CHEST Online Data Supplement

VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Table S1—*[3.0.1] Systematic Reviews Examining Fetal Safety of Maternal Therapy With Oral Anticoagulants or Aspirin (Methodologic Quality)*

Study/Year	Intervention	Inclusive Literature Search	Duplicate Study Selection and Data Extraction	List of Studies (Included and Excluded) Provided	Characteristics of Included Studies Provided	Assessment of Quality of Included Studies	Appropriate Methods Used To Combine Study Findings	Assessment of Likelihood of Publication Bias
Chan et al[1]/2000	Studies between 1966 and 1997 examining the use of VKAs and UFH or no anticoagulation in pregnant women with mechanical heart valves	Yes	No	No	No	No	Yes	No
Hassouna and Allam[2]/2010	Studies between 2000 and 2009 examining the use of VKAs and UFH or no anticoagulation in pregnant women with mechanical heart valves	No	No	No	No	No	Yes	No
Askie et al[3]/2007	Randomized trials (n = 31) comparing antiplatelet agents (low-dose aspirin or dypyridamole) with either placebo or no antiplatelet agent in pregnant women (n = 32,217) for primary prevention of preeclampsia. Aspirin given alone in 27 trials (n = 31,678; 98% of women). Meta-analysis of individual patient data	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kozer et al[4]/2002	Controlled studies (n = 2 case controlled studies, n = 5 cohort studies, n = 1 randomized control study) examining the risk of maternal exposure to aspirin during the first trimester of pregnancy and reported on congenital malformations	Yes	Yes	Included studies only	Yes	No	Yes	No
Kozer et al[5]/2003	Randomized controlled studies (n = 38) examining maternal exposure to aspirin during pregnancy and reporting on seven prespecified outcomes	Yes	Yes	Included studies only	Yes	No	Yes	No

UFH = unfractionated heparin; VKA = vitamin K antagonist.

Table S2—*[Section 3.0.1] Systematic Reviews Examining Fetal Safety of Maternal Therapy With Oral Anticoagulants and Aspirin (Results)*

Anticoagulation Regimen	Spontaneous Abortions	Total Fetal Wastage[a]	Congenital Fetal Anomalies	Fetal or Neonatal Hemorrhage
VKAs throughout with or without heparin at term				
Chan et al[1]/2000	196/792 (24.7)	266/792 (33.6)	35/549 (6.4)	
Hassouna and Allam[2]/2010	194/833 (23.3)	274/833 (32.9)	21/559 (3.7)	Not reported
Heparin in first trimester, then VKAs throughout with or without heparin near term				
Heparin use at/before 6 wk				
Chan et al[1]/2000	19/129 (14.7)	21/129 (16.3)	0/108 (0.0)	Not reported
Heparin use after 6 wk				
Chan et al[1]/2000	19/56 (33.9)	20/56 (35.7)	4/36 (11.1)	Not reported
Heparin use at unknown time in first trimester				
Chan et al[1]/2000	19/45 (42.2)	20/45 (44.4)	2/30 (6.7)	Not reported
Hassouna and Allam[2]/2010	42/322 (13.0)	64/322 (19.9)	1/258 (0.4)	Not reported
Adjusted-dose heparin				
Chan et al[1]/2000	4/16 (25.0)	7/16 (43.8)	0/12 (0.0)	Not reported
Low-dose heparin				
Chan et al[1]/2000	1/5 (20.0)	2/5 (40.0)	0/5 (0.0)	Not reported
Regimen not specified				
Hassouna and Allam[2]/2010	31/157 (21.6)	61/157 (38.8)	0/96 (0.0)	Not reported
No anticoagulation				
Nothing				
Chan et al[1]/2000	2/35 (5.7)	7/35 (20.0)	2/33 (6.1)	Not reported
Antiplatelet agent				
Chan et al[1]/2000	8/67 (11.9)	13/67 (19.4)	1/59 (1.7)	Not reported
Nothing or antiplatelet agent				
Hassouna and Allam[2]/2010	2/31 (6.4)	4/31 (12.9)	0/27 (0.0)	Not reported

Data are presented as n/N (%). See Table S1 legend for expansion of abbreviation.

[a]Wastage due to abortions, stillbirths, and neonatal deaths.

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Table S3—*[Section 3.0.1] Systematic Reviews of the Effect of Maternal Aspirin Use on Antithrombotic Therapy on Fetal Outcomes (Clinical Description and Results)*

Reference	Intervention	Neonatal Hemorrhage	Pregnancy Loss	Congenital Malformation	Developmental Delay	Small for Gestational Age
Askie et al[3]/2007	Maternal aspirin (98%) and dypyridamole vs placebo or no antiplatelet agent	Antiplatelet: 287/14,583; control: 308/14,563; RR 0.93 (95% CI, 0.80-1.09)	Fetal/neonatal death antiplatelet: 484/15,412; control: 111/15,523; RR 0.90 (95% CI, 0.83-0.98)	Not reported	Not reported	Antiplatelet: 568/10,772; Control: 624/10,654; RR 0.90 (95% CI, 0.81-1.01)
Kozer et al[4]/2002	Maternal aspirin use during the first trimester vs maternal use of other drugs or no other drugs	Not reported	Not reported	Overall: aspirin, 888/15,138; control, 1,935/49,890; OR 1.33 (95% CI, 0.94-1.89) Congenital heart defects: aspirin, 580/17,197; control, 2,406/44,774; OR 1.03 (95% CI, 0.94-1.13) Gastroschisis: aspirin, 52/261 control, 523/2,449 OR 2.37 (95% CI, 1.44-3.88)	Not reported	Not reported
Kozer et al[5]/2003	Maternal aspirin use during pregnancy vs placebo or no aspirin	Aspirin: 238/13,003; control: 231/13,055; RR 1.03 (95% CI, 0.86-1.25)	Miscarriage (exposure in first or second trimester): aspirin, 111/7,615; control, 122/7,615; RR 0.92 (95% CI, 0.71-1.19) Miscarriage (exposure in the first trimester): aspirin, 13/53; control, 10/53; RR 1.3 (95% CI, 0.63-2.69) Perinatal mortality: aspirin, 406/14,130; control, 441/14,078; RR 0.92 (95% CI, 0.81-1.05)	Not reported	Not reported	Aspirin: 417/3,705; control: 418/3,608; RR 0.96 (95% CI, 0.87-1.07)

RR = risk ratio.

Table S4—*[Section 4.0.1, 4.0.5] Prospective Studies of the Effect of Maternal Antithrombotic Therapy on Breast-fed Infants (Methodologic Quality)*

Reference	Intervention	Study Design	Randomization Concealed	Blinding	Lost to Follow-up	Analysis	Comments
Orme et al[6]/1977	Warfarin exposure during breast-feeding	Case series	NA	Patients: CN Caregivers: CN Data collectors: CN Adjudicators: CN Data analysts: CN	0/7	ITT	Limited by small sample size
McKenna et al[7]/1983	Warfarin exposure during breast-feeding	Case series	NA	Patients: CN Caregivers: CN Data collectors: CN Adjudicators: CN Data analysts: CN	0/2	ITT	Limited by small sample size
Houwert-de Jong et al[8]/1981	Acenocoumarol exposure during breast-feeding	Case series	NA	Patients: CN Caregivers: CN Data collectors: CN Adjudicators: CN Data analysts: CN	0/20	ITT	Limited by small sample size
Fondevila et al[9]/1989	Acenocoumarol exposure during breast-feeding	Case series	NA	Patients: CN Caregivers: CN Data collectors: CN Adjudicators: CN Data analysts: CN	0/7	ITT	Limited by small sample size; two mothers had two infants included
Richter et al[10]/2001	LMWH exposure during breast-feeding (maternal-dose dalteparin 2,500 International Units SC)	Case series	NA	Patients: CN Caregivers: CN Data collectors: CN Adjudicators: CN Data analysts: CN	0/15	ITT	Limited by small sample size
Ito et al[11]/1993	Low-dose aspirin exposure during breast-feeding	Subgroup of prospective cohort	NA	Patients: CN Caregivers: CN Data collectors: CN Adjudicators: CN Data analysts: CN	0/15	ITT	Limited by small samples size; effect of aspirin on platelet function not assessed

CN = certain no; ITT = intention to treat; LMWH = low-molecular-weight heparin; NA = not applicable; SC = subcutaneous.

Table S5—*[Section 4.0.1, 4.0.5] Prospective Studies of the Effect of Maternal Antithrombotic Therapy on Breast-fed Infants (Clinical Description and Results)*

Reference	Interventions	Number Patients Analyzed	Length of Follow-up Postdelivery	Infant Hemorrhage	Presence in Breast Milk (%)	Effect in Infant Blood	Comments
Orme et al[6]/1977	Warfarin exposure during breast-feeding	Breast-fed infants, 7/7	Up to 10 d	0/7	Warfarin, 0/7	Warfarin, 0/7	Warfarin levels measured by chromatography (lower limit of detection, 0.08 μmol/L)
McKenna et al[7]/1983	Warfarin exposure during breast-feeding	Breast-fed infants, 2/2	First: 56 d	0/2	Warfarin, 0/2	Elevated PT, 0 /2	Presence of warfarin in breast milk detected by spectrophotometry
			Second: 130 d				
Houwert-de Jong et al[8]/1981	Acenocoumarol exposure during breast-feeding	Breast-fed infants, 7/7	Not stated	Not reported	Acenocoumarol, 0/20	Elevated thrombotest compared with normal range for age, 0/20	Presence of acenocoumarol in breast milk detected by high-performance liquid chromatography (limit of 15 ng/mL)
Fondevila et al[9]/1989	Acenocoumarol exposure during breast-feeding	Breast-fed infants, 7/7 (n = 4 mothers)	Not stated	No predisposition to perinatal hemorrhaging complications	Not reported	Mean INR, % PT, % factor II, % factor VII-X not different from control infants	NA
Richter et al[10]/2001	LMWH exposure during breast-feeding (maternal-dose dalteparin 2,500 International Units SC)	Breast-fed infants, 15/15	Up to 8 d	Not reported	Detectable anti-Xa LMWH levels, 11/15 (range, 0.006-0.037 International Units/mL)	Not reported	Therapeutic anti-Xa LMWH level, 0.5-1.5 International Units/mL 4-6 h postinjection
Ito et al[11]/1993	Low-dose aspirin exposure during breast-feeding	Breast-fed infants, 15/15	Not reported	Not reported	Not reported	Not reported	0/15 with diarrhea, drowsiness, or irritability

INR = international normalized ratio; PT = prothrombin time. See Table S4 legend for expansion of other abbreviations.

Table S6—*[Section 5.1.1, 5.1.2] Risk of Thromboembolism in Patients Undergoing Assisted Reproductive Technology*

Study/Year	Type of Study	Participants/ Intervention	Follow-up	Risk of Thromboembolism	Strengths/Limitations
Mára et al[12]/2004	Retrospective cohort	2,748 IVF cycles	IVF cycle and pregnancy	Overall: 3/2,748 (0.1%; 95% CI, 0%-0.3%); all internal jugular DVT In women with severe ovarian hyperstimulation: 2/49 (4.1%; 95% CI, 1.1%-13.7%)	Strengths: Precision Directness Weaknesses: Single center
Aurousseau et al[13]/1995	Retrospective cohort	1,102 IVF procedures; no cases of ovarian hyperstimulation	Not stated	Overall: 3/1,102 (0.3%; 95% CI, 0.1%-0.8%); two arterial events and one PE	Strengths: Precision Directness Weaknesses: Single center Duration of follow-up, methods of investigation, diagnostic testing strategies not described
Delvigne et al[12]/1993	Multicenter retrospective cohort	128 women with ovarian hyperstimulation (cases)	Not stated	In women with ovarian hyperstimulation: 1/128 (0.8%; 95% CI, 0.1%-4.3%); cerebral thrombosis	Strengths: Multicenter Directness Weaknesses: Imprecision Unclear whether cases were consecutive Duration of follow-up, methods of investigation, diagnostic testing strategies not described 17 patients received LMWH
Morris et al[14]/1995	Prospective cohort	13 women with severe ovarian hyperstimulation	During hospitalization for treatment of severe ovarian hyperstimulation	In women with severe ovarian hyperstimulation: 0/13 (0%; 95% CI, 0%-22.8%)	Strengths: Directness Weaknesses: Imprecision Short follow-up

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Table S6—*Continued*

Study/Year	Type of Study	Participants/ Intervention	Follow-up	Risk of Thromboembolism	Strengths/Limitations
Bergh and Lundkvist[15]/1992	Survey of 12 fertility clinics	10,125 IVF cycles with 7,331 embryo transfers	Varied from clinic to clinic (range, 1-9 y)	Overall: 1/10,125 (0.01%; 95% CI, 0%-0.1%); foot thrombosis	Strengths: Multicenter Precision Directness Weaknesses: Retrospective review Diagnostic criteria and investigative protocols not specified
Jacobsen et al[16]/2008	Case-control study with cases from Norwegian Patient Register and controls from women who gave birth at a university hospital	268 cases diagnosed with VTE during pregnancy; 1,229 controls	Pregnancy and first 3 mo postpartum	Antepartum: singleton (adjusted OR, 4.3; 95% CI, 2.0-9.4); twins (adjusted OR, 6.6; 95% CI, 2.1-21.0) Postpartum: singleton (adjusted OR, 2.6; 95% CI, 0.8-8.5); twins (adjusted OR, 0.6; 95% CI, 0.1-7.6)	Strengths: Validated case diagnosis and comorbidities Collected data on potential confounders and potential risk factors Weaknesses: Controls from single center

IVF = in vitro fertilization; PE = pulmonary embolism. See Table S4 for expansion of other abbreviation.

Table S7—*[Section 5.1.1, 5.1.2] Risk of Bleeding in Patients Undergoing Transvaginal Oocyte Retrieval*

Study/Year	Type of Study	Participants/ Intervention	Follow-up	Risk of Bleeding	Strengths/Limitations and Comments
Bergh and Lundkvist[15]/1992	Survey of 12 fertility centers	10,125 retrievals	Varied from clinic to clinic (1-9 y)	Major bleeding: 2/10,125 (0.02%; 95% CI, 0%-0.1%); intraabdominal bleeding requiring laparotomy Vaginal bleeding: 33/10,125 (0.3%; 95% CI, 0.2%-0.5%)	Strengths: Multicenter Precision Directness Weaknesses: Retrospective definitions and methods of evaluating outcomes not specified
Ragni et al[17]/2009	Prospective cohort	150 consecutive retrievals	72 h	Major bleeding: 0/150 (0%; 95% CI, 0%-2.4%) Median blood loss (interquartile range): 72 (− 8 to 162 mL)	Strengths: Precision Directness Methods for detecting blood loss clearly described
Bennett et al[18]/1993	Prospective cohort	2,670 consecutive retrievals	Not stated	Major bleeding: 1/2,670 (0.04%; 95% CI, 0%-0.2%); intraabdominal bleeding with hypovolemic shock necessitating emergency laparotomy (1 L hemoperitoneum) Abdominal bleeding (nonmajor): 1/2,670 (0.04%; 95% CI, 0%-0.2%); trivial bleeding with 70 mL blood aspirated from the abdominal cavity Vaginal bleeding: 229/2,670 (8.6%; 95% CI, 7.6%-9.7%) >100 mL, 22/2,670 (0.8%; 95% CI, 0.5%-1.2%) Requiring local compression, 28/2,670 (1.0%; 95% CI, 0.7%-1.5%)	Strengths: Precision Directness Prospective Weaknesses: Follow-up not described Methods for assessment of blood loss unclear
Dicker et al[19]/1993	Retrospective	3,656 retrievals	Not stated	Major bleeding: 3/3,656 (0.08%; 95% CI, 0%-0.2%); all intraabdominal; laparotomy and 4 units of blood required in one patient; drainage and hemostasis achieved laparoscopically in the other two patients.	Strengths: Precision Directness Weaknesses: Retrospective Follow-up not described
Tureck et al[20]/1993	Retrospective	674 retrievals	Not stated	Vaginal bleeding: 2/674 (0.3%; 95% CI, 0.1%-1.1%) >100 mL, one patient required sutures Intraabdominal bleeding: 1/674 (0.1%; 95% CI, 0%-0.8%); expanding broad ligament bleed treated with diagnostic laparotomy and observation	Strengths: Precision Directness Weaknesses: Retrospective Follow-up not described

(Continued)

Table S7—*Continued*

Study/Year	Type of Study	Participants/ Intervention	Follow-up	Risk of Bleeding	Strengths/Limitations and Comments
Govaerts et al[21]/1998	Retrospective	1,500 retrievals	At least to completion of IVF	Intraabdominal bleeding: 3/1,500 (0.2%; 95% CI, 0.1%-0.6%); all three required laparoscopy	Strengths: Precision Directness Weaknesses: Retrospective
Ludwig et al[22]/2006	Prospective cohort	1,058 retrievals	2 mo postretrieval	Vaginal bleeding: 29/1,049 (2.8%; 95% CI, 1.9%-3.9%) Requiring compression, 28/1,049 (2.7%; 95% CI, 1.9%-3.9%) Requiring tamponade for > 2 h, 1/1,049 (0.1%; 95% CI, 0%-0.5%) Intraabdominal bleeding: 0/1,049 (0%; 95% CI, 0%-0.4%)	Strengths: Precision Directness Prospective
Bodri et al[23]/2008	Retrospective	4,052 retrievals	2 wk	Major bleeding: 1/4,052 (0.02%; 95% CI, 0%-0.5%) intraabdominal bleeding requiring laparotomy and transfusion Other nonmajor bleeding: 13/4,052 (0.3%; 95% CI, 0.2%-0.5%); four patients had abdominal bleeding requiring laparoscopy; in the remaining nine patients, bleeding resolved spontaneously, although six were hospitalized	Strengths: Precision Directness Weaknesses: Retrospective
Baber et al[24]/1988	Retrospective	600 retrievals	Not stated	Vaginal bleeding: 5/600 (0.8%; 95% CI, 0.4%-1.9%); requiring insertion of vaginal pack (none had significant fall in hemoglobin level) Pelvic hematoma: 3/600 (0.5%; 95% CI, 0.2%-1.5%); all managed conservatively with no drop in hemoglobin level Overt bleeding: 1/600 (0.2%; 95% CI, 0%-0.9%); 200-mL blood loss requiring suture	Strengths: Precision Directness Weaknesses: Retrospective

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Table S8—*[Section 5.1.1, 5.1.2] Risk of Thrombosis and Bleeding in Patients Receiving Prophylactic Anticoagulation Around the Time of Transvaginal Oocyte Retrieval*

Study/Year	Type of Study	Participants/Intervention	Follow-up	Outcomes	Results	Strengths/Limitations and Comments
Yinon et al[25]/2006	Retrospective	Twenty-four women considered high risk for thrombosis undergoing 73 IVF cycles and 68 oocyte retrieval procedures (five very high risk used a controlled spontaneous cycle and surrogacy). Patients received LMWH (0.6-1 mg/kg per d) starting on the day of GnRH agonist administration (when GnRH agonist protocols were used) and on the first day of gonadotropin administration in the GHrH antagonist protocol. The last injection of LMWH was administered 14-15 h prior to oocyte retrieval and resumed 12 h postprocedure. Anticoagulation was continued in pregnancy and stopped after a negative pregnancy test. Very-high-risk patients received warfarin ± aspirin prior to oocyte retrieval before transitioning to LMWH postretrieval (unless planned surrogacy).	Until delivery of embryo transfer if pregnancy not achieved.	Bleeding Thromboembolism	Bleeding: 0/24 (0; 95% CI, 0%-13.8%) Thromboembolism: 0/24 (0; 95% CI, 0%-13.8%)	Strengths: Directness Weaknesses: Imprecision Retrospective
Qublan et al[26]/2008	Randomized trial	Eighty-three women with at least three failed assisted reproduction cycles and at least one thrombophilia. Patients were allocated to enoxaparin 40 mg/d (n = 42) or placebo (n = 41) starting on the day of embryo transfer and continued until completion of pregnancy.	Until delivery. Five women in each group were lost to follow-up in the LMWH group, and three were lost to follow-up in the no-treatment group.	Implantation success, live births, complications	Bleeding: enoxaparin, 3/42 (7.1%; 95% CI, 2.5%-19.0%) Thrombocytopenia: enoxaparin, 2/42 (4.8%; 95% CI, 1.3%-15.8%) Allergic reactions: enoxaparin, 1/42 (2.4%; 95% CI, 0.4%-12.3%)	Strengths: Directness Randomized trial Weaknesses: Imprecision Only participants were blinded For 32% of participants, the qualifying thrombophilia was the *MTHFR* C677T mutation, which is not a risk factor for venous thrombosis Criteria for bleeding and thrombocytopenia not specified Bleeding not specifically reported for placebo group Thrombosis not specifically reported for either group

(Continued)

Table S8—*Continued*

Study/Year	Type of Study	Participants/Intervention	Follow-up	Outcomes	Results	Strengths/Limitations and Comments
Stern et al[27]/2003	Randomized, double-blind, placebo-controlled, crossover trial (transfer by transfer)	One hundred forty-three women with an autoantibody (either APLA, antinuclear, or anti-β_2-glycoprotein I) and at least 10 prior unsuccessful embryo transfers. Patients were allocated to either UFH 5,000 units bid SC and aspirin (158 transfers of 296 embryos) or placebo (142 transfers of 259 embryos) starting the day of embryo transfer until 14 wk gestation or pregnancy failure.	Until delivery or end of pregnancy	Successful implantation, live births, bleeding	Significant bleeding: heparin and aspirin, 0/158 (0; 95% CI, 0%-2.4%) Placebo, 0/142 (0; 95% CI, 0%-2.6%)	Strengths: Directness Randomized trial Double blinding Weaknesses: Criteria for significant bleeding not reported Thrombosis not specifically reported

APLA = antiphospholipid antibody; GHrH = growth-hormone-releasing hormone; GnRH = gonadotropin-releasing hormone; MTHFR = methylene tetrahydrofolate reductase variant. See Table S1 and S4 legends for expansion of other abbreviations.

Table S9—*[Section 5.1.1, 5.1.2] Evidence Profile: Prophylactic-Dose LMWH vs No Thromboprophylaxis for Women Who Undergo Assisted Reproductive Therapy*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[b]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Without Prophylaxis[a]	With LWMH	Relative Effect (95% CI)	Risk Without Prophylaxis[a]	Risk Difference With LMWH (95% CI)
Symptomatic VTE (critical outcome), DVT, and PE											
1,953 (6 RCTs), 27-35 d postoperative	No serious risk of bias	No serious inconsistency	Serious indirectness[a] orthopedic surgery	Serious imprecision[c]; wide CI for control group risk estimates	Undetected	Low due to indirectness and imprecision	36/862 (4.2)	15/1,091 (1.4)	RR 0.36 (0.20-0.67)	Without severe ovarian hyperstimulation syndrome	
										2 VTE per 1,000[d]	1 fewer VTE per 1,000 (from 2 fewer to 0 fewer)
										With severe ovarian hyperstimulation syndrome	
										40 VTE per 1,000[d]	26 fewer VTE per 1,000 (from 32 fewer to 13 fewer)
Major bleed (critical outcome)											
5,456 (7 RCTs), 3 wk-9 mo	No serious risk of bias	No serious inconsistency	Serious indirectness[a] orthopedic surgery	Serious imprecision[c]; wide CI for control group risk estimates	Undetected	Low	2/1,480 (0.14)	6/1,245 (0.48)	RR 0.43 (0.11-1.65)	30 bleeding events per 1,000[d]	17 fewer bleeding events per 1,000 (from 27 fewer to 20 more)

Bibliography: Hull RD, et al. Extended out of hospital low molecular weight heparin prophylaxis against deep vein thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med*. 2001;135:858-869. RCT = randomized controlled trial. See Table S4 and S6 legends for expansion of other abbreviations.

[a]The population did not include pregnant women. Different doses of LMWH were used, treatment was initiated variably before or after surgery with a duration of ~7 days (in hospital). Outcomes were variably reported, meta-analysis also provides other outcomes such as mortality, asymptomatic DVT, and specific bleed outcomes (wound hematoma, transfusion). Follow-up varied between trials from 3 wk to 9 mo.

[b]Time frame is 9 mo for all outcomes.

[c]Imprecise control group risk estimates for bleeding events and for VTE in the subset of women with ovarian hyperstimulation (Tables S6-S8).

[d]Control group risk for VTE and major bleed come from observational studies of women undergoing assisted reproductive technology (Tables S6-S8).

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Table S10—*[Section 6.2.1-6.2.4] Risk Factors for Pregnancy-Associated VTE*

Risk Factor	Adjusted OR	95% CI
Immobility (strict bed rest for ≥ 1 wk in the antepartum period) with BMI ≥ 25 kg/m² (antenatal risk)	62.3	11.5-337.0
Immobility (strict bed rest for ≥ 1 wk in the antepartum period) with BMI ≥ 25 kg/m² (postpartum risk)	40.1	8.0-201.5
Factor V Leiden homozygosity	34.4	9.9-120.1
Prothrombin G20210A homozygosity	26.4	1.2-559.3
Previous VTE	24.8	17.1-36
Postpartum infection (clinical signs/symptoms + fever + elevated WBC) following vaginal delivery	20.2	6.4-63.5
Postpartum hemorrhage ≥ 1,000 mL with surgery	12.0	3.9-36.9
Immobility (strict bed rest for ≥ 1 wk in the antepartum period) with BMI < 25 kg/m² (postpartum risk)	10.8	4.0-28.8
Systemic lupus erythematosus	8.7	5.8-13.0
Factor V Leiden heterozygosity	8.3	5.4-12.7
Immobility (strict bed rest for ≥ 1 wk in the antepartum period) with BMI < 25 kg/m² (antepartum risk)	7.7	3.2-19.0
Blood transfusion	7.6	6.2-9.4
Heart disease	7.1	6.2-8.3
Prothrombin G20210A heterozygosity	6.8	2.5-18.8
Sickle cell disease	6.7	4.4-10.1
Postpartum infection (clinical signs/symptoms + fever + elevated WBC) following cesarean section	6.2	2.4-16.2
Preeclampsia with fetal growth restriction	5.8	2.1-16
Multiple pregnancy	4.2	1.8-9.7
BMI > 30 kg/m²	5.3	2.1-13.5
Protein C deficiency	4.8	2.2-10.6
Antithrombin deficiency	4.7	1.3-17.0
Assisted reproductive techniques	4.3	2.0-9.4
Postpartum hemorrhage > 1 L	4.1	2.3-7.3
Fetal growth restriction (gestational age + sex-adjusted birth weight < 2.5th percentile)	3.8	1.4-10.2
Smoking (10-30 cigarettes/d prior to or during pregnancy) (postpartum risk)	3.4	2.0-5.5
Protein S deficiency	3.2	1.5-6.9
Preeclampsia	3.1	1.8-5.3
Emergency cesarean section	2.7	1.8-4.1
Anemia	2.6	2.2-2.9
Smoking (10-30 cigarettes/d prior to or during pregnancy) (antepartum risk)	2.1	1.3-3.4
Smoking (5-9 cigarettes/d prior to or during pregnancy) (postpartum risk)	2.0	1.1-3.7
Weight gain > 21 kg (vs 7-21 kg)	1.6	1.1-2.6
Parity > 1	1.5	1.1-1.9
Age > 35 y	1.3	1.0-1.7
Cesarean section (nonemergent)	1.3	0.7-2.2

Data are from Jacobsen et al,[16] Jacobsen et al,[28] Lindqvist et al,[29] Simpson et al,[30] Knight,[31] Roberston et al,[32] and James et al.[33]

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Table S11—*[6.2.1-6.2.4] Risk Factors for Postpartum VTE*

Risk Factor	Adjusted OR	95% CIs
Immobility (strict bed rest for ≥ 1 wk in the antepartum period) with BMI ≥ 25 kg/m^2	40.1	8.0-201.5
Postpartum infection (clinical signs/symptoms + fever + elevated WBC) following vaginal delivery	20.2	6.4-63.5
Postpartum hemorrhage ≥ 1,000 mL with surgery	12.0	3.9-36.9
Immobility (strict bed rest for ≥ 1 wk in the antepartum period) with BMI < 25 kg/m^2	10.8	4.0-28.8
Postpartum infection (clinical signs/symptoms + fever + elevated WBC) following cesarean section	6.2	2.4-16.2
Preeclampsia with fetal growth restriction	5.8	2.1-16
Postpartum hemorrhage > 1 L	4.1	2.3-7.3
Fetal growth restriction (gestational age + sex-adjusted birth weight < 2.5th percentile)	3.8	1.4-10.2
Smoking (10-30 cigarettes/d prior to or during pregnancy)	3.4	2.0-5.5
Preeclampsia	3.1	1.8-5.3
Emergency cesarean section	2.7	1.8-4.1
BMI prepregnancy > 25 kg/m^2	2.4	1.7-3.3
Smoking (5-9 cigarettes/d prior to or during pregnancy)	2.0	1.1-3.7
Cesarean section (nonemergent)	1.3	0.7-2.2

Data are from Jacobsen et al.[16]

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Table S12—*[Section 6.2.1-6.2.4] Evidence Profile: LMWH vs No Thromboprophylaxis for Prevention of VTE in Women Undergoing Cesarean Section*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)[a]			Anticipated Absolute Effects[b]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Without Prophylaxis	With LWMH	Relative Effect (95% CI)	Risk Without Prophylaxis[c]	Risk Difference With LMWH (95% CI)
Symptomatic VTE (critical outcome), DVT, and PE (only symptomatic PE, not symptomatic DVT, reported separately in meta-analysis) measured at end of follow-up											
4,890 (3 RCTs), 3 wk-9 mo	No serious risk of bias[c] Selective outcome reporting	No serious inconsistency	Serious indirectness general surgery	No serious imprecision	Undetected	Moderate	22/2,445 (0.9)	5/2,445 (0.02)	RR 0.29 (0.11-0.73)	Low risk	
										5 VTE per 1,000[d]	3 fewer VTE per 1,000 (from 4 fewer to 1 fewer)
										High risk	
										30 VTE per 1,000[d]	21 fewer VTE per 1,000 (from 27 fewer to 9 fewer)
Major bleed (critical outcome)											
5,456 (7 RCTs), 3 wk-9 mo	No serious risk of bias	No serious inconsistency	Serious indirectness[e] Heterogeneous definitions of bleeding events	No serious imprecision	Undetected	Moderate	37/2,728 (0.14)	74/2,728 (0.48)	RR 2.03 (1.37-3.01)	20 bleeding events per 1,000[f]	20 more bleeding events per 1,000 (from 8 more to 40 more)

Bibliography: Mismetti P, Laporte S, Darmon JY, Buchmüller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg.* 2001;88:913-930. Blondon M, Perrier A, Nendaz M, et al. Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery. A decision analysis. *Thromb Haemost.* 2010;103:129-137.

See Table S3, S4, S6, and S9 legends for expansion of abbreviations.

[a]The denominators for LMWH and controls were extracted by dividing total no of participants by two.

[b]Time frame is 9 mo for all outcomes.

[c]Only five of eight RCTs of LMWH vs placebo/no treatment reported mortality. We did not rate down for risk of bias.

[d]For source of control group risk estimates see text and Tables S10 and S11.

[e]Rated down for indirectness due to variable bleeding definitions in trials (bleeding leading to death, transfusion, reoperation, or discontinuation of therapy) measured at end of therapy.

[f]Control group risk estimate for major bleeding events comes from study by Blondon et al.

Table S13—*Decision and Cost-Effectiveness Analyses/Economic Analyses Study: Methodologic Key Information*

						Data Sources						
Study/Year	Type of Analysis	Type of Model	All Relevant Strategies Considered?	Perspect. of Analysis	Time Frame of Analysis	Probabilities and Rates	Costs	QOL Measures	Benefits or Costs and Benefits Completely Specified?	Are Costs and Benefits Discounted?	Were Sensitivity Analyses Performed?	Comments
Casele and Grobman[34]/2006	Cost-effective	Markov transition state model	No, pharmacol. prophylaxis not considered	Health-care payer	Life-time of cohort	RCT from different patient population	Published C/E analyses Costs included: Underlying disease treatment Treatment complications	Published C/E or decision analysis QOL metrics: Not stated	Yes	Yes, 3%	Deterministic Yes Probabilistic No	Pharmacologic prophylaxis not included as a comparator Moderate uncertainty in baseline risk and effectiveness Satisfactory quality but not definitive given data uncertainties as noted by authors Quality category[a]: Very good Good Satisfactory Unsatisfactory

QOL = quality of life. See Table S9 legend for expansion of other abbreviation.

[a] Definitions: very good, 90% to 100% of quality items present; good, 80% to 89% of quality items present; satisfactory, 60% to 79% of quality items present; unsatisfactory, < 60% of quality items present.

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Table S14—*Decision and Cost-Effectiveness Analyses/Economic Analyses Study: Description of Study*

		Outcome Measures				
Study/Year	Strategies Analyzed	Target Populations[a]	Effectiveness	Cost[b]	Funding Sources and Potential Conflicts of Interest	Study Conclusions, Assessment of Continued Relevance, Additional Comments[c]
Casele and Grobman[34]/2006	Pneumatic compression vs no prophylaxis	Pregnant women undergoing cesarean section who were not anticoagulated during pregnancy	QALYs Results (expected utilities, ICERs, etc)	USD 2004 Delta costs: + $ 104 Delta QALYs: + 0.00263 ICER: 39,545 (range up to 200,000 +, depending on assumptions)	Funding source (if any) not stated	Pharmacologic prophylaxis not included as a comparator Moderate uncertainty in baseline risk and effectiveness Satisfactory quality, but not definitive given data uncertainties as noted by authors

ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; USD = US dollar.

[a] Types of patients/multiple subgroups.

[b] Average wholesale price (eg, Redbook, Bluebook) or average sales price based estimate.

[c] Quality category definitions: very good, 90% to 100% of quality items present; good, 80% to 89% of quality items present; satisfactory, 60% to 79% of quality items present; unsatisfactory, < 60% of quality items present.

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Table S15—*[Section 7.1.2] Evidence Profile: Should LMWH Rather Than VKAs Be Used for Long-term Treatment of VTE in Pregnant Women?*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects During Pregnancy	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With VKA	With LMWH	Relative Effect (95% CI)	Risk With VKA	Risk Difference With LMWH (95% CI)
Recurrent symptomatic VTE (critical outcome), DVT, and PE											
2,496 (7 RCTs), 6 mo	Serious risk of bias No studies were blinded	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate due to risk of bias	202/1,231 (16.4)	204/1,265 (16.1)	RR 0.62 (0.46-0.84)	30 VTE per 1,000[a]	11 fewer VTE per 1,000 (from 5 fewer to 16 fewer)
Major bleeding (critical outcome)											
2,727 (8 RCTs), 6 mo	No serious risk of bias Lack of blinding not serious[b]	No serious inconsistency	No serious indirectness	Serious imprecision CI includes important benefit and harm	Undetected	Moderate due to imprecision	105/1,349 (7.8)	67/1,378 (4.9)	RR 0.81 (0.55-1.2)	20 bleeding events per 1,000[c]	4 fewer bleeding events per 1,000 (from 9 fewer to 4 more)
PTS (important outcome): self-reported leg symptoms and signs											
100 (1 RCT), not reported	Serious risk of bias Patients and investigators not blinded	No serious inconsistency	Serious indirectness Predictive value from 3 mo to long term uncertain	No serious imprecision	Undetected	Low due to risk of bias and indirectness	31/44 (70.5)	34/56 (60.7)	RR 0.85 (0.77-0.94)	480 PTS per 1,000[d]	72 fewer PTS per 1,000 (from 110 fewer to 29 fewer)

Bibliography: Kearon C, Akl EA, Comerato AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(supp 1):e418S-e494S. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*. 2002;100:3484-3488. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med*. 1998;105:91-99.

Meta-analysis is based on RCTs as referenced in the text of Kearon et al[178] in this guideline. Limited to LMWH regimens that used ≥ 50% of the acute treatment dose during the extended phase of treatment. PTS = postthrombotic syndrome. See Table S1, S3, S4, S6, and S9 legends for expansion of other abbreviations.

[a] Control group risk estimate for VTE with VKAs comes from cohort study by Prandoni et al, adjusted to 6-mo time frame.

[b] Outcome less subjective: Borderline decision.

[c] Control group risk estimate for major bleeding events comes from cohort studies by Prandoni et al and Beyth et al, adjusted to 6-mo time frame.

[d] Control group risk estimate for PTS comes from observational study of pregnant women (most mild).[171]

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Table S16—*[Section 8.2.2, 8.2.3] Risk of Recurrent VTE in Pregnant Women Without Antepartum Thrombosis Prophylaxis*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Strengths	Limitations
				Prospective studies				
Howell et al[35]/1983	RCT	N = 40; n = 20 in control arm	No antepartum prophylaxis; postpartum UFH 8,000 bid	Bleeding Osteopenia Recurrent VTE	6 wk postpartum	Antepartum: 1 (5%; 95% CI, 0.1%-25%) Postpartum: 0	RCT, concealment of allocation adequate	Primary outcome was side effects (osteopenia, antenatal bleeding) rather than VTE, no ITT analysis, mean gestational age at entry 14 wk (range, 8-37 wk), no objective diagnosis of first VTE, no description of diagnostic techniques for recurrent DVT
Lao et al[36]/1985 and de Swiet et al[37]/1987 (latter report provides additional data to the first)	Prospective cohort study	N = 59; 25% women had single previous VTE related to pregnancy; 39% had single previous VTE during OCP use	No antepartum prophylaxis (two protocol violations in which patients received antepartum anticoagulants) Dextran during delivery and heparin or warfarin for 6 wk postpartum	Recurrent VTE	6 wk postpartum	Antepartum: 0 Postpartum: 0		
Brill-Edwards et al[38]/2000	Prospective cohort	N = 125 women with one objectively diagnosed previous VTE	No antepartum prophylaxis; postpartum prophylaxis with warfarin	Recurrent VTE antepartum Recurrent VTE postpartum	3 mo postpartum	Antepartum: 3/125; 2.4% (95% CI, 0.2%-6.9%)	Prospective, single episode of prior VTE only	Inclusion at median gestational age of 15 wk, exclusion of women with known thrombophilia

(Continued)

Table S16—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Strengths	Limitations
						No recurrences in women with no thrombophilia and a provoked first VTE (0/44, 0%; 95% CI, 0%-8.0%); of women with an idiopathic first VTE or abnormal thrombophilia testing, 3/51 (5.9%; 95% CI, 1.2%-16.2%) developed recurrence Postpartum: 3/122 (2.5%; 95% CI, 0.5%-7.0%)		
				Retrospective studies				
Badaracco et al[39]/1974	Retrospective cohort study	N = 30 women with previous VTE	Not stated	Recurrent VTE during pregnancy or postpartum period	Not stated	Total: 6/15 (40%; (95% CI, 16.3%-67.7%); distribution between antepartum and postpartum not provided		Retrospective, included women with more than one previous VTE, questionnaire data, no objective diagnosis
Tengborn et al[40]/1989	Retrospective cohort study	N = 72 women with previous VTE (87 pregnancies; 67 pregnancies without antepartum prophylaxis)	No antepartum prophylaxis Postpartum: no prophylaxis (n = 30) Various anticoagulant regimens, including UFH and dextran (n = 57)	Recurrent VTE; superficial thrombophlebitis (not included in this table)	Until postpartum; time not stated	Antepartum: 5/67 (7.5%; 95% CI, 2%-14%) Postpartum: 2/30 (6.7%; 95% CI, 0%-21%) All recurrences in women with previous VTE elicited by pregnancy or OCP use		Retrospective, questionnaire data, no objective diagnosis, women with multiple previous episodes of VTE included, some women with hereditary thrombophilia (anticoagulant inhibitor deficiencies n = 3; defective fibrinolysis n = 18), wide range of postpartum regimens, potential confounding by indication

(Continued)

 DOI: 10.1378/chest.11-2300

Table S16—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Strengths	Limitations
Pabinger et al[41]/2005	Retrospective cohort study	N = 109 women with previous VTE (197 pregnancies; 284 postpartum periods, including after terminations, miscarriages, stillbirths, and live births)	No antepartum prophylaxis; inconsistent use of postpartum prophylaxis, mainly low-dose LMWH (details not stated)	Cumulative incidence of recurrent VTE antepartum Recurrent VTE postpartum	6 wk postpartum	Antepartum: 8/197 (cumulative incidence, 6.2%; 95% CI, 1.6%-10.6%) No predictive value of thrombophilia or whether first episode was idiopathic Recurrence risk in subgroup of women with first VTE associated with OCP use 10% vs 2.7% if first VTE not associated with OCP use (ns) Postpartum: overall, 15/284 (5.3%; 95% CI, 3.0%-8.6%); without prophylaxis, 10/187 (5.4%; 95% CI, 2.6%-9.6%); with prophylaxis, 5/97 (5.2%; 95% CI, 1.7%-11.6%)	Assessed risk for full period of pregnancy (ie. including early terminations, miscarriages)	Retrospective, included women with more than one previous VTE, not all VTE objectively diagnosed, potential confounding by indication

(Continued)

Table S16—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Strengths	Limitations
De Stefano et al[42]/2006	Retrospective cohort study	N = 88 women with previous VTE (155 pregnancies)	No antepartum prophylaxis; 120 pregnancies without postpartum prophylaxis	Cumulative incidence of recurrent VTE antepartum Recurrent VTE postpartum	6 wk postpartum if delivery after 16 wk gestational age	Antepartum: 9/155 (5.8%; 95% CI, 3.0%-10.6%) Subgroup of women with and without thrombophilia: 7.9% vs 4.2%	Subgroup of women with first VTE hormonally provoked (ie, related to pregnancy or OCP use), 9.5% vs unprovoked, 4.2%, vs transient nonhormonal risk factor, 0% Postpartum: 8.3% (95% CI, 4.5%-14.6%) First pregnancy-related VTE, 15.5% vs first event-related to OCP use, 0%, vs unprovoked, 3.1%, vs transient nonhormonal risk factor, 7.1%	Retrospective, included women with more than one previous VTE, not all VTE objectively diagnosed, potential confounding by indication

ns = not significant; OCP = oral contraception. See Table S1, S4, and S9 for expansion of other abbreviations.

Table S17—*[Section 8.2.2, 8.2.3] Risk of Symptomatic Recurrent VTE and Bleeding in Pregnant Women Receiving Antepartum Thrombosis Prophylaxis: RCTs*

Study/Year	Type of Study	Participants	Intervention	Control	Outcomes	Follow-up	Results	Strengths	Limitations
Howell et al[35]/1983	RCT	N = 40; n = 20 in prophylaxis arm	Antepartum prophylaxis UFH 10,000 units bid starting at enrollment (mean, 14 wk; range, 8-37 wk) Postpartum UFH 8,000 units bid for 6 wk	No antepartum prophylaxis Postpartum UFH 8,000 units bid	Bleeding Osteopenia Recurrent VTE	6 wk postpartum	Recurrent VTE Intervention arm: Antepartum, 0/20 Postpartum, 0/20 Control arm: antepartum, 1/20 (5%; 95% CI, 0.1%-25%); postpartum, 0/20 (0%; 95% CI, 0%-16.8%); estimate of effect size, RR 0.33 (95% CI, 0.01-7.72) Bleeding Intervention arm, 2/20 (10%; 95% CI, 1.24%-31.7%); control arm, 0/20 (0%, 95% CI, 0%-16.8%); estimate of effect size, RR 5.00 (95% CI, 0.26-98.00)	Concealment of allocation adequate	Primary outcome was side effects (osteopenia, antenatal bleeding) rather than VTE, no ITT analysis, mean gestational age at entry 16 wk (range 8-37 wk), no objective diagnosis of first VTE, no description of diagnostic techniques of recurrence
Gates et al[43]/2004	RCT	N = 16	Enoxaparin 40 mg started from antenatal recruitment until 6 wk postpartum	Placebo (1 mL saline)	Symptomatic confirmed VTE Symptomatic osteoporotic fractures	6 mo postpartum	Recurrent VTE Intervention arm: antepartum, 0/8 (0.0%; 95% CI, 0.0%-36.9%); postpartum, 0/8 (0.0%; 95% CI, 0.0%-36.9%) Control arm: antepartum, 0/8 (0.0%; 95% CI, 0.0%-36.9%); postpartum, 1/8 (12.5%; 95% CI, 3.1%-52.7%); estimate of effect size, RR 0.33 (95% CI, 0.02-7.14) Bleeding: none reported	Adequate concealment of allocation Adequate blinding of patients and caregivers	Pilot study, too small to draw any conclusions, recruitment at all gestational ages, the majority > 20 wk, some crossover between groups postpartum

(Continued)

 DOI: 10.1378/chest.11-2300

Table S17—*Continued*

Study/Year	Type of Study	Participants	Intervention	Control	Outcomes	Follow-up	Results	Strengths	Limitations
Pettilä et al[44]/1994	RCT	n = 102 women with previous proximal VTE or previous distal VTE and protein S and protein C deficiency, activated protein C resistance, or associated with pregnancy or OCP use (three women with VTE during current pregnancy excluded)	Antepartum dalteparin once daily at starting dose of 5,000 International Units (< 85 kg) or 7,500 International Units (> 85 kg), then dose adjusted to maintain anti-Xa levels > 0.20 units/mL 3 h after injection	Antepartum UFH bid SC starting at 7,500 International Units, then dose adjusted to maintain aPTT 5-15 s above upper limit of normal	Recurrent VTE Bleeding episodes	6 wk postpartum	Recurrent VTE Dalteparin arm: 0/48 UFH arm: 0/54 safety, any bleeding complication Dalteparin arm: 9/50 (18%; 95% CI, 7.0%-29%) UFH arm: 35/55 (64%; 95% CI, 51%-77%)	Concealment of allocation adequate, objectively confirmed previous VTE	Not blinded

aPTT = activated partial thromboplastin time. See Table S1, S3, S4, S16 for expansion of other abbreviations.

Table S18—*[8.2.2, 8.2.3] Risk of Recurrent VTE in Pregnant Women Receiving Antepartum Thrombosis Prophylaxis: Observational Studies*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Strengths	Limitations
				Prospective studies				
Blombäck et al[45]/1998	Prospective cohort study	25 women with previous VTE	Dalteparin weight-adjusted starting dose, then adjusted to target anti-Xa levels of 0.20-0.40 units/mL 3 h postinjection	Recurrent VTE Anti-Xa levels	6 wk postpartum	Antepartum recurrent VTE: 0/25 (0%; 95% CI, 0%-13.7%)	Objective diagnosis of first VTE	Uncontrolled, 14 women were recruited in the second trimester of pregnancy, 3 women did not complete the study and were withdrawn from the analysis
Brennand et al[46]/1999	Prospective cohort study	16 women with an indication for thrombosis prophylaxis during pregnancy; 14 had a history of previous VTE	Enoxaparin 40 mg once daily; postpartum not stated	Anti-Xa levels Recurrent VTE reported in the article	Not stated	Antepartum: 0/14 (0%; 95% CI, 0%-23.2%) Postpartum: 1/14 (7.1%; 95% CI, 0.2%-34%)		Pharmacodynamic study
Bauersachs et al[47]/2007	Prospective cohort management study	810 pregnant women at increased risk for VTE; 225 with previous VTE	Antepartum clinical surveillance; intermediate- and high-dose dalteparin according to risk stratification based on history (see legend) Women with previous VTE/total: low-risk group, 49/225; high-risk group, 339/469; very-high-risk group, 104/116	Symptomatic recurrent VTE, clinically relevant bleeding, serious bleeding	Not stated	Low-risk group: 0/49 (95% CI, 0%-7.3%) High-risk group: 2/338 (0.6%; 95% CI, 0.0%-2.1%) Very-high-risk group: 2/104 (1.9%; 95% CI, 0.2%-6.8%)		Uncontrolled, included women with multiple episodes of VTE, includes women without history of VTE, data in this table deduced from article
Dargaud et al[48]/2009	Prospective cohort management study	286 pregnant women at increased risk for VTE; 183 with previous VTE	Antepartum clinical surveillance; enoxaparin 40 mg once daily (60 mg in BMI >35 kg/m^2) starting in the third trimester or starting early in pregnancy according to a risk score (see legend); all in addition to class 2 stockings	Symptomatic recurrent VTE, bleeding, HIT, symptomatic osteoporosis, serious urticarial rash related to heparin	Not stated, likely 8 wk postpartum	No antenatal LMWH (risk score <3): 0/25 (95% CI, 0%-13.7%) LMWH start in third trimester (risk score 3-5): antepartum, 0/89 (0%; 95% CI, 0%-4.1%); postpartum, 1/89 (1.1%; 95% CI, 0.0%-6.1%)		Uncontrolled, may have included women with multiple episodes of VTE, included women without history of VTE, data in this table deduced from article

(Continued)

Table S18—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Strengths	Limitations
			No antenatal LWMH, n = 25 Start LMWH in third trimester, n = 89 LMWH throughout pregnancy, n = 69			LMWH throughout pregnancy (risk score ≥ 6): antepartum, 0/69 (0%; 95% CI, 0%-5.2%); postpartum, 1/69 (1.5%; 95% CI, 0.0%-7.8%) Bleeding: one postpartum hemorrhage in a woman not receiving LMWH		
Folkeringa et al[49]/2007	Prospective cohort study	55 women from families with antithrombin, protein C, and protein S deficiency; 22 with a history of VTE. 19 women received thrombosis prophylaxis during pregnancy; 18 were antithrombin, protein C, or protein S deficient	Adjusted-dose UFH or LMWH before 16 wk of gestation and after 36 wk of gestation, with VKAs in between or adjusted-dose LMWH throughout pregnancy	Fetal loss Symptomatic recurrent VTE reported in the article	Not stated	Not stated whether antepartum or postpartum: 2/19 (10.5%; 95% CI, 1.3%-33.1%) No major bleeding reported		Uncontrolled, may have included women with multiple episodes of VTE, included women without history of VTE, data in this table deduced from article

(Continued)

Table S18—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Strengths	Limitations
Rozanski et al[50]/2009	Prospective cohort management study	90 pregnant women at increased risk for VTE	Antepartum clinical surveillance in women with previous provoked VTE (major risk factor), n = 30; 37 pregnancies Dalteparin (dose not stated) in women with previous idiopathic VTE n = 60; 99 pregnancies	Symptomatic recurrent VTE	Not stated	Previous provoked VTE, clinical surveillance: antepartum recurrent VTE, 1/37 (2.7%; 95% CI, 0.5%-13.8%); postpartum, 0/36 Previous idiopathic VTE, dalteparin: antepartum, recurrent VTE 3/99 (3.0%; 95% CI, 1.0%-8.5%); postpartum, 0/96 Major bleeding: None		Uncontrolled, abstract only, definition of provoked vs idiopathic previous VTE unclear
			Retrospective studies					
Tengborn et al[40]/1989	Retrospective cohort study	72 women with previous VTE, 87 pregnancies; 20 pregnancies with antepartum prophylaxis	Antepartum: UFH 5,000 International Units bid (n = 11), 10,000 International Units bid (n = 1), 12,500 International Units bid (n = 2), aPTT-based (n = 2), Unknown regimen (n = 1) UFH started at median of 16th (range, before conception-30 wk) gestational age Postpartum: UFH, dose not stated (n = 13); dextran, dose not stated (n = 42); UFH and dextran (n = 1); UFH and antithrombin concentrate (n = 1)	Recurrent VTE, superficial thrombophlebitis (not included in this table)	Until postpartum, time not stated	Antepartum: 3/20 (15%, 95% CI, 0%-31%); two occurring in lowest UFH dose; one in woman with antithrombin deficiency who had aPTT-adjusted dose UFH Postpartum: 2/57 (3.5%; 95% CI, 0.4%-12.1%) despite prophylaxis All recurrences in women with previous VTE elicited by pregnancy or OCP use		Retrospective, questionnaire data, no objective diagnosis, women with multiple previous episodes of VTE included, some women with hereditary thrombophilia (anticoagulant inhibitor deficiencies, n = 3; defective fibrinolysis, n = 18), potential confounding by indication

(Continued)

Table S18—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Strengths	Limitations
Sanson et al[51]/1999	Systematic review of published cohort studies and cohorts from international interest group	486 pregnancies from 21 reports; 149 pregnancies in women with previous VTE	Several doses and types of LMWH; low-dose defined as < 75 anti-Xa units/kg; intermediate dose defined as 75-150 anti-Xa units/kg; high dose defined as > 150 anti-Xa units/kg	Adverse pregnancy events; adverse fetal/neonatal events Secondary: VTE, thrombocytopenia, osteoporosis, hemorrhagic episodes	Not stated	3/149 (2%; 95% CI, 0.7-5.6%) had phlebitis; 2 had thrombophilia; 1 had APLAs; 1 low-dose; 2 intermediate-dose		Review of small case series and ad hoc identified cohorts, potential for publication and reporting bias, risk per dose LMWH cannot be calculated from the published data, diagnostic criteria first and recurrent VTE not stated, number of previous VTE not stated
Lepercq et al[52]/2001	Retrospective cohort study	604 women with 649 pregnancies	Several doses and indications of enoxaparin thrombosis prophylaxis in 574 cases	Maternal safety, pregnancy outcome, neonatal safety, VTE recurrence		Antepartum recurrence, n = 5 (denominator unclear), all in women who had had previous VTE in current pregnancy while taking 40 mg Postpartum recurrence, n = 3		Primary outcome safety rather than recurrent VTE Denominator of women with history of VTE cannot be extracted from the article, unclear whether recurrences are real recurrences or extensions from recent acute VTE, diagnostic criteria first and recurrent VTE not stated, number of previous VTE not stated

(Continued)

Table S18—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Strengths	Limitations
Pabinger et al[41]/2005	Retrospective cohort study	Unknown number of women with previous VTE who had 87 pregnancies with antepartum prophylaxis 284 postpartum periods, including after terminations, miscarriages, stillbirths, and live births	Antepartum UFH 5,000 bid or low-dose enoxaparin or dalteparin (dose not stated); inconsistent use of postpartum prophylaxis, mainly low-dose LMWH (details not stated)	Cumulative incidence of recurrent VTE antepartum, recurrent VTE postpartum	6 wk postpartum	Antepartum: 0/87 (0%; 95% CI, 0%-4.1%) Postpartum: overall, 15/284 (5.3%; 95% CI, 3.0%-8.6%); without prophylaxis, 10/187 (5.3%; 95% CI, 2.6%-9.6%); with prophylaxis, 5/97 (5.2%; 95% CI, 1.7%-11.6%)	Assessed risk of full period of pregnancy (ie, including early terminations, miscarriages)	Included women with more than one previous VTE, not all VTE objectively diagnosed, potential confounding by indication

Bauersachs et al[47]: Risk stratification for women with previous VTE: (1) low-risk patients, prior secondary VTE (not associated with thrombophilia, pregnancy, oral contraception); (2) high-risk patients, prior VTE and thrombophilia, prior idiopathic VTE, prior VTE during pregnancy or oral contraception, recurrent secondary VTE; (3) very-high-risk patients, antithrombin deficiency and prior VTE, antiphospholipid syndrome and prior VTE or arterial thromboembolism, acute VTE in current pregnancy after day 11. Dargaud et al[48]: Risk stratification using an individual risk score, see Table 1 in original publication. HIT = heparin-induced thombocytopenia. See Table S1, S4, S8, S16, and S17 legends for expansion of other abbreviations.

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Table S19—*[Section 8.2.2, 8.2.3] Antepartum and Postpartum Prevention of VTE With Prophylactic-Dose LMWH vs No Prophylaxis in Pregnant Women With Prior VTE*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects During Pregnancy	
Participants (Studies), Follow up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Without Prophylaxis	With LWMH	Relative Effect (95% CI)	Risk Without Prophylaxis	Risk Difference With LMWH (95% CI)
Symptomatic VTE (critical outcome), DVT and PE											
1,953 (6 RCTs), 27-35 d postoperative	No serious risk of bias	No serious inconsistency	Serious indirectness[a] orthopedic surgery	Serious imprecision[b] Wide CI for control group risk estimates	Undetected	Low due to indirectness and imprecision	36/862 (4.2)	15/1,091 (1.4)	RR 0.36 (0.20-0.67)	Low risk (transient risk factor)	
										20 VTE per 1,000[c]	13 fewer VTE per 1,000 (from 16 fewer to 7 fewer)
										Intermediate and high risk (pregnancy or estrogen related, idiopathic, or multiple prior VTE but discontinued VKA)	
										40 VTE per 1,000[c]	26 fewer VTE per 1,000 (from 32 fewer to 13 fewer)

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 DOI: 10.1378/chest.11-2300

Table S19—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects During Pregnancy	
Participants (Studies), Follow up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Without Prophylaxis	With LWMH	Relative Effect (95% CI)	Risk Without Prophylaxis	Risk Difference With LMWH (95% CI)
Major bleed (critical outcome)[d]											
5,456 (7 RCTs), 3 wk-9 mo	No serious risk of bias	No serious inconsistency	Serious indirectness[a] orthopedic surgery	Serious imprecision CI includes benefit and harm	Undetected	Low due to indirectness and imprecision	2/1,480 (0.14)	6/1,245 (0.48)	RR 0.43 (0.11-1.65)	Antepartum period	
										5 bleeding events per 1,000[e]	3 fewer bleeding events per 1,000 (from 4 fewer to 3 more)
										Postpartum period	
										20 bleeding events per 1,000[e]	11 fewer bleeding events per 1,000 (from 18 fewer to 13 more)

Hull RD et al. Extended out of hospital low molecular weight heparin prophylaxis against deep vein thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med.* 2001;135:858-869. 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;106:401-407. See Table S3, S4, S6, S9 legends for expansion of abbreviations.

[a] Population is indirect; the population did not include pregnant women. Different doses of LMWH were used, treatment was initiated variably before or after surgery with a duration of ~7 days (in hospital). Outcomes variably reported. Meta-analysis also provides other outcomes, such as mortality, asymptomatic DVT, and specific bleed outcomes (wound hematoma, transfusion). Follow-up varied among trials from 3 wk to 9 mo.

[b] Baseline risk estimates for VTE in the antepartum and postpartum period come from studies summarized in Table S16. Quality of evidence is rated down because of imprecision in these risk estimates. We consider the distribution of VTE antepartum and postpartum to be equal.

[c] Baseline risk estimates for VTE in the antepartum and postpartum period come from studies summarized in Table S16. We consider the distribution of VTE antepartum and postpartum to be equal.

[d] Defined nonfatal maternal hemorrhage (according to section 1.0) as a symptomatic bleeding complication noted during pregnancy or within 6 weeks postpartum that involved bleeding into a critical site, bleeding causing a fall in hemoglobin level of 2 g/dL or more, and bleeding leading to transfusion of ≥ 2 units of whole blood or red cells.

[e] Baseline risk estimate for major maternal hemorrhage comes from a systematic review by Greer et al.[38]

Table S20—*[Section 9.2.1-9.2.4] Evidence Profile: Antepartum and Postpartum Prophylactic-Dose LMWH vs No Thromboprophylaxis for Pregnant Women With a Known Thrombophilia*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects Antepartum and Postpartum (Different Risk Estimates for Bleeding Events)	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Without Prophylaxis	With LWMH	Relative Effect (95% CI)	Risk Without Prophylaxis	Risk Difference With LMWH (95% CI)
Symptomatic VTE (critical outcome), DVT, and PE											
1,953 (6 RCTs), 27-35 d postoperative	No serious risk of bias	No serious inconsistency	Serious indirectness[a] orthopedic surgery	Serious imprecision[b] Wide CI for control group risk estimates	Undetected	Low due to indirectness and imprecision	36/862 (4.2)	15/1,091 (1.4)	RR 0.36 (0.20-0.67)	Positive family history VTE and heterozygous factor V Leiden or prothrombin 202010A	
										15 VTE per 1,000[c]	10 fewer VTE per 1,000 (from 12 fewer to 5 fewer)
										Positive family history VTE and antithrombin, protein C or protein S deficiency	
										20 VTE per 1,000[c]	13 fewer VTE per 1,000 (from 16 fewer to 6 fewer)
										Positive family history VTE and homozygous factor V Leiden or prothrombin 20210A	
										70 VTE per 1,000[c]	47 fewer VTE per 1,000 (from 56 fewer to 21 fewer)
										No family history of VTE but homozygous factor V Leiden or prothrombin 20210A	
										20 VTE per 1,000[c]	13 fewer VTE per 1,000 (from 16 fewer to 6 fewer)

(Continued)

 DOI: 10.1378/chest.11-2300

Table S20—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects Antepartum and Postpartum (Different Risk Estimates for Bleeding Events)	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Without Prophylaxis	With LWMH	Relative Effect (95% CI)	Risk Without Prophylaxis	Risk Difference With LMWH (95% CI)
Major bleed (critical outcome)											
5,456 (7 RCTs), 3 wk-9 mo	No serious risk of bias	No serious inconsistency	Serious indirectness orthopedic surgery	Serious imprecision CI includes benefit and harm	Undetected	Low due to indirectness and imprecision	2/1,480 (0.14)	6/1,245 (0.48)	RR 0.43 (0.11-1.65)	Antepartum period	
										5 bleeding events per 1,000[d]	3 fewer bleeding events per 1,000 (from 4 fewer to 3 more)
										Postpartum period	
										20 bleeding events per 1,000[d]	11 fewer bleeding events per 1,000 (from 18 fewer to 13 more)

Bibliography: Hull RD, et al. Extended out of hospital low molecular weight heparin prophylaxis against deep vein thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med*. 2001;135:858-869. 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;106:401-407. See Table S3, S4, S6, and S9 legends for expansion of abbreviations.

[a] The population did not include pregnant women. Different doses of LMWH were used, treatment was initiated variably before or after surgery with a duration of ~7 days in hospital and 25 days out of hospital. Outcomes were variably reported.

[b] Imprecision in baseline risk estimates for all thrombophilias (see Table S22) results in imprecise anticipated absolute effects.

[c] Baseline risk estimate for VTE comes from observational studies summarized in Table S22. Our antepartum risk estimate is based on assumed equal distribution of antepartum and postpartum VTE events based on data from observational studies (I. A. Greer, MD, personal communication, November 8, 2010).

[d] Baseline risk estimate for major bleeding events antepartum and postpartum come from systematic review by Greer.

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Table S21—*[Section 10.2.3. 10.2.4] Randomized Trials and Observational Studies of the Prevention of Complications in Pregnant Women With Thrombophilia: Clinical Description and Results*

Study/Year	Intervention	Number Patients Analyzed	Length of Follow-up	Pregnancy Loss (%)	Fetal Growth Restriction (%)	Preeclampsia (%)	Placental Abruption (%)	Maternal Bleeding (%)	Comments
Randomized trials									
Thrombophilia-APLA									
Aspirin vs placebo									
Cowchock and Reece[53]/1997	Aspirin 81 mg/d	Aspirin = 11	Pregnancy loss or delivery	Aspirin = 1/11 (9.1)	Aspirin = 0/10	NR	NR	NR	
	Usual care	Usual = 8		Usual = 0/8	Usual = 1/8 (12.5)				
				RR 2.25 (0.10-49.04)	RR 0.27 (0.01-5.92)				
Tulppala et al[54]/1997	Aspirin 50 mg/d	Aspirin = 6	Pregnancy loss or delivery	Aspirin = 5/6 (83)	NR	NR	NR	NR	Pregnancy losses include: ASA 1/6 = blighted ovum; control 3/6 = blighted ovum or ectopic pregnancy
	Placebo	Placebo = 6		Placebo = 3/6 (50.0)					
				RR 1.20 (0.48-2.99)					
Pattison et al[55]/2000	Aspirin 75 mg/d	Aspirin = 20/25 (80.0%)	Pregnancy loss or delivery	Aspirin = 4/20 (20.0)	Aspirin = 1/16 (6.2)	Aspirin = 3/20 (15.0)	NR	Aspirin = 9/20 (45.0)	All bleeding events minor
	Placebo	Placebo = 20/25 (80.0%)		Placebo = 3/20 (15.0)	Placebo = 4/17 (23.5)	Placebo = 3/20 (15.0)		Placebo = 7/20 (35.0)	
				RR 1.33 (0.34-5.21)	RR 0.27 (0.03- 2.13)	RR 1.00 (0.23- 4.37)		RR 1.29 (0.6-2.72)	
UFH + aspirin vs aspirin alone									
Rai et al[56]/1997	UFH 5,000 units SC bid + aspirin 75 mg/d	UFH + aspirin = 45/45	Pregnancy loss or delivery	UFH + aspirin = 13/45 (28.9)	UFH + aspirin = 3/32 (9.4)	UFH + aspirin = 0/32 (0.0)	NR	NR	
	Aspirin 75 mg/d	Aspirin = 45/45		Aspirin = 26/45 (57.8)	Aspirin = 1/19 (5.3)	Aspirin = 1/19 (2.2)			
				RR 0.50 (0.30- 0.84)	RR 1.78 (0.20-15.93)	RR 0.33 (0.01-7.92)			
Goel et al[57]/2006	UFH 5,000 International Units SC bid + aspirin 80 mg/d	UFH + aspirin = 33/33 (100%)	Pregnancy loss or delivery	Overall: UFH + aspirin = 5/33 (15.2)	UFH + aspirin = 2/28 (15)	UFH + aspirin = 0/28 (0)	NR	No major bleeding due to heparin	

(Continued)

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Table S21—*Continued*

Study/Year	Intervention	Number Patients Analyzed	Length of Follow-up	Pregnancy Loss (%)	Fetal Growth Restriction (%)	Preeclampsia (%)	Placental Abruption (%)	Maternal Bleeding (%)	Comments
	Aspirin 80 mg/d	Aspirin = 39/39 (100%)		Aspirin = 15/39 (38.5) RR 0.39 (0.16-0.97) First trimester loss: UFH + aspirin = 4/33 (12.1) Aspirin = 13/39 (33.3)	Aspirin = 1/24 (4.2)	Aspirin = 2/24 (8.3)			
Kutteh[58]/1996	UFH 5,000 units SC bid adjusted to attain 6 h postinjection aPTT at 1.2-1.5 times baseline + aspirin 81 mg/d	UFH + aspirin = 25/25	Pregnancy loss or delivery	UFH + aspirin = 5/25 (20.0)	UFH + aspirin = 3/20 (15.0)	UFH + aspirin = 2/20 (10.0)	NR	UFH + aspirin = 3/20 (15.05)	All bleeding events considered minor
	Aspirin 81 mg/d	Aspirin = 25/25		Aspirin = 14/25 (56.0) RR 0.36 (0.15- 0.84)	Aspirin = 1/11 (9.1) RR 1.65 (0.19-14.03)	Aspirin = 1/11 (9.1) RR 1.10 (0.11-10.81)		Aspirin = 1/11 (9.1) RR 1.65 (0.19- 14.03)	
				LMWH + aspirin vs aspirin alone					
Farquharson et al[59]/2002	LMWH 5,000 units/d SC until delivery + aspirin 75 mg/d	LMWH + aspirin = 51/51	Pregnancy loss or delivery	LMWH + aspirin = 11/51 (21.6)	NR	NR	NR	NR	
	Aspirin 75 mg/d	Aspirin = 47/47		Aspirin = 13/47 (27.6) RR 0.78 (0.39- 1.57)					
Laskin et al[60]/2009	LMWH 5,000 International Units SC daily until delivery + aspirin 81 mg/d	LMWH + aspirin = 22/22 (100%)	Pregnancy loss or delivery	LMWH + aspirin = 5/22 (22.7)	LMWH + aspirin = 3/17 (17.6)	NR	NR	NR	Early losses not stratified by thrombophilia type

(Continued)

Table S21—*Continued*

Study/Year	Intervention	Number Patients Analyzed	Length of Follow-up	Pregnancy Loss (%)	Fetal Growth Restriction (%)	Preeclampsia (%)	Placental Abruption (%)	Maternal Bleeding (%)	Comments
	Aspirin 81 mg/d	Aspirin = 20/20 (100%)		Aspirin = 5/20 (25.0)	Aspirin = 6/15 (40) (IUGR numbers include one twin who was stillborn)				
				RR 0.91 (0.31-2.68)					
				LMWH + aspirin vs UFH + aspirin					
Stephenson et al[61]/2004	Aspirin 81 mg/d starting prior to conception + LMWH luteal phase or first trimester dalteparin 2,500 International Units SC once daily; second trimester dalteparin 5,000 International Units SC once daily; third trimester dalteparin 7,500 International Units SC once daily	LMWH + aspirin = 14/14 (100.0)	Pregnancy loss or delivery	LMWH + aspirin = 4/13 (30.7)	NR	LMWH + aspirin = 1/9 (11.1)	NR	NR	
	Aspirin 81 mg/d starting prior to conception + UFH luteal phase or first trimester 5,000 units SC bid; second trimester 7,500 units SC bid; third trimester 10,000 units SC bid	UFH + aspirin = 14/14 (100.0)		UFH + aspirin = 9/13 (69.2)		UFH + aspirin = 0/4 (0.0)			
				RR 0.44 (0.18-1.08)		RR 3.00 (0.13-67.52)			

(Continued)

Table S21—*Continued*

Study/Year	Intervention	Number Patients Analyzed	Length of Follow-up	Pregnancy Loss (%)	Fetal Growth Restriction (%)	Preeclampsia (%)	Placental Abruption (%)	Maternal Bleeding (%)	Comments
Hereditary thrombophilia									
LMWH vs aspirin									
Gris et al[62]/2004	LMWH (enoxaparin 40 mg/d SC) + folic acid 5 mg/d	LMWH = 80/80	Pregnancy loss or delivery	LMWH = 11/80 (13.7)	LMWH = 7/71 (9.9)	LMWH = 4/71 (5.6)	NR	NR	
	Aspirin 100 mg/d + folic acid 5 mg/d	Aspirin = 80/80		Aspirin = 57/80 (71.2)	Aspirin = 7/23 (30.4)	Aspirin = 3/23 (13)			
				RR 0.19 (0.11- 0.34)	RR 0.32 (0.13-0.83)	RR 1.33 (4.77-0.69)			
Observational Studies									
Thrombophilia–APLA									
LMWH + aspirin vs UFH + aspirin									
Noble et al[63]/2005	Aspirin 81 mg daily starting prior to conception + LMWH (enoxaparin 40 mg/d SC)	LMWH + aspirin = 25/25	2 wk postdelivery	LMWH + aspirin = 4/25 (16.0)	LMWH + aspirin = 1/21 (4.8)	LMWH + aspirin = 0/21 (0)	NR	LMWH + aspirin = 3/25 (12.0)	All bleeding events classified as minor
	Aspirin 81 mg daily starting prior to conception + UFH (5,000-6,000 units SC bid, depending on weight)	UFH + aspirin = 25/25		UFH + aspirin = 5/25 (20.0)	UFH + aspirin = 1/20 (5.0)	UFH + aspirin = 0/20 (0)		UFH + aspirin = 2/25 (5.0)	
				RR 0.80 (0.24-2.64)	RR 0.95 (0.06-14.22)	RR 1.00 (0.02-48.53)		RR 1.5 (0.27-8.22)	
UFH higher dose + aspirin vs UFH lower dose + aspirin									
Kutteh and Ermel[64]/1996	UFH 5,000 units SC bid adjusted to maintain aPTT at 1.2-1.5 × baseline (higher dose) + aspirin 81 mg/d	UFH higher dose + aspirin = 25/25	Pregnancy loss or delivery	UFH higher dose + aspirin = 5/25 (20.0)	NR	NR	NR	NR	

(Continued)

Table S21—*Continued*

Study/Year	Intervention	Number Patients Analyzed	Length of Follow-up	Pregnancy Loss (%)	Fetal Growth Restriction (%)	Preeclampsia (%)	Placental Abruption (%)	Maternal Bleeding (%)	Comments
	UFH 5,000 units SC bid adjusted to maintain aPTT at upper limit of normal (lower dose) + aspirin 81 mg/d	UFH lower dose + aspirin = 25/25		UFH lower dose + aspirin = 6/25 (24.0) RR 0.83 (0.29-2.38)					
Hereditary thrombophilia									
LMWH vs control									
Carp et al[65]/2003	LMWH (enoxaparin 40 mg/d SC) Retrospective control (no prophylaxis)	LMWH = 37/37 (100%) Control = 48/48 (100%)	Pregnancy loss or delivery	LMWH = 11/37 (29.7) Control = 27/48 (56.3) RR 1.89 (1.09-3.29)	NR	LMWH = 2/26 (7.6) Control = 1/21 (4.8) RR 2.00 (0.19-0.72)	NR	NR	
LMWH vs control (untreated)									
Leduc et al[66]/2007	LMWH (dalteparin) varied between 3,500 and 7,500 International Units SC bid Aspirin 80 mg/d	LMWH = 13/13 (100%) Aspirin = 11/11 (100%)	Chart review 1994-2001	Data on pregnancy loss not stratified by treatment	LMWH OR 0.81 Aspirin OR 0.88	LMWH OR 0.92 Aspirin OR 0.87	Data on placental abruption not stratified by treatment	No major bleeding or maternal mortality reported	OR: the probability of developing an obstetric complication despite prophylactic therapy (interpreted to mean the odds of complication compared with no treatment)

(Continued)

 DOI: 10.1378/chest.11-2300

Table S21—*Continued*

Study/Year	Intervention	Number Patients Analyzed	Length of Follow-up	Pregnancy Loss (%)	Fetal Growth Restriction (%)	Preeclampsia (%)	Placental Abruption (%)	Maternal Bleeding (%)	Comments
				LMWH + aspirin vs control (untreated)					
Leduc et al[66]/2007	LMWH (dalteparin) varied between 3500 IU SC and 7500 IU SC bid + aspirin 80 mg/d	LMWH + aspirin = 26/26 (100%)	Chart review 1994-2001	NR	LMWH + aspirin OR 0.70	LMWH + aspirin OR 0.80	NR	NR	OR: the probability of developing an obstetric complication despite prophylactic therapy (interpreted to mean the odds of complication compared with no treatment)
	LMWH (dalteparin) varied between 3500 and 7,500 International Units SC bid	LMWH = 13/13 (100%)			LMWH OR 0.81	LMWH OR 0.92			
				Aspirin vs control (untreated)					
Leduc et al[66]/2007	LMWH (dalteparin) varied between 3,500 and 7,500 International Units SC bid + aspirin 80 mg/d	LMWH + aspirin = 26/26 (100%)	Chart review 1994-2001	NR	LMWH + aspirin OR 0.70	LMWH + aspirin OR 0.80	NR	NR	OR: the probability of developing an obstetric complication despite prophylactic therapy (interpreted to mean the odds of complication compared with no treatment)
	Aspirin 80 mg/d	Aspirin = 11/11 (100%)			Aspirin 0.88	Aspirin 0.87			

ASA = acetylsalicyclic acid; IUGR = intrauterine growth restriction; NR = not reported. See Table S1, S3, S4, S8, S9, and S17 legends for expansion of other abbreviations.

Table S22—*[Section 10.2.3, 10.2.4] Randomized Trials and Observational Studies of the Prevention of Complications in Pregnant Women With Thrombophilia: Methodologic Quality*

Randomized Trials							
Study/Year	Intervention	Study Design	Randomize Concealed	Blinding	Lost to Follow-up	Analysis	Comments
Thrombophilia-APLA							
Aspirin vs placebo							
Cowchock et al[53]/1997	Aspirin 81 mg/d Usual care	RCT, multicenter	PN	Patients: PN Caregivers: PN Data Collectors: PN Adjudicators: PN Data Analysts: PN	Aspirin = 0/11 Usual care = 0/9	ITT	Population: pregnant women with APLA and either 0 (10/19 patients) or 1 (9/19 patients) prior spontaneous abortion. Women with thrombosis history or lupus excluded. No definition of usual care.
Tulppala et al[54]/1997	Aspirin 50 mg/d Placebo	RCT, single center	PY	Patients: CY Caregivers: PY Data Collectors: PY Adjudicators: PN Data Analysts: PN	Aspirin = 0/6 Placebo = 0/6	ITT	Population: subgroup of 66 pregnant women with three to eight consecutive losses: 12 pregnant women with APLA of whom two had blighted ova (one in each treatment arm), and two had ectopic pregnancies (placebo group).
Pattison et al[55]/2000	Aspirin 75 mg/d Placebo	RCT, single center	CY	Patients: CY Caregivers: CY Data Collectors: CY Adjudicators: PN Data Analysts: PN	Aspirin = 5/25 Placebo = 5/25 (5 postrandomization exclusions from each treatment arm)	Not ITT	Population: pregnant women with APLA and three or more fetal losses. Women with thrombosis history or lupus excluded. Ten exclusions after randomization because of inappropriate inclusion. Randomization not balanced for mean gravidity and number of first trimester losses (both favoring aspirin).
UFH + aspirin vs aspirin alone							
Rai et al[56]/1997	UFH 5,000 units SC bid + aspirin 75 mg/d Aspirin 75 mg/d	RCT, single center	PN	Patients: CN Caregivers: CN Data Collectors: PN Adjudicators: PN Data Analysts: PN	UFH + aspirin = 0/45 Aspirin = 0/45	ITT	Population: pregnant women with APLA and three or more consecutive miscarriages. Women with prior thrombosis or lupus excluded. Treatment stopped at 34 wk or miscarriage.

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 DOI: 10.1378/chest.11-2300

Table S22—*Continued*

Randomized Trials							
Study/Year	Intervention	Study Design	Randomize Concealed	Blinding	Lost to Follow-up	Analysis	Comments
Goel et al[57]/2006	UFH 5,000 International Units SC bid + aspirin 80 mg/d Aspirin 80 mg/d	RCT, multicenter	NR	Patients: DN Caregivers: DN Data Collectors: PN Adjudicators: PN Data Analysts: PN	UFH + aspirin = 0/39 Aspirin = 0/33	ITT	Population: pregnant women with APLA (anticardiolipin) with two or more first or second trimester miscarriages. Treatment discontinued at 36 wk gestation.
Kutteh[58]/1996	UFH 5,000 units SC bid adjusted to attain 6 h postinjection aPTT at 1.2-1.5 times baseline + aspirin 81 mg/d Aspirin 81 mg/d	RCT, single center	Quasi-randomized	Patients: DN Caregivers: DN Data Collectors: PN Adjudicators: PN Data Analysts: PN	UFH + aspirin = 0/25 Aspirin = 0/25	No	Population: pregnant women with APLA and three or more consecutive miscarriages (women with NSI or lupus excluded). Alternate assignment of treatment. USPSTF rating of evidence is II-1.
LMWH + aspirin vs aspirin alone							
Farquharson et al[59]/2002	LMWH 5,000 units/d SC until delivery + aspirin 75 mg/d Aspirin 75 mg/d	RCT, single center	CY	Patients: CN Caregivers: CN Data Collectors: CN Adjudicators: CN Data Analysts: CN	LMWH = 0/51 Aspirin = 0/47	ITT	Population: pregnant women with APLA and at least three consecutive losses or two losses with fetal death after 10 wk.
Laskin et al[60]/2009	LMWH 5,000 International Units SC daily until delivery + aspirin 81 mg/d Aspirin 81 mg/d	Open label, RCT, single center	Not NR	Patients: DN Caregivers: DN Data Collectors: PN Adjudicators: PN Data Analysts: PN	LMWH + aspirin = 0/22 (0%) Aspirin = 0/20 (0%)	ITT	Population: pregnant women with APLA or inherited thrombophilia or ANA (only APLA able to be considered here) with two or more unexplained consecutive pregnancy losses prior to 32 wk. Treatment with LMWH stopped at 35 wk or delivery.

(Continued)

 DOI: 10.1378/chest.11-2300

Table S22—*Continued*

Randomized Trials							
Study/Year	Intervention	Study Design	Randomize Concealed	Blinding	Lost to Follow-up	Analysis	Comments
LMWH + aspirin vs UFH + aspirin							
Stephenson et al[61]/2004	Aspirin 81 mg/d starting prior to conception + LMWH (luteal phase or first trimester dalteparin 2,500 International Units SC once daily; second trimester dalteparin 5,000 International Units SC once daily; third trimester dalteparin 7,500 International Units SC once daily) Aspirin 81 mg/d starting prior to conception + UFH (luteal phase or first trimester 5,000 units SC bid; second trimester 7,500 units SC bid; third trimester 10,000 units SC bid)	Open-label, RCT, single center	CY	Patients: CN Caregivers: CN Data Collectors: CN Adjudicators: PN Data Analysts: PN	In patients who became pregnant: LMWH + aspirin = 0/13 UFH + aspirin = 0/13	Unclear whether ITT	Population: women with APLA and recurrent losses. Patients randomized prior to conception (one patient in each group did not become pregnant during study). Hereditary thrombophilia.
Hereditary thromphilia							
LMWH vs aspirin alone							
Gris et al[62]/2004	LMWH (enoxaparin 40 mg/d SC) and folic acid 5 mg/d Aspirin 100 mg/d and folic acid 5 mg/d	RCT	CY	Patients: CN Caregivers: CN Data Collectors: PN Adjudicators: PN Data Analysts: PN	14/174 (8%) lost prior to allocation LMWH = 0/80 Aspirin = 0/80	Unclear whether ITT	Population: women with factor V Leiden, prothrombin gene mutation, or protein S deficiency and a single loss after 10 wk. Women with other hereditary thrombophilia, lupus, APLA, or prior thrombosis were excluded.

(Continued)

Table S22—*Continued*

Observational Studies								
Study/Year	Intervention	Study Design	Intervention/Control Setting Similar?	Intervention/Control Time Frame Similar?	Adjustment	Effectively Blinded Assessment of Outcome	Lost to Follow-up	Comments
Noble et al[63]/2005	Aspirin 81 mg/d starting prior to conception + LMWH (enoxaparin 40 mg/d SC) Aspirin 81 mg/d starting prior to conception + UFH (5,000-6,000 units SC bid, depending on weight)	Prospective cohort, two center	Very	Identical	All relevant variables	No	LMWH + aspirin = 0/25 UFH + aspirin = 0/25	Population: women with APLA and three or more pregnancy losses before 20 wk. Treatment regimen based on enrolling center. LMWH stopped 3 wk before estimated due date or 5 d prior to scheduled induction or cesarean section. UFH discontinued with spontaneous labor.
UFH higher dose + aspirin vs UFH lower dose + aspirin								
Kutteh and Ermel[64]/1996	UFH 5,000 units SC bid adjusted to maintain aPTT at 1.2 to 1.5 times baseline (higher dose) + aspirin 81 mg/d UFH 5,000 units SC bid adjusted to maintain aPTT at upper limit of normal (lower dose) + aspirin 81 mg/d	Prospective cohort, single center	Very	Close	All relevant variables	No	UFH (higher dose) + aspirin = 0/25 UFH (lower dose) + aspirin = 0/25	Population: pregnant women with APLA and at least three consecutive miscarriages. Women with NSI or lupus excluded. Alternate assignment of treatments.

(Continued)

Table S22—*Continued*

Observational Studies								
Study/Year	Intervention	Study Design	Intervention/Control Setting Similar?	Intervention/Control Time Frame Similar?	Adjustment	Effectively Blinded Assessment of Outcome	Lost to Follow-up	Comments
Hereditary thrombophilia								
LMWH vs control								
Carp et al[65]/2003	LMWH (enoxaparin 40 mg/d SC) Retrospective control (no prophylaxis)	Prospective cohort, single center	Very	Close	Most	No	LMWH = 0/37 Control = 0/48	Population: women with hereditary thrombophilia and three or more consecutive losses in first or second trimesters. Patients were excluded if prior thrombosis or APLA. Controls were women retrieved from a database, matched for number of miscarriages, maternal age, and time taken to conceive.
LMWH + aspirin vs aspirin vs LMWH								
Leduc et al[66]/2007	LMWH (dalteparin) varied between 3,500 and 7,500 International Units SC bid + aspirin 80 mg/d Aspirin 80 mg/d LMWH (dalteparin) varied between 3,500 and 7,500 International Units SC bid	Retrospective cohort, single center	Very	Identical	Some: use of LMWH or ASA and gestation age	No	LMWH + aspirin = 0/26 Aspirin = 0/11 LMWH = 0/13	Population: women who received antithrombotic prophylaxis during pregnancy between 1997 and 2001 or a history of previous pregnancy complicated by severe preeclampsia, placental abruption, fetal growth restriction, second or third trimester fetal loss, and associated hereditary thrombophilia. Excluded if previous thromboembolic disorder or APLA.

ANA = antinuclear antibody; CY = certain yes; DN = definite no; NSI = nonspecific inhibitor; PN = probable no; PY = probable yes. See Table S1, S4, S8, S9, and legends S17 for expansion of other abbreviations.

Table S23—*[Section 10.2.1,10.2.3] Evidence Profile: Should UFH Plus Aspirin or Aspirin Alone Be Used for Pregnant Women With APLA and Recurrent Pregnancy Loss?*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[a]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Aspirin[b]	With UFH + Aspirin	Relative Effect (95% CI)	Risk With Aspirin[b]	Risk Difference With Addition of UFH (95% CI)
Pregnancy loss (critical outcome)											
212 (3 RCTs), not reported	Serious risk of bias Issues of randomization, allocation concealment, and blinding	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate due to risk of bias	55/109 (50)	23/103 (22)	RR 0.44 (0.30-0.66)	500 pregnancy losses per 1,000	283 fewer pregnancy losses per 1,000 (from 172 fewer to 353 fewer)
IUGR (critical outcome) estimated fetal weight < 10th percentile for gestational age											
134 (3 RCTs), not reported	Serious risk of bias Issues of randomization, allocation concealment, and blinding	No serious inconsistency	No serious indirectness	Very serious imprecision CI includes important benefit and harm	Undetected	Very low due to risk of bias and imprecision	3/54 (5.6)	8/80 (10)	RR 1.71 (0.48-6.17)	56 IUGR per 1,000	39 more IUGR per 1,000 (from 29 fewer to 287 more)

(Continued)

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Table S23—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[a]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Aspirin[b]	With UFH + Aspirin	Relative Effect (95% CI)	Risk With Aspirin[b]	Risk Difference With Addition of UFH (95% CI)
Preeclampsia (critical outcome) not clearly defined											
134 (3 RCTs), not reported	Serious risk of bias Issues of randomization, allocation concealment, and blinding	No serious inconsistency	No serious indirectness	Serious imprecision CI includes important benefit and harm	Undetected	Low due to risk of bias and imprecision	4/54 (7.4)	2/80 (2.5)	RR 0.43 (0.09-2.08)	74 preeclampsia per 1,000	42 fewer preeclampsia per 1,000 (from 67 fewer to 80 more)
Major Bleeding (critical outcome) not reported[c]											

Bibliography: Data from unpublished meta-analysis based on three trials: Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol*. 1996;174:1584-1589. Rai R, Cohen H, Dave M, et al. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ*. 1997;314:253-257. Goel N, Tuli A, Choudhry R. The role of aspirin versus aspirin and heparin in cases of recurrent abortions with raised anticardiolipin antibodies. *Med Sci Monit*. 2006(3):CR132-CR136. PO Vandvik, MD, personal communication, October 2010. See Table S1, S3, S9, and S21 legends for expansion of abbreviation.

[a] Time frame is 9 mo for all outcomes.

[b] Estimates for baseline risk with aspirin comes from the meta-analysis of three trials.

[c] Although a patient important outcome defined as in 1, none of the three trials reported major bleeding events.

Table S24—*[Section 11.1.1] Evidence Profile: Should Aspirin Rather Than No Treatment Be Used for Prevention of Preeclampsia in Women Without Thrombophilia?*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects During Pregnancy	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Without Prophylaxis	With LWMH	Relative Effect (95% CI)	Risk Without Prophylaxis	Risk Difference With LMWH (95% CI)
Preeclampsia (critical outcome) defined as proteinuric preeclampsia in Cochrane systematic review											
32,590 (43 RCTs,) not reported	No serious risk of bias Variability across trials but not considered to introduce bias	Serious inconsistency[a] $I^2 = 46$, $P < .001$	No serious indirectness	No serious imprecision Benefit even at lower end of CI	Undetected	Moderate due to inconsistency	1,292/16,194 (8)	1,081/16,396 (6.6)	RR 0.83 (0.77-0.89)	Low risk for preeclampsia	
										60 cases per 1,000[b]	10 fewer per 1,000 (from 14 fewer to 7 fewer)
										High risk for preeclampsia	
										210 per 1,000[b]	38 fewer per 1,000 (from 46 fewer to 23 fewer)
Major bleed (critical outcome)[c]											
95,000 (6 RCTs), 3.8-10 y	No serious risk of bias	No serious inconsistency	Serious indirectness[d] Primary prevention cardiovascular disease	No serious imprecision	Undetected	Moderate due to indirectness	219/47,500 (0.5)	335/47,500 (0.7)	RR 1.54 (1.30-1.82)	15 bleeding events per 1,000[e]	8 more bleeding events per 1,000 (from 5 more to 12 more)

Bibliography: Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev.* 2007;(2):CD004659. 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;106:401-407. See Table S3, S4, and S9 legends for expansion of abbreviations.

[a] Heterogeneity might be related to different types and doses of antiplatelet agents, the lack of placebo in the control group in many of the trials, different populations of pregnant women concerning risk of preeclampsia, and effect of treatment.

[b] Control group risk estimate for preeclampsia is based on control event rates in studies included in subgroup analyses in the meta-analysis. High risk was defined in the systematic review as women who either were normotensive or had chronic hypertension without superimposed preeclampsia at trial entry and were classified as being at high risk if they had one or more of the following: previous severe preeclampsia, diabetes, chronic hypertension, renal disease, or autoimmune disease.

[c] Major antenatal maternal hemorrhage.

[d] Rated down for indirectness due to population (people included in trials of primary prevention cardiovascular disease). The Cochrane review does not report the effects of antiplatelet therapy on major bleeding events in pregnant women.

[e] Control group risk estimate for major bleeding events antepartum from systematic review by Greer et al.

Table S25—*[Section 11.2.1] Evidence Profile: Should LMWH and Aspirin Rather Than No Treatment Be Used for Prevention of Recurrent Pregnancy Loss in Women Without Thrombophilia?*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects During Pregnancy	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Without Treatment	With LMWH and Aspirin	Relative Effect (95% CI)	Risk Without Treatment	Risk Difference With LMWH and Aspirin (95% CI)
Miscarriage (critical outcome)											
294 (2 RCTs), 9 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision CI includes important benefit and harm	Undetected	Moderate due to imprecision	62/250 (25.2)	62/244 (25.4)	RR 1.01 (0.84-1.38)	300 cases per 1,000[a]	3 more per 1,000 (from 48 fewer to 114 more)
Major bleeding (critical outcome) antepartum hemorrhage[b,c]											
294 (1 RCT), 9 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision CI includes benefit and harm	Undetected	Moderate due to imprecision	10/147 (6.8)	10/147 (6.8)	RR 1.00 (0.42-2.33)	15 bleeding events per 1,000[c]	0 more bleeding events per 1,000 (from 9 fewer to 20 more)

Bibliography: 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;106:401-407. Data from an unpublished meta-analysis[d] of two RCTs by Kaandorp SP, Mariëtte Goddijn M, van der Post JAM, et al. Aspirin combined with low-molecular-weight heparin and aspirin alone in women with recurrent miscarriage. A randomized placebo-controlled trial: the ALIFE study. *N Engl J Med*. 2010;29:1586-1596 and Clark P, Walker ID, Langhorne P, et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. *Blood*. 2010;115:4162-4167. See Table S3, S4, and S9 legends for expansion of abbreviations.

[a] Control group risk for miscarriage comes from study event rates in the two available randomized trials by Kaandorp and Clark.

[b] Bleeding outcomes variably reported in the two trials. We use data from Clark et al on serious adverse events and antepartum hemorrhage to generate both relative risks and baseline risks for anticipated absolute effects. Kaandorp et al reported nose bleed, GI problem, hematuria, and bleeding gums. There were no major bleeding events (S. Middeldorp, MD, personal communication, October 2010).

[c] Control group risk estimate for major bleeding events antepartum comes from systematic review by Greer et al.

[d] Meta-analysis performed in RevMan version 5 with fixed-effects model for heterogeneity.

Table S26—*[Section 11.2.1] Evidence Profile: Should Aspirin Rather Than No Treatment Be Used for Prevention of Recurrent Pregnancy Loss in Women Without Thrombophilia?*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects During Pregnancy	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Without Treatment	With Aspirin	Relative Effect (95% CI)	Risk Without Treatment	Risk Difference With Aspirin (95% CI)
Miscarriage (critical outcome)											
202 (1 RCTs), 9 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision CI includes important benefit and harm	Undetected	Moderate due to imprecision	34/103 (33)	38/99 (38)	RR 1.16 (0.80-1.69)	300 cases per 1,000[a]	48 more per 1,000 (from 60 fewer to 207 more)
Major bleeding (critical outcome) antepartum hemorrhage[b,c]											
95,000 (6 RCTs), 3.8-10 y	No serious risk of bias	No serious inconsistency	Serious indirectness[c] Primary prevention cardiovascular disease	No serious imprecision	Undetected	Moderate due to indirectness	219/47,500 (0.5)	335/47,500 (0.7)	RR 1.54 (1.30-1.82)	15 bleeding events per 1,000[d]	8 more bleeding events per 1,000 (from 5 more to 12 more)

Bibliography: Kaandorp SP, Mariëtte Goddijn M, van der Post JAM et al. Aspirin combined with low-molecular-weight heparin and aspirin alone in women with recurrent miscarriage. A randomized placebo-controlled trial: the ALIFE study. *New Engl J Med.* 2010;29;362:1586-1596. Clark P, Walker ID, Langhorne P, et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. *Blood.* 2010;115:4162-4167. 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;106:401-407. See Table S3 and S9 legends for expansion of abbreviations.

[a] Baseline risk for miscarriage comes from study event rates in the two available randomized trials by Kaandorp et al and Clark et al.

[b] Major antenatal nonfatal hemorrhage.

[c] Rated down for indirectness due to population (primary prevention cardiovascular disease). There were no major bleeding events in the ALIFE Study (personal communication with authors).

[d] Control group risk estimate for major bleeding events antepartum comes from systematic review by Greer et al.

[e] Only study identified that compared aspirin to placebo in this population.

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Table S27—*[Section 12.1.1-12.1.3] Systematic Reviews Examining Maternal and Fetal Safety of Anticoagulant Regimens in Pregnant Women With Mechanical Heart Valves (Methodologic Quality)*

Study/Year	Intervention	Inclusive Literature Search	Duplicate Study Selection and Data Extraction	List of Studies (Included and Excluded) Provided	Characteristics of Included Studies Provided	Assessment of Quality of Included Studies	Appropriate Methods Used to Combine Study Findings	Assessment of Likelihood of Publication Bias
Chan et al[1]/2000	Studies between 1966 and 1997 examining the use of VKAs and UFH or no anticoagulation in pregnant women with mechanical heart valves	Yes	No	No	No	No	Yes	No
Hassouna and Allam[2]/2010	Studies between 2000 and 2009 examining the use of VKAs and UFH or no anticoagulation in pregnant women with mechanical heart valves	No	Bi	No	No	No	Yes	No
James et al[67]/2006	Studies between 1966 and 2006 involving pregnant women with mechanical heart valves receiving LMWH	No	No	No	Yes	No	N/A	No
Oran et al[68]/2004	Studies between 1989 and 2004 involving pregnant women with mechanical heart valves who received heparin	Yes	No	No	Yes	No	N/A	No

See Table S1 and S4 legends for expansion of abbreviations.

Table S28—*[Section 12.1.1-12.1.3] Antithrombotic Therapy in Pregnant Women With Mechanical Heart Valves—Maternal Outcomes (Clinical Description and Results)*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Maternal Deaths, n/N (%)	Maternal Intracranial Bleeding events, n/N (%)	Maternal Extracranial Bleeding events, n/N (%)	Maternal Systemic Thromboembolism, n/N (%)
Cohort studies with comparator groups							
Iran, retrospective, Khamooshi et al[69]/2007	110 women 196 pregnancies	Pregnant women with mechanical heart valves Valve type Tilting: 98 Bileaflet: 98 Valve position Aortic: 26 Mitral: 128 Aortic and mitral: 42	Regimen 1 warfarin throughout pregnancy; INR checked monthly and kept 2.5-3.5	Regimen 1, 5/142 (3.5)	Regimen 1, 0/142 (0.0)	Regimen 1, 0/142 (0.0)	Regimen 1, 6/142 (3.1) (3 valve thrombosis, 3 embolism)
			Regimen 2 SC UFH for the first trimester, warfarin until week 36, then UFH for remainder of pregnancy; aPTT kept 2 times control	Regimen 2, 2/54 (3.7)	Regimen 2, 0/54 (0.0)	Regimen 2, 2/54 (3.7) (2 vaginal bleeding events treated conservatively)	Regimen 2, 9/54 (16.7) (7 valve thrombosis, 2 embolism)
				No fatal maternal bleeding events		No major GI or major obstetrical bleeding events	
Korea, retrospective, Lee et al[70]/2007	25 women 31 pregnancies	Pregnant women with mechanical heart valves Valve position Aortic: 4 Mitral: 21 Double valve replacement: 5	Regimen 1 coumarin and aspirin throughout pregnancy with target INR 2.5-3.5, then nadroparin 7,500 units SC q12h for 2 wk before due date	Regimen 1, 0/8 (0)	Regimen 1, 0/8 (0.0)	Regimen 1, 0/23 (0.0)	Regimen 1, 2/8 (25.0) (1 valve thrombosis, 1 TIA)
			Regimen 2 nadroparin 7,500 units SC q12h until week 12, then coumarins until week 38 when nadroparin resumed. Aspirin 100 mg/d throughout pregnancy	Regimen 2, 0/23 (0)	Regimen 2, 0/23 (0.0)	Regimen 2, 023 (0.0)	Regimen 2, 3/23 (13.0) (2 valve thrombosis, 1 TIA)
				No fatal maternal bleeding events		No maternal major GI or major obstetrical bleeding events	

(Continued)

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Table S28—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Maternal Deaths, n/N (%)	Maternal Intracranial Bleeding events, n/N (%)	Maternal Extracranial Bleeding events, n/N (%)	Maternal Systemic Thromboembolism, n/N (%)
New Zealand, retrospective audit, McLintock et al[71]/2009	31 women 47 pregnancies	Pregnant women with mechanical heart valves Valve type Starr-Edwards: 12 Tilting disc or bileaflet: 19 Valve position Mitral:14 Aortic: 4 Mitral and aortic: 13	Regimen 1 predominantly warfarin and aspirin (100-150 mg) throughout with enoxaparin (1 mg/kg SC q12h) and aspirin substituted between weeks 6 and 12 and at 34 and 36 wk gestation Regimen 2 enoxaparin (1 mg/kg SC q12h) and aspirin (100-150 mg) predominantly In both regimens, enoxaparin monitored by anti-Xa levels every 3-7 d; dose adjusted to attain a target predose level: 0.4-0.7 International Units/mL	Regimen 1, 0/13 (0.0) Regimen 2, 0/34 (0.0) No fatal maternal bleeding events	Regimen 1, 0/13 (0.0) Regimen 2, 0/34 (0.0)	Unable to separate by regimen Maternal major GI bleeding events: 0/47 (1 minor hematemesis with enoxaparin) Maternal major obstetrical bleeding events: 19/47 (2 abruptions and 1 antepartum hemorrhage with enoxaparin; 1 additional abruption during IV UFH around delivery; 1 additional minor antepartum hemorrhage with enoxaparin; 6 primary postpartum hemorrhages and 9 secondary postpartum hemorrhages) Major bleeding from other site: 1/47 (rectus sheath and epistaxis with IV UFH around delivery)	Regimen 1, 0/13 (0) Regimen 2, 5/34 (14.7) (1 valve thrombosis, 4 TIA, 3/5 associated with noncompliance, 2 events postpartum)

(Continued)

Table S28—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Maternal Deaths, n/N (%)	Maternal Intracranial Bleeding events, n/N (%)	Maternal Extracranial Bleeding events, n/N (%)	Maternal Systemic Thromboembolism, n/N (%)
			Single-group cohort studies				
Norway, retrospective, Abildgaard et al[72]/2009	11 women 12 pregnancies	Pregnant women with mechanical heart valves Valve position Mitral: 4 Aortic: 6 Aortic and mitral: 2	Therapeutic doses of LMWH q12h throughout pregnancy. Aspirin 75 mg/d recommended but discontinued 1 wk before expected delivery date Doses adjusted to attain peak anti-Xa level of 0.7-1.2 units/mL	0/12 (0.0) 1 subject who died suddenly at 11 wk with no autopsy evidence of bleeding or thrombosis excluded from analysis No maternal fatal bleeding events reported	0/12 (0.0)	4/12 (33.3) No maternal major GI bleeding events Maternal major obstetrical bleeding events: 4 (all postpartum or postcesarean section)	2/12 (16.7) (both associated with subtherapeutic dosing of LMWH) Maternal ischemic stroke: 1 Maternal nonstroke systemic embolism: 0 Maternal valve thrombosis: 1
Japan, retrospective, Kawamata et al[73]/2007	12 women 16 pregnancies	Pregnant women with mechanical heart valves Valve position Mitral: 7 Aortic: 2 Tricuspid: 7	Substitution of warfarin with UFH starting between 6-13 wk and until term Doses adjusted to maintain aPTT levels 2-3 times control (between 20,000 and 30,000 International Units/d)	1/16 (6.3) (death of mother and fetus during replacement of thrombosed valve) No fatal maternal bleeding events	2/16 (12.5)	7/16 (43.8) No maternal major GI bleeding events Maternal major obstetrical bleeding events: 7 (4 perinatal bleeding, 3 subchorionic bleeding events)	3/16 (13.8) Maternal ischemic stroke: 0 No maternal nonstroke systemic embolism: 0 Maternal valve thrombosis: 2

(Continued)

Table S28—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Maternal Deaths, n/N (%)	Maternal Intracranial Bleeding events, n/N (%)	Maternal Extracranial Bleeding events, n/N (%)	Maternal Systemic Thromboembolism, n/N (%)
England, prospective, Quinn et al[74]/2009	11 women 12 pregnancies	Pregnant women with mechanical heart valves Valve position Mitral: 4 Aortic: 2 Aortic and mitral: 3 Systemic right atrioventricular valve: 2	Dalteparin 100 International Units/kg q12h (8) or enoxaparin 1 mg/kg q12h (4) + aspirin 81 mg/d LMWH doses adjusted to attain an anti-Xa level 1.0-1.2 units/mL	0/12 (0.0) No maternal fetal bleeding events reported	Not reported	6/12 (50.0) (3 minor, epistaxis, placental hematoma, secondary postpartum hemorrhage; 3 major as below) No maternal major GI bleeding events reported Maternal major obstetrical bleeding events: 3 (antepartum hemorrhage with placenta previa, persistent cervical hematoma and vaginal bleeding leading to cesarean section, postpartum hemorrhage)	1/12 (8.3) (associated with subtherapeutic anti-Xa levels) No maternal ischemic stroke reported. No maternal nonstroke systemic embolism reported. Maternal valve thrombosis: 1
Canada, prospective, Yinon et al[75]/2009	17 women 23 pregnancies	Pregnant women with mechanical heart valves Valve position Mitral: 14 Aortic: 8 Aortic and mitral: 1	LMWH SC q12h. Low-dose aspirin (81 mg/d) administered to all patients LWMH dose adjusted to maintain 4 h postinjection anti-Xa level 1-1.2 International Units/mL	1/23 (4.3) (fatal TIA/valve thrombosis) No fatal maternal bleeding events	0/23 (0.0)	3/23 (13.0) (2 minor postpartum and 1 major bleeding events as below) No major maternal GI bleeding events Major maternal obstetrical bleeding events: 1/23 (large uterine hematoma postcesarean section requiring transfusion)	1/23 (4.3) Maternal ischemic stroke: 1 Maternal nonstroke systemic embolism: 0 Maternal valve thrombosis: 1

(Continued)

Table S28—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Maternal Deaths, n/N (%)	Maternal Intracranial Bleeding events, n/N (%)	Maternal Extracranial Bleeding events, n/N (%)	Maternal Systemic Thromboembolism, n/N (%)
			Systematic reviews				
Canada, Chan[1]/2000	976 women 1,234 pregnancies	Studies between 1966 and 1997 involving pregnant women with mechanical heart valves Valve type Cage and ball: 433 Single-tilting disc: 356 Bileaflet: 62 Other: 20 Heterograft: 1 Unknown: 104 Position Mitral: 647 Aortic: 202 Tricuspid: 1 >1 valve: 126 Valve position Mitral: 647 Aortic: 202 Tricuspid: 1 >1 valve: 126 Total: 976	Regimen 1 oral anticoagulants throughout pregnancy Regimen 2 substitution of UFH in the first trimester either at or before 6 wk, after 6 wk, or at unknown time in the first trimester Regimen 3 UFH throughout pregnancy-adjusted dose or low dose (≤15,000 units/d) Regimen 4 no anticoagulants, including use of antiplatelet agents alone	Overall: 25/854 (2.9%) Regimen 1, 10/561 (1.8) Regimen 2, 7/167, (4.2) Regimen 3, 3/20 (15.0) Adjusted-dose UFH: 1/15 (6.7) Low-dose UFH: 2/5 (40) Regimen 4, 5/106, (4.7) Nothing: 2/3, (5.4) Antiplatelet: 3/69 (4.3) Fatal maternal bleeding events: 2	Overall: 0/1234 (0.0)	Overall major bleeding events: 31/1234 (2.5) (25 at delivery, 6 outside delivery); unable to separate by regimen or specific location	Regimen 1, 31/788 (3.9) Regimen 2, 21/229 (9.2) Regimen 3, 7/21 (33.3) Adjusted-dose UFH: 4/16 (25.0) Low-dose UFH: 3/5 (60.0) Regimen 4, 26/107 (24.3) Nothing: 6/38 (15.8) Antiplatelet: 20/69 (29) Maternal ischemic stroke: 0 Maternal nonstroke systemic embolism: 0 Maternal valve thrombosis: 17 [all fatal]

(Continued)

Table S28—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Maternal Deaths, n/N (%)	Maternal Intracranial Bleeding events, n/N (%)	Maternal Extracranial Bleeding events, n/N (%)	Maternal Systemic Thromboembolism, n/N (%)
United States, James et al[67]/2006	76 pregnancies	Studies between 1966 and 2006 involving pregnant women with mechanical heart valves receiving LMWH Valve type Cage and ball: 4 Single-tilting disc: 2 Bileaflet: 8 Sorin: 1 Unknown: 61 Valve position Mitral: 24 Aortic: 12 Bjork-Shiley: 2 Unknown: 40	Conversion to LMWH prior to pregnancy or by the end of first trimester LMWH Enoxaparin: 32 Nadroparin: 20 Dalteparin: 13 Tinzaparin: 2 Reviparin: 1 Unknown: 8 Addition of low-dose aspirin: 13 Varying regimens ranging from a fixed subtherapeutic dose to weight-adjusted therapeutic doses Monitoring of anti-factor Xa levels: 43. The minimum value for the target ranges was 0.5, and the maximum was 1.2.	3/76 (3.9) Fatal maternal bleeding events: 1 (1 intracranial bleed during conversion to warfarin postdelivery)	1/76 (1.3) (1 intracranial bleed during conversion to warfarin postdelivery)	6/76 (7.9) (4 minor bleeding events [2 hematomas, 1 subchorionic hematoma, 1 delayed broad ligament hematoma] and 2 major bleeding events as below) No major maternal GI bleeding events Major maternal obstetrical bleeding events: 2 (1 peripartum hemorrhage requiring transfusion, 1 delayed postpartum hemorrhage requiring transfusion)	17/76 (22.4) Maternal ischemic stroke: 2 Maternal nonstroke systemic embolism: 2 (myocardial infarction) Maternal valve thrombosis: 13 (2 fatal)

(Continued)

Table S28—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Maternal Deaths, n/N (%)	Maternal Intracranial Bleeding events, n/N (%)	Maternal Extracranial Bleeding events, n/N (%)	Maternal Systemic Thromboembolism, n/N (%)
United States, Oran et al[68]/2004	75 women 81 pregnancies	Studies between 1989 and 2004 involving pregnant women with mechanical heart valves who received LMWH Valve position Mitral: 44 Aortic: 8 Mitral and aortic: 5 Unknown: 18	Cases were included if LMWH was received during pregnancy irrespective of this type, dose and duration and administration of different anticoagulant regimens other than LMWH during the same pregnancy. Conversion to LMWH occurred 1 mo before conception in 2 women; in the remainder, conversion to LMWH occurred during pregnancy LMWH use during second half of first trimester and at term: 21 LMWH throughout pregnancy: 60. LMWH Enoxaparin: 35 Nadroparin: 21 Daltaparin: 11 Tinzaparin: 3 Reviparin: 1 Unknown: 10 Dose adjusted to therapeutic anti-Xa level: 51 Fixed dose: 30	1/81 (1.2) Fatal maternal bleeding events: 1 (intracranial bleed 3 mo postpartum with no monitoring of INRs)	1/81 (1.2) (intracranial bleed 3 mo postpartum with no monitoring of INRs)	3/81 (3.7) Anti-Xa-adjusted LMWH: 2 (hematomas at cesarean incision) Fixed-dose LMWH: 1 (peripartum hemorrhage) No major maternal GI bleeding events Major maternal obstetrical bleeding events: 1 (peripartum)	10/81 (12.3) Anti-Xa-adjusted LMWH: 1 (valve thrombosis) Fixed-dose LMWH: 9 (6 valve thrombosis, 2 cerebrovascular accidents, 1 embolism) Maternal ischemic stroke: 2 Maternal nonstroke embolism (type not reported): 1 Maternal valve thrombosis: 7 (8.64%)

(Continued)

Table S28—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Maternal Deaths, n/N (%)	Maternal Intracranial Bleeding events, n/N (%)	Maternal Extracranial Bleeding events, n/N (%)	Maternal Systemic Thromboembolism, n/N (%)
Egypt, Hassouna and Allam[2]/2009	892 women 1,231 pregnancies	Studies published between January 2000 and September 2009 involving pregnant women with mechanical heart valves who received defined anticoagulant regimens Valve type Cage and ball: 134 Tilting disc: 382 Bileaflet: 341 Undefined: 256 Valve position Mitral: 671 Aortic: 141 Mitral and aortic: 147 + 147 Tricuspid: 7	Regimen 1 VKAs throughout pregnancy with and without UFH or LMWH substitution near term Regimen 2 UFH or LMWH substitution during the first trimester and near term Regimen 3 UFH or LMWH throughout pregnancy Regimen 4 no anticoagulants	Overall: 16/974, (1.6) Regimen 1, 7/605 (1.1) Regimen 2, 4/236 (1.7) Regimen 3, 5/107 (4.7) Regimen 4, 0/26 (0) Fatal maternal fatal bleeding events: 2 Fatal maternal thrombosis: 8	Not reported	Overall: 65/1343 (4.8) Regimen 1, 35/833 (4.2) Regimen 2, 11/322 (3.4) Regimen 3, 17/157 (10.8) Regimen 4, 2/31 (6.4) Major maternal GI bleeding events: not reported Maternal major obstetrical bleeding events: 55 (occurred at delivery)	Overall: 77/1343 (5.7) Regimen 1, 24/833 (2.9%) Regimen 2, 23/322 (7.2%) Regimen 3, 21/157 (13.4%) Regimen 4, 9/31 (29%) Maternal ischemic stroke and nonstroke systemic embolism: 26 Maternal valve thrombosis: 51

TIA = transient ischemic attack. See Tables S1, S4, and S17 for expansion of other abbreviations.

Table S29—*[Section 12.1.1-12.1.3] Antithrombotic Therapy in Pregnant Women With Mechanical Heart Valves—Fetal and Neonatal Outcomes (Clinical Description and Results)*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Congenital Malformations, n/N (%)	Fetal and/or Neonatal Hemorrhage, n/N (%)	Total Pregnancy Loss, n/N (%)	Early Pregnancy Loss, n/N (%)	Late Pregnancy Loss, n/N (%)	Neonatal Death
Cohort studies with comparator groups									
Iran, retrospective, Khamooshi et al[75]/2007	110 women 196 pregnancies	Pregnant women with mechanical heart valves Valve type Tilting: 98 Bileaflet: 98 Valve position Aortic: 26 Mitral: 128 Aortic and mitral: 42	Regimen 1 warfarin throughout pregnancy; INR checked monthly and kept 2.5-3.5 Regimen 2 SC UFH for the first trimester, warfarin until week 36, then UFH for remainder of pregnancy; aPTT kept 2 times control	Regimen 1, 7/142 (4.9) Regimen 2, 1/54 (1.9) Malformations included hydrocephalus (2), stabismus (3), telebrachydactyly (1), nasal hypoplasia (1)	Not reported	Regimen 1, 71/142 (50) Regimen 2, 10/54 (18.5)	Regimen 1, 66/142 (46.5) Regimen 2, 8/54 (14.8)	Regimen 1, 5/142 (3.5) Regimen 2, 2 /54 (3.7)	Unable to separate neonatal deaths from premature births

(Continued)

Table S29—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Congenital Malformations, n/N (%)	Fetal and/or Neonatal Hemorrhage, n/N (%)	Total Pregnancy Loss, n/N (%)	Early Pregnancy Loss, n/N (%)	Late Pregnancy Loss, n/N (%)	Neonatal Death
Korea, retrospective, Lee et al[73]/2007	25 women 31 pregnancies	Pregnant women with mechanical heart valves Valve position Aortic: 4 Mitral: 21 Double valve replacement: 5	Regimen 1 coumarin and aspirin throughout pregnancy with target INR 2.5-3.5, then nadroparin 7,500 units SC q12h for 2 wk before due date	Regimen 1, 1/23 (3.2) (hydrocephalus)	Not reported	Regimen 1, 4/8 (50) (1 loss was associated with maternal valve thrombosis)	Not specified	Not specified	Not specified
			Regimen 2 nadroparin 7,500 units SC q12 until week 12, then coumarins until week 38 when nadroparin resumed Aspirin 100 mg/d throughout pregnancy	Regimen 2, 0/8 (0.0)		Regimen 2, 2/23 (8.7) (1 loss was associated with maternal valve thrombosis)			

(Continued)

Table S29—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Congenital Malformations, n/N (%)	Fetal and/or Neonatal Hemorrhage, n/N (%)	Total Pregnancy Loss, n/N (%)	Early Pregnancy Loss, n/N (%)	Late Pregnancy Loss, n/N (%)	Neonatal Death
New Zealand, retrospective, McLintock et al[71]/2009	31 women 47 pregnancies	Pregnant women with mechanical heart valves Valve type Starr-Edwards: 12 Tilting disc or bileaflet: 19 Valve position Mitral:14 Aortic: 4 Mitral and aortic: 13	Regimen 1 predominantly warfarin and aspirin (100-150 mg) throughout with enoxaparin (1 mg/kg SC q12h) and aspirin substituted between weeks 6 and 12 and at 34-36 wk gestation Regimen 2 enoxaparin (1 mg/kg SC q12h) and aspirin (100-150 mg) predominantly In both regimens, enoxaparin monitored by anti-Xa levels every 3-7 d; dose adjusted to attain a target predose level: 0.4-0.7 International Units/mL	Regimen 1, 3/13 (23.1) (warfarin embyropathy, hydrocephalus, cardiac anomalies) Regimen 2, 0/34 (0.0)	Regimen 1, 2/13 (15.3) (fetal intracerebral hemorrhage resulting in stillbirth) Regimen 2, 0/34 (0.0)	Regimens 1 and 2, 11/47 (23.4)	Regimens 1 and 2, 8/47 (17.0)	Regimen 1, 2/13 (15.3) (fetal intracerebral hemorrhage resulting in stillbirth) Regimen 2, 1/34 (2.9)	Regimen 1, 2/13 (15.3) (warfarin embryopathy, complex congenital heart disease) Regimen 2, 0/34 (0/0)

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Table S29—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Congenital Malformations, n/N (%)	Fetal and/or Neonatal Hemorrhage, n/N (%)	Total Pregnancy Loss, n/N (%)	Early Pregnancy Loss, n/N (%)	Late Pregnancy Loss, n/N (%)	Neonatal Death
Single-group cohort studies									
Norway, retrospective, Abildgaard et al[72]/2009	11 women 12 pregnancies	Pregnant women with mechanical heart valves Valve position Mitral: 4 Aortic: 6 Aortic and mitral: 2	Therapeutic doses of LMWH q12h throughout pregnancy Aspirin 75 mg/d recommended but discontinued 1 wk before expected delivery date Doses adjusted to attain peak anti-Xa level of 0.7-1.2 units/mL	1/12 (8.3) (patent ductus arteriosus)	Not reported	0/12 (0.0)	0/12 (0.0%)	0/12 (0.0)	0/12 (0.0)
Japan, retrospective, Kawamata et al[73]/2007	12 women 16 pregnancies	Pregnant women with mechanical heart valves Valve position Mitral: 7 Aortic: 2 Tricuspid: 7	Substitution of warfarin with UFH starting between 6 and 13 wk and until term Doses adjusted to maintain aPTT levels 2-3 times control (between 20,000 and 30,000 International Units/d)	1/16 (6.3) (hydrocephalus)	2/16 (12.5) (intraventricular hemorrhage, intraventricular and pulmonary hemorrhage)	5/16 (31.3)	4/16 (25)	1/16 (8.3) (intrauterine fetal death during extracorporeal circulation)	2/16 (12.5) (see under Fetal and/or Neonatal Hemorrhage)

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Table S29—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Congenital Malformations, n/N (%)	Fetal and/or Neonatal Hemorrhage, n/N (%)	Total Pregnancy Loss, n/N (%)	Early Pregnancy Loss, n/N (%)	Late Pregnancy Loss, n/N (%)	Neonatal Death
England, prospective, Quinn et al[74]/2009	11 women 12 pregnancies	Pregnant women with mechanical heart valves Valve position Mitral: 4 Aortic :2 Aortic and mitral: 3 Systemic right atrioventricular valve: 2	Dalteparin 100 International Units/kg q12h (8) or enoxaparin 1 mg/kg q12h (4) + aspirin 81 mg/d Doses adjusted to attain an anti-Xa level 1.0-1.2 units/mL	Not reported	Not reported	1/12 (8.3)	0/12 (0.0)	1/12 (8.3)	0/12 (0.0)
Canada, prospective, Yinon et al[75]/2009	17 women 23 pregnancies	Pregnant women with mechanical heart valves Valve position Mitral: 14 Aortic: 8 Aortic and mitral: 1	LMWH SC q12h Low-dose aspirin (81 mg/d) administered to all patients LWMH dose adjusted to maintain 4 h postinjection anti-Xa level 1-1.2 International Units/mL	0/23 (0.0)	Not reported	Total pregnancy loss: 4 (17.4)	2/23 (8.7)	2/23 (8.7)	1/12 (4.3)

(Continued)

Table S29—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Congenital Malformations, n/N (%)	Fetal and/or Neonatal Hemorrhage, n/N (%)	Total Pregnancy Loss, n/N (%)	Early Pregnancy Loss, n/N (%)	Late Pregnancy Loss, n/N (%)	Neonatal Death
				Systematic reviews					
Canada, Chan et al[1]/2000	976 women 1,234 pregnancies	Studies between 1966-1997 involving pregnant women with mechanical heart valves: Valve type Cage and ball: 433 Single-tilting disc: 356 Bileaflet: 62 Other: 20 Heterograft: 1 Unknown: 104 Position Mitral: 647 Aortic: 202 Tricuspid: 1 > 1 valve: 126 Valve position Mitral: 647 Aortic: 202 Tricuspid: 1 > 1 valve: 126 Total: 976	Regimen 1 oral anticoagulants throughout pregnancy Regimen 2 substitution of UFH in the first trimester either at or before 6 wk, after 6 wk, or at unknown time in the first trimester Regimen 3 UFH throughout pregnancy, adjusted dose, or low dose (≤ 15,000 units/d)	Regimen 1, 35/549 (6.4) Regimen 2, 6/174 (3.4) ≤ 6 wk: 0/108 (0) > 6 wk: 4/36 (11.1) Unknown: 2/30 (6.7) Regimen 3, 0/12 (0) Adjusted dose: 0/12 (0) Low dose: 0/5 (0)	Not reported	Regimen 1, 266/792 (33.6%) Regimen 2, 61/230 (26.5) ≤ 6 wk: 21/129 (16.3) > 6 wk: 20/56 (35.37) Unknown: 20/45 (44.4) Regimen 3, 9/21 (42.9) Adjusted dose: 7/16 (43.8) Low-dose: 2/5 (40)	Regimen 1, 196/792 (24.7) Regimen 2, 57/230 (24.8) ≤ 6 w: 19/129 (14.7) > 6 wk: 19/56 (33.9) Unknown: 19/45 (42.2) Regimen 3, 5/21 (23.8) Adjusted dose: 4/16 (25) Low-dose: 1/5 (20)	Not specified	Not specified

(Continued)

Table S29—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Congenital Malformations, n/N (%)	Fetal and/or Neonatal Hemorrhage, n/N (%)	Total Pregnancy Loss, n/N (%)	Early Pregnancy Loss, n/N (%)	Late Pregnancy Loss, n/N (%)	Neonatal Death
			Regimen 4, no anticoagulants, including use of antiplatelet agents alone	Regimen 4, 3/92 (3.3) Nothing: 2/33 (6.1) Antiplatelet: 1/59 (1.7) Malformations include warfarin embryopathy (29), CNS abnormalities (4), cleft lip and cleft palate (4), left ventricular hypoplasia (1), corneal leukoma (1), bilateral hand polydactyly (1), single kidney-toe-finger deformity (1)		Regimen 4, 20/102 (19.6) Nothing: 7/35 (20) Antiplatelet: 13/67 (19.4)	Regimen 4, 10/102 (9.8) Nothing: 2/35 (5.7) Antiplatelet: 8/67 (11.9)		

(Continued)

Table S29—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Congenital Malformations, n/N (%)	Fetal and/or Neonatal Hemorrhage, n/N (%)	Total Pregnancy Loss, n/N (%)	Early Pregnancy Loss, n/N (%)	Late Pregnancy Loss, n/N (%)	Neonatal Death
United States, James et al[67]/2006	76 pregnancies	Studies between 1966 and 2006 involving pregnant women with mechanical heart valves receiving LMWH Valve type Cage and ball: 4 Single-tilting disc: 2 Bileaflet: 8 Sorin: 1 Unknown: 61 Valve position Mitral: 24 Aortic: 12 Bjork-Shiley: 2 Unknown: 40	Conversion to LMWH prior to pregnancy or by the end of first trimester LMWH Enoxaparin: 32 Nadroparin: 20 Dalteparin: 13 Tinzaparin: 2 Reviparin: 1 Unknown: 8 Addition of low-dose aspirin: 13 Varying regimens ranging from a fixed subtherapeutic dose to weight-adjusted therapeutic doses Monitoring of anti-factor Xa levels: 43 The minimum value for the target ranges was 0.5 and the maximum was 1.2	0/76 (0.0)	Not reported	12 (15.8)	8/76 (10.5)	2/76 (2.6) *Additional 2 demises secondary to fatal maternal valve thrombosis **Not included elective termination at 14 wk	Not reported
United States, Oran et al[68]/2004	75 women 81 pregnancies	Studies between 1989 and 2004 involving pregnant women with mechanical heart valves who received LMWH	Cases were included if LMWH was received during pregnancy irrespective of this type, dose, and duration and administration of different anticoagulant regimens other than LMWH during the same pregnancy	1/81 (1.2) (hydrocephalus, LMWH received during first trimester, warfarin subsequent to that)	Not reported	9/81 (11.1) Anti-Xa adjusted dose: 3/81 (3.7) Fixed dose: 4/81 (4.9) Unknown: 2/81 (3.7)	6/81 (7.4) Anti-Xa adjusted dose: 3/81 (3.7) Fixed dose: 3/81 (3.7)	3/81 (3.7) Anti-Xa adjusted dose: 0/81 (0.0) Fixed dose: 1/81 (1.2) Unknown: 2/81 (3.7)	Not reported

(Continued)

Table S29—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Congenital Malformations, n/N (%)	Fetal and/or Neonatal Hemorrhage, n/N (%)	Total Pregnancy Loss, n/N (%)	Early Pregnancy Loss, n/N (%)	Late Pregnancy Loss, n/N (%)	Neonatal Death
		Valve position Mitral: 44 Aortic: 8 Mitral and aortic: 5 Unknown: 18	Conversion to LMWH occurred 1 mo before conception in 2 women; in the remainder, conversion to LMWH occurred during pregnancy LMWH use during second half of first trimester and at term: 21 LMWH throughout pregnancy: 60 LMWH enoxaparin: 35 Nadroparin: 21 Daltaparin: 11 Tinzaparin: 3 Reviparin: 1 Unknown: 10 Dose adjusted to therapeutic anti-Xa level: 51 Fixed dose: 30				*Not included: 1 first trimester elective termination		

(Continued)

Table S29—*Continued*

Country, Study/Year	Number of Patients and Pregnancies	Population	Treatment Regimens	Congenital Malformations, n/N (%)	Fetal and/or Neonatal Hemorrhage, n/N (%)	Total Pregnancy Loss, n/N (%)	Early Pregnancy Loss, n/N (%)	Late Pregnancy Loss, n/N (%)	Neonatal Death
Egypt, Hassouna and Allam[2]/2009	892 women 1,231 pregnancies	Studies published between January 2000-September 2009 involving pregnant women with mechanical heart valves who received defined anticoagulant regimens Valve type Cage and ball: 134 Tilting disc: 382 Bileaflet: 341 Undefined: 256 Valve position Mitral: 671 Aortic: 141 Mitral and aortic: 147 + 147 Tricuspid: 7	Regimen 1 VKAs throughout pregnancy with and without UFH or LMWH substitution near term Regimen 2 UFH or LMWH substitution during the first trimester and near term Regimen 3 UFH or LMWH throughout pregnancy Regimen 4 no anticoagulants	Overall 22/942 (2.3)* Regimen 1 21/559 (3.7) Regimen 2 1/258 (0.4) Regimen 3 0/96 (0) Regimen 4 0/27 (0) *Includes hydrocephalus (4), nasal hypoplasia, epiphyseal stippling (7) strabismus (3), mental retardation (2), cleft lip/palate (2), telebrachydactyly (1), and other (3)	Not reported	Overall 403/1343 (30) Regimen 1 274/833 (32.9) Regimen 2 64/322 (19.9) Regimen 3 61/157 (38.8) Regimen 4 4/31 (12.9)	Overall 272/1343 (20.2) Regimen 1 194/833 (23.3) Regimen 2 42/322 (13) Regimen 3 34/157 (21.6) Regimen 4 2/31 (12.9)	Not specified	Not reported

* and ** denote additional data referring to the number of late losses two of 76 (2.6). See Tables S1, S4, and S17 for expansion of abbreviations.

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