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Pharmacological interventions for the prevention of fetal growth restriction: a systematic review and network meta-analysis

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Pharmacological Interventions for the Prevention of Fetal Growth Restriction: A Systematic Review and Network Meta-Analysis

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The prevention of fetal growth restriction (FGR) is challenging in clinical practice. To date, no meta-analysis summarized evidence on the relative benefits and harms of pharmacological interventions for FGR prevention. We performed a systematic review and network meta-analysis (NetMA), searching PubMed, Embase, Cochrane Library, and ClinicalTrials. gov from inception until November 2019. We included clinical trials and observational studies on singleton gestating women evaluating antiplatelet, anticoagulant, or other treatments, compared between each other or with controls (placebo or no treatment), and considering the pregnancy outcome FGR (primary outcome of the NetMA). Secondary efficacy outcomes included preterm birth, placental abruption, and fetal or neonatal death. Safety outcomes included bleeding and thrombocytopenia. Network meta-analyses using a frequentist framework were conducted to derive odds ratios (ORs) and 95% confidence intervals (CIs). Of 18,780 citations, we included 30 studies on 4,326 patients. Low molecular weight heparin (LMWH), alone or associated with low-dose aspirin (LDA), appeared more efficacious than controls in preventing FGR (OR 2.00, 95% CI 1.27–3.16 and OR 2.67, 95% CI 1.21–5.89 for controls vs. LMWH and LDA + LMWH, respectively). No difference between active treatments emerged in terms of FGR prevention, but estimates for treatments other than LMWH +/- LDA were imprecise. Only the confidence in the evidence regarding LMWH vs. controls was judged as moderate, according to the Confidence in Network Meta-Analysis framework. No treatment was associated with an increased risk of bleeding, although estimates were precise enough only for LMWH. These results should inform clinicians on the benefits of active pharmacological prophylaxis for FGR prevention.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ The prevention of fetal growth restriction (FGR) is challenging in clinical practice.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This comprehensive systematic review and network meta-analysis (NetMA) aimed to summarize current evidence on the benefits and harms of different pharmacological treatments for the prevention of FGR.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ This NetMA of randomized controlled trials and observational studies represents the largest evidence on

treatments for the prevention of FGR. Based on our results, use of anticoagulant and/or antiplatelet treatments is more effective than nontreatment in preventing FGR. Use of these treatments, also during early pregnancy, did not increase the risk of bleeding, nor of thrombocytopenia or osteopenia.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Use of preventive pharmacological approaches should be considered in pregnancies at risk of FGR. Our findings should reassure both patients and clinicians on the absence of concrete safety concerns related to these prophylactic treatments.

Fetal growth restriction (FGR) is a relatively common pregnancy complication and is usually defined based on the discrepancy between actual and expected fetal ultrasound biometric measurements for a given gestational age.[1] Fetuses with FGR do not achieve the genetically predetermined growth potential as a result of maternal (e.g., undernutrition, exposure to toxins,

hypoxemic, hypovolemic, and cardiovascular conditions), fetal (chromosomal or genetic abnormalities, malformations, and infections), or placental disorders.[2] However, the majority of cases of FGR occur as a result of placental dysfunction.[3,4] The earlier and more severe forms of FGR, the higher is the risk of deterioration of the intrauterine fetal well-being, with possible short-term and long-term consequences.[5,6]

Many international scientific societies have developed guidelines for the management of FGR,[7–9] which is mainly based on a balance between the pros of improving fetal maturity by the addition of some intrauterine days-weeks, thus avoiding preterm birth, and the cons related to the intrauterine detriment, often associated with an increased risk of stillbirth. Notably, when newborns affected by FGR survive, they still present a high risk of complications in childhood, adolescence, and adulthood,[10] particularly in terms of impaired neurodevelopment[11,12] and cardiovascular and metabolic complications.[13]

Therefore, currently, it becomes imperative to switch from management to prevention of FGR. Unfortunately, to date, no clear evidence has been provided on the efficacy of pharmacological interventions to improve the placental function. Literature studies suggest that vasoactive, antiplatelet, or anticoagulant agents might play a role in the establishment of adequate placental to fetal perfusion, but no conclusive evidence exists.

A systematic review and network meta-analysis (NetMA) of existing literature evidence may provide useful information about the clinical challenge of identifying the ideal therapeutic strategy for FGR prevention. In this study, we performed a comprehensive systematic review and NetMA to summarize the evidence on the benefits and harms of different pharmacological treatments for the prevention of FGR.

METHODS
Search strategy and study selection
We performed a systematic review and NetMA. We electronically searched PubMed and Embase databases, and Cochrane Library from inception until May 6, 2019, and updated on November 15, 2019, prior to the final data analysis. The search strategies for PubMed and Embase are available in **Table S1**. Additional related studies were sought by reviewing the reference lists of relevant articles. Abstracts and conference proceedings retrieved by the search strategy were considered for inclusion, and additional data were requested to the authors. The electronic database searches were supplemented with manual searches of Clinicaltrials. gov database.

We included randomized controlled trials (RCTs) and observational cohort studies, either prospective or retrospective, written in English and performed on singleton pregnancies at high risk of FGR, defined as those with at least one of the follow: history of FGR in the previous pregnancies, history of late pregnancy loss or recurrent early pregnancy loss, hypertensive disorders, inherited (Factor V Leiden gene mutation, prothrombin gene mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency) or acquired (antiphospholipid syndrome or persistent positivity of antiphospholipid antibodies) thrombophilia.

We included studies on women treated with unfractionated heparin (UFH) or low molecular weight heparin (LMWH), low-dose aspirin (LDA), other antiplatelet agents, phosphodiesterase type 5 inhibitors, phosphodiesterase type 3 inhibitors, maternal vascular endothelial growth factor gene therapy, nanoparticles, microRNA, statins, nitric oxide donors, hydrogen sulfide, proton pump inhibitors, melatonin, creatine, N-acetylcysteine, or insulin-like growth factor 1 and 2, either as monotherapy or in association, compared with each other or vs. placebo or no treatment (defined as controls).

We excluded studies with cases of fetal genetic or chromosomal anomalies, fetal malformations, multiple pregnancies, congenital intrauterine infections, maternal history of drug or alcohol abuse, maternal uterine malformations, maternal pre-existing disorders (such as mechanic heart valves or previous major cardiovascular events) leading to the use of antithrombotic agents outside pregnancy.

The primary efficacy outcome was FGR, defined according to the definition and diagnosis provided by the authors of the studies. Only studies providing data for the primary outcome were included.

The secondary efficacy outcomes were: (i) preterm birth, defined as a birth before 37 weeks of gestation, (ii) placental abruption, and (iii) fetal or neonatal death, defined as all events related to intrauterine or neonatal death (i.e., beyond the first trimester).

The safety outcomes were: bleeding at any time throughout pregnancy and childbirth, bleeding during pregnancy, bleeding at childbirth, and thrombocytopenia. In addition, data on osteoporosis and/or bone fractures, as well as the occurrence of any adverse event were narratively summarized.

We contacted study authors to provide data for publications available only as conference abstract, or for studies with incomplete data (**Table S9**).

Three investigators (A.B., N.L., and G.C.) independently selected the studies, reviewed the main reports and supplementary material, extracted the relevant information for the included studies, and assessed the risk of bias. Discrepancies were resolved through discussion or in consultation with a fourth reviewer (L.A.).

The NetMA protocol has been published[14]; the differences between the protocol and the final article are summarized in the **Table S8**.

Quality assessment and risk of bias
The risk of bias for the eligible studies was assessed by three independent reviewers (A.B., N.L., and G.C.) using the Cochrane Collaboration risk of bias tool available in RevMan version 5.3, and the Newcastle-Ottawa Quality Assessment scale for randomized trials and observational studies, respectively. To assess the risk of reporting bias, registered details of selected clinical trials were sought in the Clinicaltrials.gov database, or in other registry platforms reported by the authors of the studies. We used contour-enhanced funnel plots for the primary outcome to investigate the presence of publication bias in pairwise meta-analyses when at least 10 available studies. We used Comparison-adjusted funnel plot in NetMAs.

Data synthesis and statistical analysis
For studies published more than once (i.e., duplicates), we included only the most informative and complete report.

All outcomes considered were dichotomous. For each efficacy and safety outcome, a NetMA was performed within a frequentist framework to estimate the odds ratios (ORs) and 95% confidence intervals (95% CIs). The Mantel–Haenszel method was used for the fixed effect models, if tests of heterogeneity were not significant. If statistical heterogeneity was observed, random effects models were used.

Analyses were conducted using the "network" and "network graphs" packages in Stata (StataCorp, version 14.0).[15]

The $I2$ statistic was used to assess the heterogeneity of pairwise meta-analyses. To evaluate the presence of inconsistency locally in the NetMA, we used the node-splitting approach.[16] To check the assumption of consistency in the entire network, we used the "design-by-treatment" model using the "network" command in STATA,[17] which accounts for different sources of inconsistency.

To limit the possible confounding related to different clinical characteristics among the study populations, a subgroup analysis was conducted for

the primary outcome, including only studies performed on women with: (i) acquired thrombophilia (overt antiphospholipid syndrome and/or with persistent isolated positivity for antiphospholipid antibodies); (ii) inherited thrombophilia; and (iii) no acquired or inherited thrombophilic conditions.

We evaluated whether treatment effects for the primary outcome was robust in subgroup analyses: (i) including only RCTs; (ii) stratifying studies according to the timing of treatment beginning (< 12, < 16, > 12, and > 16 weeks of gestation).

All analyses were performed using Stata version 14 (StataCorp).

Confidence in the evidence assessment

For the primary outcome, the confidence in the evidence produced by the synthesis was evaluated using the framework of the Confidence in Network Meta-Analysis,[15,18] and was graded as high, moderate, low, and very low. The Confidence in Network Meta-Analysis was applied only for the primary outcome, and only for comparisons between active treatments and controls.

Registration

This study is registered in PROSPERO, number CRD42019122831.

Data sharing

The full database is freely available upon request to the corresponding author.

RESULTS

Study selection

The reference flow is summarized in **Figure 1**. We identified 18,780 references through electronic searches of PubMed ($n = 7,072$), Embase ($n = 11,464$), Cochrane Library ($n = 210$), and

ClinicalTrials.gov ($n = 34$). After removing duplicates, 17,288 reference were screened. We excluded 16,974 clearly irrelevant references and retrieved 314 references for further assessment. We excluded 263 references for the reasons listed in **Figure 1**. Another 20 references were excluded after the attempt of contacting their authors failed (**Table S9**). Overall, 30 studies met the inclusion criteria (23 RCTs and 7 observational studies), for a total of 4,326 patients.

Study characteristics

The characteristics of the included studies are summarized in **Table S2**.[19–48]

The studied interventions included: LDA (16 studies; 893 patients); LMWH (13 studies; 1,378 patients); LDA + LMWH (10 studies; 578 patients); LDA + UFH (2 studies; 55 patients); LDA + dipyridamole (1 study; 121 patients); LMWH + dipyridamole (1 study; 21 patients); dipyridamole (1 study; 52 patients); and controls (14 studies with no treatment and 5 with placebo on 1,035 and 193 patients, respectively). All other interventions reported in our search strategy were not evaluated in the included studies.

The specific comparisons between treatments evaluated in the different studies are illustrated in **Figure 2a**.

Risk of bias of included studies

The assessment of the risk of bias is reported in **Table S3** and **Figure S2**. The network map for the primary outcome FGR illustrating the within-study risk of bias is reported in **Figure S3**.
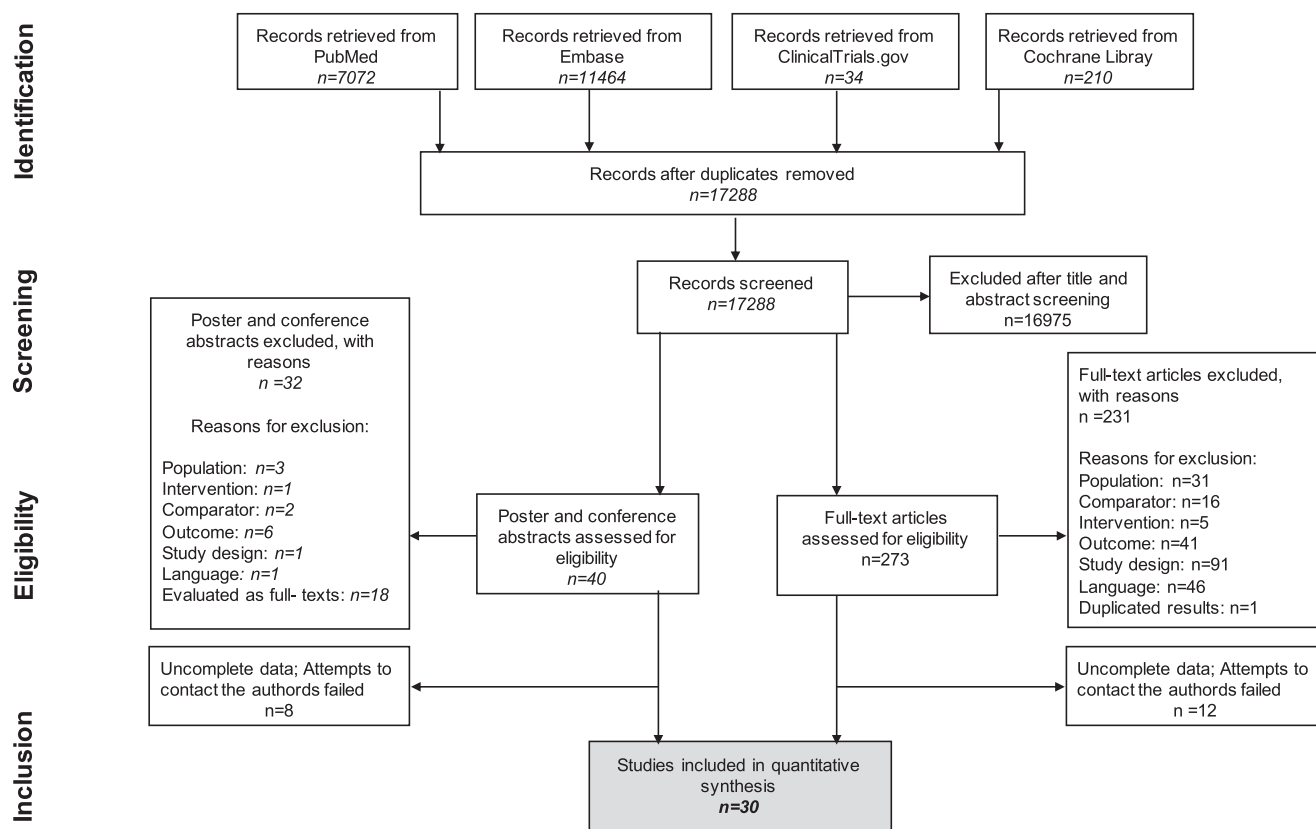

Figure 1 Flow chart.

Considering nonrandomized studies, five studies were judged at high risk of bias,[24,25,38,44,45] and two at moderate risk of bias, as they were prospective studies with comparable patients' characteristics between treatment groups and with no concerns related to exposure assessment.[29,41]

As for RCTs, four studies were judged at high-risk of bias,[23,26,31,33] as they were judged at high-risk of selection bias. Eight studies were judged at moderate risk of bias, as they presented an uncertain risk of selection bias and/or a high risk of attrition bias.[19,20,30,36,37,39,42,47] All other RCTs were judged at low risk of bias.[21,22,27,28,32,34,35,40,43,46,48]

Funnel plot for the evaluation of the risk of publication bias was constructed only for the primary outcome, only the comparison between LMWH and controls, which was based on more than 10 studies (**Figure S4**). The plot did not show a marked asymmetry; however, two studies with positive outlier values were reported. The Egger's test did not indicate a significant risk of publication bias ($P = 0.291$).

Synthesis of results

Primary outcome: Effect on FGR. Of the 4,326 patients included in these studies, 468 cases of FGR were reported. In particular, the reported events were 127 of 1,228 in the control group (10.3%), 148 of 893 in the LDA group (16.6%), 89 of 578 in the LDA + LMWH group (15.4%), 5 of 55 in the LDA + UFH group (9.1%), 17 of 121 in the LDA + dipyridamole group (14.0%), 78 of 1,378 in the LMWH group (5.7%), 4 of
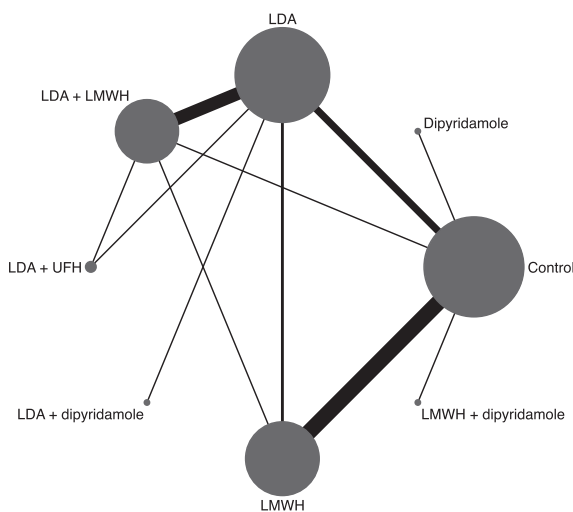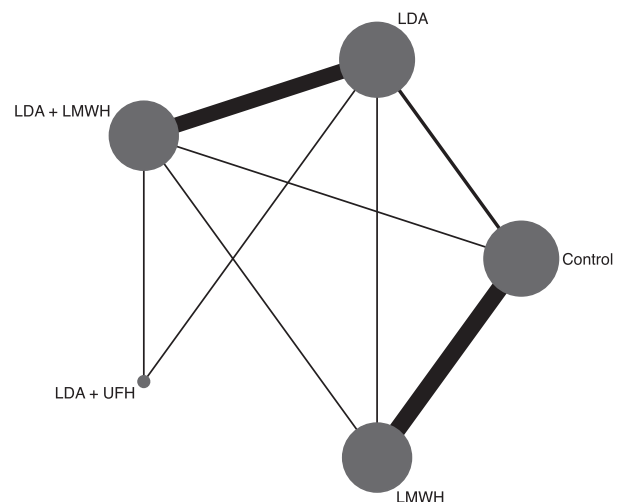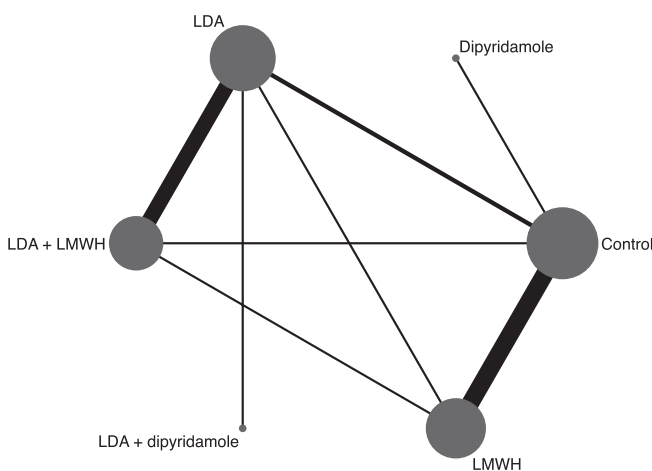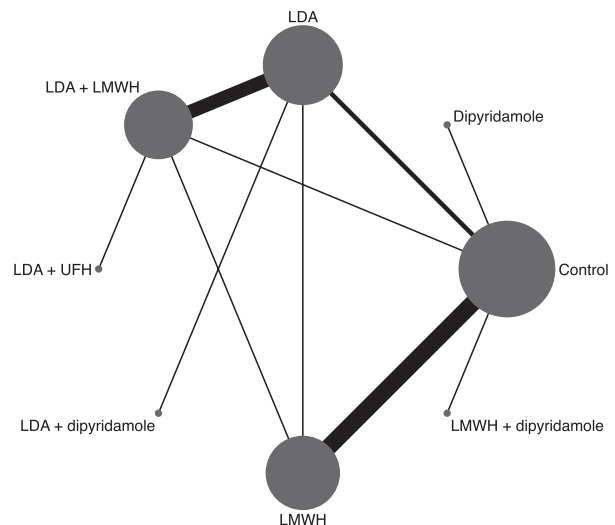
Figure 2 Network meta-analysis of eligible comparisons for the outcomes fetal growth restriction (**a**), preterm birth (**b**), placental abruption (**c**), and fetal or neonatal death (**d**). LDA, low-dose aspirin; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

52 in the dipyridamole group (7.7%), and 0 of 21 in the LMWH + dipyridamole group.

The contribution matrix for the evidence related to the primary outcome is reported in **Figure S5**.

Mixed evidence showed that treatment with LDA + LMWH, LMWH, LMWH + dipyridamole, or dipyridamole alone were associated with a significant lower risk of FGR as compared with controls, although most estimates showed poor precision. Specifically, the estimated OR of FGR was of 2.67 (95% CI 1.21–5.89) for the control group as compared with LDA + LMWH, OR 2.00 (95% CI 1.27–3.16) as compared with LMWH, OR 22.15 (95% CI 1.08–454.64) as compared with LMWH + dipyridamole, and OR 4.22 (95% CI 1.02–17.49) as compared with dipyridamole alone (**Table 1**).

These results from mixed evidence were confirmed also when limiting the analysis to the 20 studies defining FGR as a birthweight < 10th percentile for a given gestational age.[19,20,21,22,26–30,32,37–40,43–48] Specifically, the estimated OR of FGR was of 3.01 (95% CI 1.19–7.63) for the control group as compared with LDA + LMWH, OR 1.94 (95% CI 1.12–3.37) as compared with LMWH, and OR 4.22 (95% CI 1.01–17.59) as compared with dipyridamole alone (data not shown).

The effects of the different pharmacological interventions on the prevention of FGR were further analyzed stratifying the evidence according to the clinical conditions of the studies populations (namely acquired thrombophilia, inherited thrombophilia, or no thrombophilic status; **Table 1**). However, this evidence was sparse and there was little benefit in conducting mixed comparisons. When we limited the analysis to the five studies (4 RCTs, 1 nonrandomized study; 231 patients and 24 cases of FGR) conducted on women with acquired thrombophilia,[26,29,40,42,46] direct and mixed comparisons showed no difference among other interventions in terms of risk of FGR.

When we considered only the five studies on women with inherited thrombophilia (3 RCTs and 2 observational studies; 942 patients),[23,25,43,44,47] mixed comparisons showed that treatment with LDA + LMWH or with LMWH were associated with a significantly lower risk of FGR as compared with controls (OR 3.99, 95% CI 1.24–12.84) for controls vs. LDA + LMWH from mixed comparisons, OR 3.19 (95% CI 1.65–6.17) for controls vs. LMWH).

Conversely, when we limited the analysis to studies on women without acquired or inherited thrombophilia (5 studies, 3 RCTs, and 2 observational, on 860 patients, all comparing LMWH vs. controls),[20,24,32,33,41] both direct and mixed comparisons showed no significant effect of LMWH as compared with controls in preventing FGR (OR 1.27, 95% CI 0.49–3.25) for controls vs. LMWH from mixed comparisons.

Secondary outcomes

Considering the secondary outcomes, 22 studies (15 RCTs and 7 observational studies) evaluated the secondary efficacy outcome "preterm birth" (**Figure 2b**).[20–27,29,32–36,38,40,41,43–46,48] Of 3,561 patients included in these studies, 558 cases of preterm birth were reported.

Mixed comparisons showed that treatment with LMWH was associated with a significant lower risk of preterm birth as compared with controls. Specifically, untreated women had an OR of preterm birth of 1.64 (95% CI 1.02–2.64) as compared with women treated with LMWH (**Table 2**).

Eighteen studies evaluated the secondary outcome "placental abruption"[19–25,27,32–34,37–40,43,44,48] (**Figure 2c**), which occurred in 66 of 3,206 patients. Both direct and mixed evidence showed a significantly lower risk of placental abruption in women treated with LMWH as compared with controls (OR from mixed evidence 2.77, 95% CI 1.18–6.54; **Table 2**). No statistically significant difference was found from the other comparisons.

Twenty-six studies (19 RCTs and 7 observational studies) evaluated the secondary efficacy outcome "fetal or neonatal death" (**Figure 2d**).[19–25,27–29,31–41,43–46,48] Of 4,045 patients included in these studies, 127 cases of fetal or neonatal death were reported. Direct and mixed comparisons showed that treatment with LDA + LMWH was associated with a lower risk of fetal or neonatal death as compared with LDA alone (OR of 0.45, 95% CI 0.24–0.83). No statistically significant difference was found from the other comparisons (**Table 2**).

Safety outcomes. Regarding safety outcomes, 19 studies evaluated the outcome bleeding at any time throughout pregnancy, 12 bleeding during pregnancy, 11 bleeding during childbirth, and 19 studies evaluated thrombocytopenia.

The network maps for these safety outcomes are reported in **Figure S1**.

Regarding bleeding at any time, 90 events of 876 patients were reported in the control group (10.3%), 49 of 547 in the LDA group (9.0%), 44 of 405 in the LDA + LWMH group (10.9%), 3 of 55 in the LDA + UFH group (5.5%), 80 of 875 in the LMWH group (9.1%), 0 of 21 in the LMWH + dipyridamole group, and 0 of 52 in the dipyridamole group.

Table 3 summarizes the results of frequentist NetMA for the safety outcomes. We did not find a significant difference in the risk of the considered safety outcomes among active treatments, nor between active treatments and controls. However, regarding the main adverse event (bleeding), sufficiently precise estimates were obtained only for LMWH, (OR upper limit of the 95% CI of 1.58), thus, excluding a clinically relevant increase of bleeding at the observed prevalence in controls.

Of note, eight studies specifically evaluated the occurrence of osteoporosis and/or bone fractures in women treated with LMWH[22,26,28,34,38,45–47]: in all studies, no events related to this complication were reported.

All other adverse events, as well as pregnancy or neonatal complications not included in the efficacy or safety outcomes of this meta-analysis, are reported in the table of study characteristics (**Table S2**).

Confidence in the evidence

The confidence in the evidence was assessed for the primary outcome, for comparisons between each active treatment vs. controls (**Table S7**). The confidence in the evidence was judged as moderate for the comparisons of LMWH vs. controls, very low for the comparisons of LMWH + dipyridamole vs. controls, and low for all other comparisons vs. controls.

Table 1 Comparisons derived from direct and mixed evidence for the outcome fetal growth restriction

Overall (N = 30 studies)

	LDA	LDA + LMWH	LDA + UFH	LDA + dipyridamole	LMWH	LMWH + dipyridamole	Dipyridamole	Control
LDA	LDA	0.74 (0.55–1.00)	3.00 (0.29–30.84)	1.12 (0.54–2.32)	0.83 (0.36–1.91)	—	—	1.78 (0.76–4.20)
	0.67 (0.44–1.02)	LDA + LMWH	2.00 (0.17–23.25)	—	0.87 (0.22–3.43)	—	—	3.06 (0.68–13.74)
	2.17 (0.36–12.96)	3.25 (0.54–19.50)	LDA + UFH	—	—	—	—	—
	1.14 (0.40–3.30)	1.72 (0.55–5.38)	0.53 (0.07–4.22)	LDA + dipyridamole	—	—	—	—
	0.89 (0.43–1.82)	1.33 (0.61–2.93)	0.41 (0.06–2.79)	0.78 (0.21–2.79)	LMWH	—	—	**1.61 (1.16–2.24)**
	0.08 (0.00–1.79)	0.12 (0.01–2.74)	0.04 (0.00–1.33)	0.07 (0.00–1.87)	0.09 (0.00–1.92)	LMWH + dipyridamole	—	14.92 (0.81–273.96)
	0.42 (0.09–2.07)	0.63 (0.12–3.23)	0.19 (0.02–2.12)	0.37 (0.05–2.49)	0.48 (0.11–2.12)	5.25 (0.19–148.21)	Dipyridamole	**3.38 (1.03–11.07)**
	1.78 (0.87–3.63)	**2.67 (1.21–5.89)**	0.82 (0.12–5.59)	1.56 (0.43–5.58)	**2.00 (1.27–3.16)**	**22.15 (1.08–454.64)**	**4.22 (1.02–17.49)**	Control

Acquired thrombophilia (N = 5 studies)

	LDA	LDA + LMWH	LDA + UFH	Control
LDA	LDA	0.63 (0.22–1.85)	3.00 (0.29–30.84)	4.06 (0.15–112.40)
	0.64 (0.23–1.79)	LDA + LMWH	2.00 (0.17–23.25)	—
	2.13 (0.37–12.42)	3.32 (0.56–19.64)	LDA + UFH	—
	4.60 (0.16–128.54)	7.17 (0.22–233.88)	2.16 (0.05–93.30)	Control

Inherited thrombophilia (N = 5 studies)

	LDA	LDA + LMWH	LMWH	Control
LDA	LDA	0.66 (0.34–1.29)	0.83 (0.36–1.89)	—
	0.62 (0.32–1.21)	LDA + LMWH	0.87 (0.22–3.43)	—
	0.78 (0.34–1.76)	1.25 (0.48–3.28)	LMWH	**2.89 (1.51–5.51)**
	2.48 (0.87–7.08)	**3.99 (1.24–12.84)**	**3.19 (1.65–6.17)**	Control

No thrombophilic status (N = 5 studies)

	LMWH	Control
LMWH	LMWH	1.07 (0.66–1.72)
	1.27 (0.49–3.25)	Control

In the white area (direct evidence), odds ratios (ORs) higher than 1 favor the row-defining treatment. In the grey area (mixed evidence), ORs higher than 1 favor the column-defining treatment.
No evidence of heterogeneity of inconsistency was found.
LDA, low-dose aspirin; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

Table 2 Comparisons derived from direct and mixed evidence for the outcome preterm birth

Preterm birth (N = 22 studies)

LDA	0.84 (0.64–1.11)	3.00 (0.29–20.84)	0.34 (0.09–1.30)	1.76 (0.55–5.62)
0.77 (0.46–1.30)	**LDA + LMWH**	0.67 (0.10–4.28)	0.82 (0.18–3.83)	3.94 (0.70–22.15)
1.09 (0.20–6.00)	1.41 (0.26–7.66)	**LDA + UFH**	–	–
0.82 (0.26–2.57)	1.06 (0.32–3.46)	0.75 (0.10–5.73)	**LMWH**	1.37 (0.93–2.02)[a]
1.34 (0.43–4.18)	1.74 (0.53–5.64)	1.24 (0.16–9.37)	**1.64 (1.02–2.64)**	**Control**

Placental abruption (N = 18 studies)

LDA	0.85 (0.41–1.76)	0.53 (0.13–2.16)	0.57 (0.05–6.40)	–	2.94 (0.17–49.74)
0.89 (0.42–1.89)	**LDA + LMWH**	–	3.28 (0.13–82.11)	–	3.91 (0.15–102.26)
0.52 (0.13–2.11)	0.58 (0.12–2.89)	**LDA + dipyridamole**	–	–	–
0.87 (0.20–3.74)	0.99 (0.20–4.77)	1.69 (0.22–12.80)	**LMWH**	–	**3.07 (1.31–7.20)**
0.19 (0.01–4.97)	0.22 (0.01–5.93)	0.37 (0.01–12.86)	0.22 (0.01–4.59)	**Dipyridamole**	11.44 (0.62–212.18)
2.42 (0.57–10.28)	2.73 (0.57–13.09)	4.68 (0.62–35.26)	**2.77 (1.18–6.54)**	12.69 (0.68–235.84)	**Control**

Fetal or neonatal death (N = 26 studies)

LDA	**0.46 (0.25–0.84)**	–	2.12 (0.19–23.63)	0.38 (0.02–9.43)	–		0.96 (0.04–24.73)
0.45 (0.24–0.83)	**LDA + LMWH**	3.00 (0.12–76.58)	–	No events	–	–	No events
1.40 (0.05–37.70)	3.10 (0.12–79.22)	**LDA + UFH**	–	–	–	–	–
2.13 (0.19–23.85)	4.75 (0.39–57.17)	1.53 (0.03–91.02)	**LDA + dipyridamole**	–	–	–	–
0.58 (0.10–3.42)	1.29 (0.20–8.16)	0.42 (0.01–17.31)	0.27 (0.01–5.44)	**LMWH**		–	1.31 (0.80–2.16)
0.04 (0.00–1.31)	0.10 (0.00–3.01)	0.03 (0.00–3.51)	0.02 (0.00–1.32)	0.07 (0.00–1.46)	**LMWH + dipyridamole**	–	13.16 (0.71–244.24)
0.06 (0.00–1.88)	0.14 (0.00–4.34)	0.04 (0.00–5.06)	0.03 (0.00–1.90)	0.11 (0.01–2.10)	1.45 (0.02–91.10)	**Dipyridamole**	11.44 (0.62–212.18)
0.79 (0.14–4.54)	1.77 (0.29–10.85)	0.57 (0.01–23.36)	0.37 (0.02–7.31)	1.37 (0.81–2.30)	18.43 (0.98– 345.61)	12.69 (0.68–235.84)	**Control**

In the white areas (direct evidence), odds ratios (ORs) higher than 1 favor the row-defining treatment. In the grey areas (mixed evidence), ORs higher than 1 favor the column-defining treatment.

LDA, low-dose aspirin; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

No evidence of heterogeneity of inconsistency was found for the outcomes "placental abruption" and "fetal or neonatal death."

[a]Evidence of statistically significant heterogeneity was found for the comparison between LMWH and Control for the outcome "preterm birth" (χ^2 = 17.07, P = 0.048; I-squared = 47.3%). Estimate is calculated using random effect models.

The certainty of evidence for all comparisons was downgraded to −1 point for the risk of bias; in case of major concerns related to the within-study risk of bias, the certainty of evidence was downgraded to −2. In addition, the certainty of evidence was downgraded to −1 point in case of major concerns for the items related to indirectness, imprecision, or heterogeneity. The certainty of evidence was upgraded to + 1 point in case of low concerns related to reporting bias.

Investigation of heterogeneity

No evidence of statistically significant overall or loop-specific inconsistency, or heterogeneity in pairwise meta-analyses, was found for the primary efficacy outcome, for "placental abruption" and "fetal or neonatal death." Conversely, for the secondary efficacy outcome "preterm birth," evidence of statistically significant heterogeneity was found for the direct comparison between LMWH and controls (χ^2 = 17.07, P = 0.048; I-squared = 47.3%).

Subgroup and sensitivity analysis

The robustness of the results for the primary outcome was assessed in two subgroup analyses.

In a first one (**Table S4**), we limited the analysis to the 23 RTCs, thus including a total of 3,422 patients.[19–23,26–28,30–37,39,40,42,43,46–48] Mixed comparisons from this subgroup of studies confirmed that LMWH + dipyridamole and dipyridamole alone were associated with a lower risk of FGR as compared with controls.

In a second subgroup analysis (**Table S5**), we stratified studies according to the timing of intervention. When we limited the analysis to the 22 studies with interventions started < 12 weeks of gestation,[20–29,32–35,37,40,41,43,45–48] including a total of 3,337 patients, results from both direct and mixed comparisons confirmed that LMWH was associated with a significantly lower risk of FGR as compared with controls. These results were confirmed also when modifying the timing cutoff, including the 24

Table 3 Comparisons derived from direct and mixed evidence for the safety outcomes bleeding (any time), bleeding during pregnancy, bleeding during childbirth and thrombocytopenia

Bleeding any time (N = 19 studies)

LDA	1.21 (0.75–1.95)	3.00 (0.29–30.84)	No events	–	–	1.21 (0.41–3.56)
1.26 (0.76–2.10)	**LDA+ LMWH**	No events	–	–	–	No events
2.56 (0.36–19.30)	2.02 (0.26–15.75)	**LDA + UFH**	–	–	–	–
1.25 (0.42–3.71)	0.99 (0.30–3.27)	0.49 (0.05–4.85)	**LMWH**	–	–	1.04 (0.75–1.45)
1.50 (0.02–89.98)	1.18 (0.02–73.28)	0.59 (0.01–56.40)	1.20 (0.02–64.58)	**LMWH+ Dipyridamole**	–	No events
1.26 (0.02–74.24)	1.00 (0.20–60.48)	0.49 (0.01–46.65)	1.01 (0.02–53.26)	0.84 (0.00–227.12)	**Dipyridamole**	No events
1.31 (0.47–3.64)	1.04 (0.34–3.21)	0.51 (0.05–4.94)	1.05 (0.70–1.58)	0.88 (0.02–46.40)	1.04 (0.02–53.69)	**Control**

Bleeding during pregnancy (N = 12 studies)

LDA	**No events**	3.00 (0.29–30.84)	–	1.21 (0.41–3.56)
0.95 (0.11–8.35)	**LDA + LMWH**	No events	–	No events
3.27 (0.32–33.84)	3.44 (0.14–83.58)	**LDA + UFH**	–	–
1.42 (0.47–4.30)	1.49 (0.14–15.63)	0.43 (0.03–5.75)	**LMWH**	0.93 (0.64–1.35)
1.32 (0.46–3.74)	1.38 (0.14–14.08)	0.40 (0.03–5.19)	0.93 (0.64–1.35)	**Control**

Bleeding during childbirth (N = 12 studies)

LDA	1.09 (0.66–1.79)	No events	–			
1.14 (0.68–1.91)	**LDA+ LMWH**	–	–			No events
1.00 (0.02–52.36)	0.88 (0.02–47.59)	**LDA+UFH**	–	–	–	–
1.94 (0.06–67.36)	1.70 (0.05–59.21)	1.94 (0.01–394.37)	**LMWH**	–	–	1.10 (0.47–2.60)
2.36 (0.01–450.34)	2.07 (0.01–395.81)	2.36 (0.001693.46)	1.22 (0.02–70.01)	**LMWH+ Dipyridamole**	–	No events
1.99 (0.01–373.48)	1.75 (0.01–328.26)	1.99 (0.00–1409.48)	1.03 (0.02–57.75)	0.84 (0.00–225.35)	**Dipyridamole**	No events
2.07 (0.07–65.02)	1.82 (0.06–57.15)	2.07 (0.01–393.98)	1.07 (0.46–2.49)	0.88 (0.02–46.15)	1.04 (0.02–53.40)	**Control**

Thrombocytopenia (N = 18 studies)

LDA	**0.50 (0.09–2.80)**	No events	No events	No events
0.70 (0.23–2.19)	**LDA + LMWH**	No events	–	No events
0.84 (0.05–14.53)	1.19 (0.07–20.72)	**LDA + UFH**	–	–
1.47 (0.14–15.14)	2.10 (0.17–25.59)	1.76 (0.05–67.84)	**LMWH**	0.36 (0.10–1.25)
1.08 (0.12–9.82)	1.54 (0.14–16.58)	1.29 (0.04–45.87)	0.73 (0.22–2.41)	**Control**

LDA, low-dose aspirin; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

studies with interventions started < 16 weeks of gestation (3,747 patients).[20–30,32–35,37,40,41,43–48] When we limited the analyses to the 4 studies with interventions started beyond 12 or 16 weeks of gestation[19,31,36,39] (476 patients), results from both direct and mixed comparisons showed that dipyridamole was associated with a significantly lower risk of FGR as compared with controls. In

addition, mixed comparison (but not direct ones) showed that also LMWH + dipyridamole was associated with a significant lower risk of FGR as compared with controls.

To assess the robustness of our results regarding the safety outcome "bleeding at any time," we limited these analyses to the 15 studies with interventions started within 12 weeks of gestation

(Table S6). We confirmed no significant difference in the risk of bleeding at any time among active treatments, nor between active treatments and controls.

DISCUSSION

This systematic review and NetMA is based on 30 studies on 4,326 pregnant women treated with 7 different pharmacological treatments (LDA, LMWH, LDA + LMWH, LDA + UFH, LDA + dipyridamole, LMWH + dipyridamole, and dipyridamole) or with placebo or no treatment, for the prevention of FGR.

To date, this represents the largest synthesis of evidence on treatments for the prevention of FGR, obtained through exhaustive search for published and unpublished information and NetMA of the extracted estimates.

Overall, we found that treatment with LDA + LMWH, LMWH, LMWH + dipyridamole, and dipyridamole were all significantly more efficacious than controls in preventing FGR. However, estimates were largely unprecise, particularly for LMWH + dipyridamole and dipyridamole alone, and the confidence in the evidence regarding these two interventions was judged as very low. Conversely, the effect observed for LMWH was more precise, and the confidence in the evidence regarding this intervention was judged as moderate. Particularly, the estimates from the NetMA suggested that treatment with LMWH can reduce the occurrence of FGR, from 10.3% (i.e., the occurrence of FGR observed in the control group) to 5.2% (3.3–8.1%), whereas treatment with LDA + LMWH can reduce its occurrence to 3.9% (1.7–8.5%).

As timing of treatment beginning is known to be a key factor in obstetric prevention, we performed a subgroup analysis including only studies with interventions started early during pregnancy. Our assessment revealed that only LMWH significantly prevented FGR as compared with controls, when initiated early during pregnancy.

When we further stratified studies according to the patients' thrombophilic status, we confirmed a possible role of LMWH, alone or in association with LDA, in women with inherited thrombophilia, but not in women with acquired thrombophilia. In women without specific thrombophilic factors, only treatment with LMWH had been evaluated, and no significant benefit was observed in terms of FGR prevention as compared with controls. It is worth specifying that these treatment effect estimates from subgroup analysis presented high imprecision, also due to the small sample size included in these subgroup analyses.

Of major note, our study provided reassuring results on the safety profile of all pharmacological interventions. Indeed, we did not find a significant increase in the risk of bleeding for all the considered treatments. Specifically, the most precise estimates regarding the risk of bleeding were available for LMWH. Based on our estimates and considering that the occurrence of bleeding events in the control group was of 10.3%, occurrence of bleeding would be of 10.8% (7.2–16.3%) in patients treated with LMWH.

Moreover, our results indicated no increased risk of thrombocytopenic or osteoporotic complications in women treated with these interventions, particularly with LMWH.

Our study failed to identify a specific role of the considered pharmacological interventions for the prevention of preterm birth and/

or fetal or neonatal mortality. However, criteria for the inclusion of the studies in this NetMA were based on the primary outcome (i.e., FGR) and did not consider these secondary outcomes; thus, key studies evaluating the role of anticoagulant and/or antiplatelet treatments for the prevention of preterm birth and/or fetal or neonatal mortality (but not of FGR) might be missing. In addition, as this is not a meta-analysis of individual participant data, we could not define the contribution of FGR on the occurrence of preterm birth and/or mortality. Moreover, the analysis of preterm birth included all cases of birth occurring < 37 weeks of gestation reported in the studies, irrespectively of whether they were spontaneous or elective, as the 2 types of events could not be clearly distinguished.

Our review has some other limitations that deserve discussion. First, the high heterogeneity in terms of clinical characteristics among patients in the included studies might have affected the transitivity assumption on which the NetMA approach is based. In order to control for this heterogeneity, we excluded studies with fetuses with chromosomal abnormalities or malformations, as these are known to be a major risk factor for FGR,[49] and we performed stratified analysis according to the thrombophilic status. However, the presence of residual heterogeneity cannot be excluded.

Second, the definition of the outcomes FGR and bleeding was not defined *a priori*, and definitions used by authors of the included studies were accepted. This choice was based on the fact the definition of FGR is widely debated and is undergoing a significant revision by international societies. However, a sensitivity analysis considering only FGR cases defined as a birthweight < 10th percentile confirmed the results from the primary analysis of our NetMA.

Third, the therapeutic approach significantly varied among studies, particularly in terms of treatment dosages and length of treatments. We considered timing of intervention as a key factor for FGR prevention, and performed subgroup analyses. However, the possible influence of treatment dosages on their efficacy was not evaluated. Particularly, we found that LDA dosage significantly varied among the included studies (from 75 to 150 mg/day). This variability might have accounted for the lack of a specific benefic effect of LDA alone in preventing FGR and deserves future investigations. In addition, evidence on some interventions (such as dipyridamole) mainly came from old studies, as the use of this treatment in routine clinical practice is becoming uncommon.

Fourth, the inclusion of nonrandomized evidence might have accounted for additional heterogeneity. However, observational studies represent a relevant source in pharmacovigilance, and their inclusion in this NetMA should guarantee more complete data on safety outcomes.

Fifth, most comparisons in this NetMA were based on a low number of studies directly comparing the pharmacological interventions. This poses major concerns of the certainty of our evidence.

Notwithstanding these limitations, this NetMA represents the most comprehensive evidence currently available on pharmacological interventions for FGR prevention.

Based on our results, use of anticoagulant and/or antiplatelet treatments is more effective than nontreatment in preventing

FGR. Particularly, LMWH, alone or in association with LDA, seemed to effectively prevent FGR in women with inherited thrombophilia, whereas the benefit of prophylactic anticoagulant treatment in women without specific thrombophilic factors is unclear. Furthermore, our findings should reassure both patients and clinicians on the absence of concrete safety concerns related to these treatments. However, all statements comparing the merits of pharmacological interventions for the prevention of FGR should be tempered by the potential limitations of the methodology, the complexity, and heterogeneity of the populations, particularly in terms of clinical conditions. Finally, our analysis was not able to provide information on the relative effects of one active treatment compared with another, and no superior treatment for FGR prevention was identified. Thus, new high-quality and pragmatic trials comparing different active prophylactic treatments for FGR prevention are advocated, to help future clinical decision making.

SUPPORTING INFORMATION
Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

CONFLICT OF INTEREST
The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
A.B. and L.A. wrote the manuscript. A.B., L.A., G.E., M.L.U., C.R., and A.V. designed the research. A.B., L.A., N.L., and G.C. performed the research. A.B. and G.V. analyzed the data.

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