 (21%)	−2·3% (−17·6 to 13·0), p=0·77	21/86 (24%)	17/91 (19%)	5·7% (−5·1 to 16·5), p=0·29	0/26	7/23 (30%)	−30·0% (−49·2 to −11·6), p=0·0029
Moderate thrombophilia (deficiency of protein C or S)	6/40 (15%)	9/53 (17%)	−2·0% (−13·8 to 9·9), p=0·74	6/40 (15%)	8/51 (16%)	−0·7% (−11·6 to 10·2), p=0·90	0	0	..
Strong thrombophilia (antithrombin deficiency, antiphospholipid antibodies, homozygous FVL or PGM, or more than one thrombophilia)	9/34 (26%)	4/20 (20%)	*	9/34 (26%)	3/19 (16%)	*	0	0	..
LMWH treatment									
Low dose (nadroparin 2850 IU or 3800 IU; enoxaparin 4000 IU; or dalteparin ≤5000 IU per day)	42/354 (12%)	95/433 (22%)	−10·1% (−18·3 to −1·9), p=0·016	27/173 (16%)	47/255 (18%)	−2·8% (−12·8 to 7·2), p=0·58	15/181 (8%)	48/178 (27%)	−18·7% (−21·6 to −15·7), p<0·0001
Intermediate dose (>5000 IU dalteparin per day)	20/90 (22%)	95/433 (22%)	0·28% (−6·5 to 7·1), p=0·93	20/90 (22%)	47/255 (18%)	3·8% (−2·7 to 10·3), p=0·25	..	..	..
Aspirin treatment									
Daily aspirin	37/260 (14%)	72/262 (27%)	−13·3% (−23·2 to −3·3), p=0·0091	26/146 (18%)	32/140 (23%)	−5·1% (−15·7 to 5·6), p=0·35	11/114 (10%)	40/122 (33%)	−23·1% (−37·4 to −8·9), p=0·0014
No aspirin	25/181 (14%)	22/156 (14%)	−0·3% (−9·0 to 8·4), p=0·95	21/114 (18%)	14/100 (14%)	4·4% (−3·3 to 12·2), p=0·26	4/67 (6%)	8/56 (14%)	−8·3% (−19·1 to 2·5), p=0·13
Time of LMWH initiation									
Before 10 weeks' gestation	38/303 (13%)	95/433 (22%)	−9·4% (−19·1 to 0·3), p=0·06	23/122 (19%)	47/255 (18%)	0·4% (−12·1 to 12·9), p=0·95	15/181 (8%)	48/178 (27%)	−18·7% (−21·6 to −15·7), p<0·0001
Before 16 weeks' gestation	58/416 (14%)	95/433 (22%)	−8·0% (−17·8 to 1·8), p=0·11	43/235 (18%)	47/255 (18%)	−0·1% (−11·0 to 10·7), p=0·98	15/181 (8%)	48/178 (27%)	−18·7% (−21·6 to −15·7), p<0·0001
Before 20 weeks' gestation	62/441 (14%)	95/443 (21%)	−7·9% (−17·4 to 1·6), p=0·10	47/260 (18%)	47/255 (18%)	−0·4% (−10·4 to 9·7), p=0·94	15/181 (8%)	48/178 (27%)	−18·7% (−21·6 to −15·7), p<0·0001

Data are n/N (%). LMWH=low-molecular-weight heparin. SGA=small for gestational age. FVL=Factor V Leiden. PGM=prothrombin gene mutation. ..=not applicable . *Expected counts were less than five, therefore an adjustment was considered unfeasible and no formal test was done.

***Table 5*: Primary outcome according to patient subgroup**

Exploration of differences in treatment dose, timing of low-molecular-weight heparin initiation, and concomitant aspirin use subgroups revealed a similar pattern of no benefit of low-molecular-weight heparin in multicentre trials but suggestion of a low-molecular-weight heparin benefit in single-centre trials (table 5).

In the analysis of safety outcomes, we noted few events and no differences between groups. We saw no serious adverse reactions to low-molecular-weight heparin, including heparin-induced thrombocytopenia, osteoporotic fractures, or maternal death. Ten allergic reactions occurred that were severe enough to require discontinuation of low-molecular-weight heparin; one was a control group crossover to low-molecular-weight heparin. In the antepartum period, four women haemorrhaged and met our definition of major bleeding.

All of these events were attributable to placental abruption and are captured as primary outcome events. Two of these women were randomly assigned to low-molecular-weight heparin; the other two were in the control group and did not receive either low-molecular-weight heparin or aspirin. In the peripartum and postpartum periods, the incidence of major bleeding did not differ between the treatment and control groups.

Discussion

In this individual patient data meta-analysis, low-molecular-weight heparin did not significantly reduce the risk of recurrent placenta-mediated pregnancy complications in women with previous complications. Importantly, this finding also applies to subgroups of women with previous pre-eclampsia, previous severe pre-eclampsia, previous early-onset pre-eclampsia, previous late pregnancy loss (one or more losses after 16 weeks), previous recurrent late pregnancy loss (two or more losses after 12 weeks), previous births of babies who were mildly SGA (<10th percentile) or more severely SGA (<5th percentile).

The absence of effect of low-molecular-weight heparin might reflect the multifactorial pathophysiology for these placenta-mediated pregnancy complications. Indeed, the cumulative observational scientific literature exploring the association between thrombophilia and placenta-mediated pregnancy complications suggests a weak association with pregnancy loss, severe pre-eclampsia, SGA birth less than the 3rd percentile, and abruption, but no association with any pre-eclampsia or less severe SGA birth.[29,30] Overall, findings from observational research, and now experimental research, suggest that placental thrombosis might not be a major contributor to placenta-mediated pregnancy complications. As we learn more about the underlying disease mechanisms for placenta-mediated pregnancy complications and develop pragmatic diagnostic tools to identify when these mechanisms are in play, we might be able to define patient subgroups that could benefit from low-molecular-weight heparin.

Results in a small subgroup of patients with previous abruption suggest low-molecular-weight heparin might prevent placenta-mediated pregnancy complications in subsequent pregnancies but this finding requires confirmation in future multicentre trials before it can be adopted in routine clinical practice. This finding might seem counter-intuitive, given that placental abruption is a bleeding complication. However, low-molecular-weight heparin might prevent the placental infarction that often precedes bleeding into placental infarcts, which manifests clinically as placental abruption. In the absence of strong evidence or proven treatment alternatives, personalised medicine and counselling will be important in the decision-making process when considering low-molecular-weight heparin for women with a history of placental abruption.

Our previous pooled summary-based meta-analysis[23] of six trials included 848 pregnant women with a history of pre-eclampsia, birth of an SGA neonate (<10th percentile), placental abruption, or late pregnancy loss (after more than 12 weeks' gestation). The primary finding was that 67 of 358 (19%) women given low-molecular-weight heparin during pregnancy had recurrent severe placenta-mediated pregnancy complications, compared with 127 of 296 (43%) women with no low-molecular-weight heparin (RR reduction 48%, 95% CI 14–68%; I^2 69%). However, since these meta-analysis results applied to a heterogeneous group of women with a mixture of previous placenta-mediated pregnancy complications of varying severity, and the primary outcome for the meta-analysis was a composite of all placenta-mediated complications (also of varying severity), which subgroups of women derive the most benefit from low-molecular-weight heparin was unclear (ie, which outcomes were reduced and outcomes of what severity were affected). The limitations of this meta-analysis supported the need to do an individual patient data meta-analysis.

A strength of our study was the inclusion of individual patient data from the largest, and almost all, completed trials that assessed low-molecular-weight heparin to prevent placenta-mediated pregnancy complications. Limitations included that the primary analysis of the individual patient data meta-analysis also included a heterogeneous group of women with different previous placenta-mediated pregnancy complications, the interventions in the eight trials included three low-molecular-weight heparins of differing doses, gestational age varied at treatment initiation, co-intervention with aspirin varied, and that the primary outcome was a composite of four complications. However, the advantages of individual patient data meta-analyses lie in the ability to do subgroup analyses that are hypothesised to be clinically relevant, provision of a rich dataset from individual patient data, and greater statistical power than conventional meta-analyses.[31,32] The individual patient data meta-analysis enabled us to explore clinical, methodological, and statistical heterogeneity more robustly. We acknowledge that some of the subgroups included patients with rare outcomes and these analyses were restricted by small samples.

Other limitations of our study are that there might have been smaller absolute decreases in event rates than we had sufficient power to explore. However, this limitation depends strongly on what is valued as the minimal clinically important difference. Given our observed composite primary outcome event rate of 18% in the control group of the multicentre trials, an adequately powered (80%) trial to detect a 3%, 6%, or 9% absolute reduction (17%, 33%, or 50% RR reduction, or number needed to treat of 33, 17, or 11) would require 2400, 555, or 226 participants per group, respectively. Hence, if clinicians, patients, and policy makers are

willing to accept high numbers needed to treat, and hence small minimal clinically important differences, then larger clinical trials will be required to definitively answer this question. However, we believe that most would agree that numbers needed to treat must be reasonably small (eg, ten or less) to justify using these burdensome and expensive injections throughout pregnancy. Finally, three ongoing trials (NCT00986765, NCT01388322, and ACTRN12609000699268) comparing low-molecular-weight heparin to no low-molecular-weight heparin in women with previous pre-eclampsia will provide additional data to explore smaller absolute risk differences with improved power.

The results obtained in single-centre trials contrasted starkly with those from the multicentre trials. However, this effect has been observed in critical-care trials[33] and in many other disease areas.[34] Indeed, in a meta-epidemiological study, single-centre trials exaggerated treatment effects by more than 25%, and the investigators suggested that results from single-centre trials should be considered separately from those from multicentre trials when meta-analyses are interpreted. Possible explanations for differences in treatment effects in single-centre trials compared with multicentre trials exploring low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications include publication bias, lower trial quality, and co-interventions.

Publication bias might occur when findings from small, single-centre trials with negative results are not published and hence would not be included in our meta-analysis. Although we searched trial registration websites for any trials to avoid publication bias, clinical trial registration only became mandatory in many jurisdictions in the early 2000s, leading to the possibility that small trials with negative results were unpublished and never registered. Single-centre trials are sometimes of lower quality and empirically trials of lower quality are associated with larger treatment effects.[35,36] Indeed, our risk of bias assessment suggests that the single-centre trials in our individual patient data meta-analysis were at higher risk of bias because the single-centre trials were not registered. Finally, co-intervention, such as closer follow-up of women in the low-molecular-weight heparin arms in the single-centre trials, could have led to an apparent low-molecular-weight heparin treatment effect. Closer follow-up, in and of itself, might prevent recurrent pregnancy loss.[37,38] We do not believe that the single-centre trials showed a greater treatment effect because of differences in treatment regimens, because the highest doses of low-molecular-weight heparin were used in a multicentre trial.

In conclusion, overall low-molecular-weight heparin does not seem to reduce the risk of recurrent placenta-mediated pregnancy complications. Results in a small subgroup of women with previous abruption suggest low-molecular-weight heparin might prevent placenta-mediated complications in this population, but this finding should be replicated in future multicentre trials.

Contributors

MAR was the lead individual patient data meta-analysis (IPDMA) investigator, conceived the study concept, obtained peer-reviewed funding, wrote the first draft of the protocol and first draft of the manuscript, developed the IPDMA variable definitions and analysis plan, interpreted the IPDMA results, and critically revised and approved the final manuscript. J-CG contributed to study design, developed detailed definitions for study outcomes and eligibility, recoded the original data from the NOH-AP and NOH-PE trials and responded to trial-related data queries, and reviewed and approved the final manuscript. JIPdV contributed to study design, developed detailed definitions for study outcomes and eligibility, provided input on IPDMA variable definitions, supervised the recoding of the original data from the FRUIT Trial, and critically revised and approved the final manuscript. IM contributed to study design, developed detailed definitions for study outcomes and eligibility, supervised the recoding of the original data from the HAPPY trial, and critically revised and approved the final manuscript. ÉR contributed to study design, developed detailed definitions for study outcomes and eligibility, provided input on IPDMA variable definitions, recoded the original data from the trial by Rey and colleagues and responded to trial-related data queries, and critically revised and approved the final manuscript. ES contributed to study design, developed detailed definitions for study outcomes and eligibility, provided input on IPDMA variable definitions, supervised the recoding of the original data from the ETHIG II Trial, and critically revised and approved the final manuscript. SM contributed to study design, developed detailed definitions for study outcomes and eligibility, supervised the recoding of the original data from the ALIFE trial, and reviewed and approved the final manuscript. RK approved the methods for the study, recoded original data from the HABENOX trial and responded to trial-related data queries, and reviewed and approved the final manuscript. NJL was the project coordinator for the IPDMA, assisted in writing the first draft of the protocol and first draft of the manuscript, developed the first draft of the data dictionary and template for the IPDMA Common Dataset, reviewed the recoded data and confirmed participants' eligibility, did the study-quality assessments, populated the figure, and critically revised and approved the final manuscript. TR contributed to study design, particularly the data-analysis plan (as lead statistician), supervised the statistical analysis, and reviewed and approved the final manuscript. RM contributed to study design, particularly the data analysis plan (as coordinating statistician), replicated the original analyses from all included trials, did validity checks on the IPDMA dataset and did all the IPDMA analyses, contributed to data interpretation, populated the figure, and critically revised and approved the final manuscript. SMB contributed to study design, particularly knowledge-translation planning, and critically revised and approved the final manuscript. CNHA contributed to study design, developed detailed definitions for study outcomes and eligibility, recoded original data from the FRUIT trial and responded to trial-related data queries, and critically revised and approved the final manuscript. AP contributed to study design, developed detailed definitions for study outcomes and eligibility, recoded original data from the HAPPY Trial and responded to trial-related data queries, and reviewed and approved the final manuscript. DP contributed to study design including the statistical analysis plan and developed detailed definitions for study outcomes and eligibility, provided input on IPDMA variable definitions, recoded original data from the ETHIG II trial and responded to trial-related data queries, and critically revised and approved the final manuscript. PdJ contributed to study design, developed detailed definitions for study outcomes and eligibility, recoded the original data from the ALIFE trial and responded to trial-related data queries, and reviewed and approved the final manuscript. MEvH contributed to study design, developed detailed definitions for study outcomes and eligibility, provided input on IPDMA variable definitions, and critically revised and approved the final manuscript. PDB contributed to study design, developed detailed definitions for study outcomes and eligibility, and reviewed and approved the final manuscript. ADM planned, led, and did the study-quality assessments, drafted the results of the assessments, and reviewed and approved the final manuscript.

Declaration of interests

MAR is supported by a Heart and Stroke Foundation of Canada Career Investigator Award, number CI 7441, and a University of Ottawa Faculty of Medicine Tier 1 Research Chair in Venous Thromboembolism and

Thrombophilia. JIPdV received support from Pfizer for a follow-up study of the FRUIT-RCT with a 1-year investigator grant in 2014 and a half-year research grant in 2015. SMB receives a partial salary support from the Eli Lilly Canada/May Cohen Chair in Women's Health. SM holds a VIDI Innovative Grant from the Netherlands Organisation for Health Research and Development (NWO, 2012) on Thrombophilia and Reproduction. At the time he worked on this paper, ADM worked for the Cochrane Methods Bias Group—the group was supported by the Canadian Institutes of Health Research (Funding Reference Number CON-105529). All other authors declare no competing interests.

Acknowledgments

This meta-analysis was funded by the Canadian Institutes of Health Research, reference number KRS 126593. We acknowledge the Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study Group, which consists of the site investigators of the component studies including: ALIFE trial: Stef P Kaandorp, Moriëtte Goddijn, Joris A M van der Post, Barbara A Hutten, Harold R Verhoeve, Karly Hamulyák, Ben M Mol, Nienke Folkeringa, Marleen Nahuis, Dimitri N M Papatsonis, Harry R Büller, Fulco van der Veen, and the ALIFE study investigators. FRUIT trial: Mariëlle G van Pampus, William M Hague, and Johanna H Joosten, and the rest of the FRUIT investigators. HABENOX trial investigators. HAPPY trial: Piero Ruggenenti, Irene Cetin, Giorgio Pardi (deceased), Patrizia Vergani, Barbara Acaia, Fabio Facchinetti, Giovanni Battista La Sala, Maddalena Bozzo, Stefania Rampello, Luca Marozio, Olimpia Diadei, Giulia Gherardi, Sergio Carminati, Giuseppe Remuzzi, and Pier Mannuccio Mannucci, and the HAPPY study investigators. NOH trials: Céline Chauleur, Nicolas Molinari, Pierre Marès, Pascale Fabbro-Peray, Isabelle Quéré, Jean-Yves Lefrant, Bassam Haddad and Michel Dauzat from Nimes. Rey and colleagues' trial: Pascale Garneau, Michèle David, Robert Gauthier, Lyne Leduc, Nicole Michon, Francine Morin, and Susan R Kahn, and the investigators of the study by Rey and colleagues. TIPPS trial: William M Hague, John Kingdom, Susan R Kahn, Alan Karovitch, Mathew Sermer, Anne-Marie Clement, Suzette Coat, Wee Shian Chan, Joanne Said, Évelyne Rey, Susan Robinson, Rshmi Khurana, Michael J Kovacs, Susan Solymoss, Kim Hinshaw, Graeme Smith, Sarah McDonald, Jill Newstead- Angel, Anne McLeod, Meena Khandelwal, Robert M Silver, Grégoire Le Gal, Erin Keely, Karen Rosene-Montella, Mark Walker, Philip S Wells, and the TIPPS study investigators including Nancy Thomas, Jocelyne Martel, Carl Nimrod (deceased), Lucie Opatrny, Mark Blostein, Marc Carrier, Ranjeeta Mallick, Timothy Ramsay, Elisabeth Pasquier, Dean Fergusson, and Michael Paidas. Also includes the following members of the data safety monitoring board: Mary Cushman (Chair 2007–12), Peter Garner (deceased; Chair 2000–02), Richard Lee (deceased), Alan Tinmouth, and Catherine Code.

References

1 Centre for Maternal and Child Enquiries (CMACE). Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–08. The eighth report on confidential enquiries into maternal deaths in the United Kingdom. *BJOG* 2011; **118** (suppl 1): 1–203.

2 Berg CJ, Atrash HK, Koonin LM, Tucker M. Pregnancy-related mortality in the United States, 1987–1990. *Obstet Gynecol* 1996; **88:** 161–67.

3 Stillbirth Collaboration Research Network Writing Group. Causes of death among stillbirths. *JAMA* 2011; **306:** 2459–68.

4 van Rijn BB, Hoeks LB, Bots ML, Franx A, Bruinse HW. Outcomes of subsequent pregnancy after first pregnancy with early-onset preeclampsia. *Am J Obstet Gynecol* 2006; **195:** 723–28.

5 Sibai BM, Mercer B, Sarinoglu C. Severe preeclampsia in the second trimester: recurrence risk and long-term prognosis. *Am J Obstet Gynecol* 1991; **165:** 1408–12.

6 Van Oostwaard MF, Langenveld J, Schuit E, et al. Recurrence of hypertensive disorders of pregnancy: an individual patient data metaanalysis. *Am J Obstet Gynecol* 2015; **212:** 624–17.

7 Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet* 2007; **369:** 1791–98.

8 Bujold E, Roberge S, Lacasse Y, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010; **116:** 402–14.

9 Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood* 2005; **106:** 401–07.

10 Drewlo S, Levytska K, Sobel M, Baczyk D, Lye SJ, Kingdom JC. Heparin promotes soluble VEGF receptor expression in human placental villi to impair endothelial VEGF signaling. *J Thromb Haemost* 2011; **9:** 2486–97.

11 Sobel ML, Kingdom J, Drewlo S. Angiogenic response of placental villi to heparin. *Obstet Gynecol* 2011; **117:** 1375–83.

12 de Vries JIP, van Pampus MG, Hague WM, Bezemer PD, Joosten JH. Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT. *J Thromb Haemost* 2012; **10:** 64–72.

13 Gris JC, Chauleur C, Molinari N, et al. Addition of enoxaparin to aspirin for the secondary prevention of placental vascular complications in women with severe pre-eclampsia. The pilot randomised controlled NOH-PE trial. *Thromb Haemost* 2011; **106:** 1053–61.

14 Mello G, Parretti E, Fatini C, et al. Low-molecular-weight heparin lowers the recurrence rate of preeclampsia and restores the physiological vascular changes in angiotensin-converting enzyme DD women. *Hypertension* 2005; **45:** 86–91.

15 Rey E, Garneau P, David M, et al. Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women without thrombophilia: a pilot randomized controlled trial. *J Thromb Haemost* 2009; **7:** 58–64.

16 Gris JC, Chauleur C, Faillie JL, et al. Enoxaparin for the secondary prevention of placental vascular complications in women with abruptio placentae. The pilot randomised controlled NOH-AP trial. *Thromb Haemost* 2010; **104:** 771–79.

17 Martinelli I, Ruggenenti P, Cetin I, et al. Heparin in pregnant women with previous placenta-mediated pregnancy complications: a prospective, randomized, multicenter, controlled clinical trial. *Blood* 2012; **119:** 3269–75.

18 Rodger MA, Hague WM, Kingdom J, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. *Lancet* 2014; **384:** 1673–83.

19 Visser J, Ulander VM, Helmerhorst FM, et al. Thromboprophylaxis for recurrent miscarriage in women with or without thrombophilia. HABENOX: a randomised multicentre trial. *Thromb Haemost* 2011; **105:** 295–301.

20 Kaandorp SP, Goddijn M, van der Post JA, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *N Engl J Med* 2010; **362:** 1586–96.

21 Schleussner E, Kamin G, Seliger G, et al. Low-molecular-weight heparin for women with unexplained recurrent pregnancy loss: a multicenter trial with a minimization randomization scheme. *Ann Intern Med* 2015; **162:** 601–09.

22 Clark P, Walker ID, Langhorne P, et al. SPIN: the Scottish Pregnancy Intervention Study: a multicentre randomised controlled trial of low molecular weight heparin and low dose aspirin in women with recurrent miscarriage. *Blood* 2010; **115:** 4162–67.

23 Rodger MA, Carrier M, Le Gal G, et al. Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. *Blood* 2014; **123:** 822–28.

24 Rodger MA, Langlois NJ, de Vries JI, et al. Low-molecular-weight heparin for prevention of placenta-mediated pregnancy complications: protocol for a systematic review and individual patient data meta-analysis (AFFIRM). *Syst Rev* 2014; **3:** 69.

25 Giancotti A, La TR, Spagnuolo A, et al. Efficacy of three different antithrombotic regimens on pregnancy outcome in pregnant women affected by recurrent pregnancy loss. *J Matern Fetal Neonatal Med* 2012; **25:** 1191–94.

26 Salman SA, Shaaban OM, Zahran KM, Fathalla MM, Anan MA. Low molecular weight heparin (LMWH) for treatment of recurrent miscarriage negatively tested for antiphospholipid antibodies: a randomized controlled trial. *Fertil Steril* 2012; **98:** S191.

27 Laskin CA, Spitzer KA, Clark CA, et al. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. *J Rheumatol* 2009; **36:** 279–87.

28 Higgins JPT, Green SE. Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March, 2011). Chapter 8: Assessing risk of bias in included studies. www.cochrane-handbook.org (accessed May 29, 2015).

29 Rodger MA, Walker MC, Smith GN, et al. Is thrombophilia associated with placenta-mediated pregnancy complications? A prospective cohort study. *J Thromb Haemost* 2014; **12:** 469–78.

30 Lykke JA, Bare LA, Olsen J, et al. Thrombophilias and adverse pregnancy outcomes: results from the Danish National Birth Cohort. *J Thromb Haemost* 2012; **10:** 1320–25.

31 Sud S, Douketis J. The devil is in the details…or not? A primer on individual patient data meta-analysis. *Evid Based Med* 2009; **14:** 100–01.

32 Clarke MJ. Individual patient data meta-analyses. *Best Pract Res Clin Obstet Gynaecol* 2005; **19:** 47–55.

33 Unverzagt S, Prondzinsky R, Peinemann F. Single-center trials tend to provide larger treatment effects than multicenter trials: a systematic review. *J Clin Epidemiol* 2013; **66:** 1271–80.

34 Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. *Ann Intern Med* 2011; **155:** 39–51.

35 Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008; **336:** 601–05.

36 Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; **352:** 609–13.

37 Liddell HS, Pattison NS, Zanderigo A. Recurrent miscarriage--outcome after supportive care in early pregnancy. *Aust N Z J Obstet Gynaecol* 1991; **31:** 320–22.

38 Musters AM, Koot YE, van den Boogaard NM, et al. Supportive care for women with recurrent miscarriage: a survey to quantify women's preferences. *Hum Reprod* 2013; **28:** 398–405.