Thrombosis and pregnancy

Highlow and ALIFE2

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Disclosures

Research Support and Lecture Fees
Abbvie
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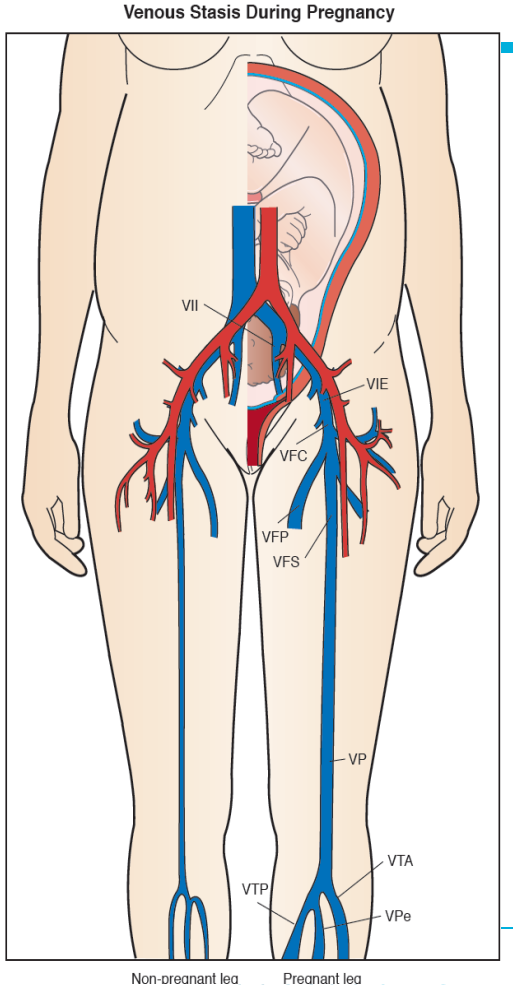
Daiichi Sankyo
GSK
Norgine
Portola/Alexion
Sanofi
Viatris

Outline

- Prevention of pregnancy-related VTE
- Thrombophilia and pregnancy complications

- Pulmonary embolism major cause of maternal death in developing countries
  - 2-3/100,000 births
- DVT > PE
- VTE rates (/1,000 pt yrs)
  - Overall rate 1.4
    - Antepartum 1
    - Postpartum 5
  - Not pregnant 0.5



Nijkeuter, Coppens, Middeldorp: Hemostasis and Thrombosis Basic Principles and Clinical Practice, 6th Edition. Editors Marder et al.; Heit Ann Int Med 2005

Outline

- **Prevention of pregnancy-related VTE**
- Thrombophilia and pregnancy complications

Which women are at high risk?

Women with

- **Personal history of VTE**
- Thrombophilia
- Strong family history

- Consider thrombosis prophylaxis based on absolute risks
  - Postpartum alone
  - Also during pregnancy
    - What agents
    - Which dose
    - Monitoring
    - Around delivery

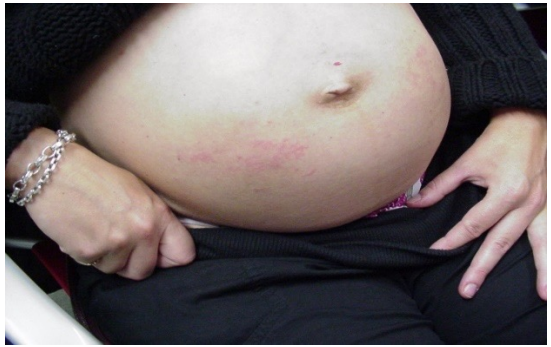
Women with history of VTE – what we know

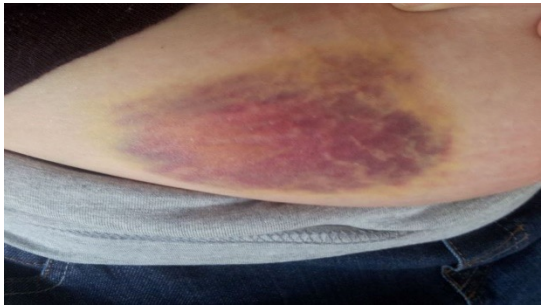
- Risk of pregnancy-related recurrence
  - During pregnancy considerable risk **(~6%)** without prophylaxis
  - Potential influence on recurrence risk of thrombophilia or estrogen exposure during first VTE
  - Very low risk in women with elicited first VTE (major risk factor) and without thrombophilia in one prospective study

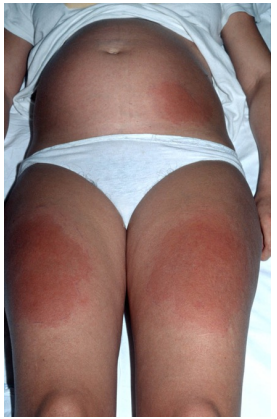
Brill-Edwards et al. New Engl J Med 2000; Pabinger et al, J Thromb Haemost 2005; De Stefano et al, Br J Haematol 2006

Side Effects of LMWH

- Daily injections
- Skin reactions
  - 20-40% of women, type IV delayed type hypersensitivity
  - Bleeding
  - Around delivery
- Caveat epidurals
- HIT? <0.1%

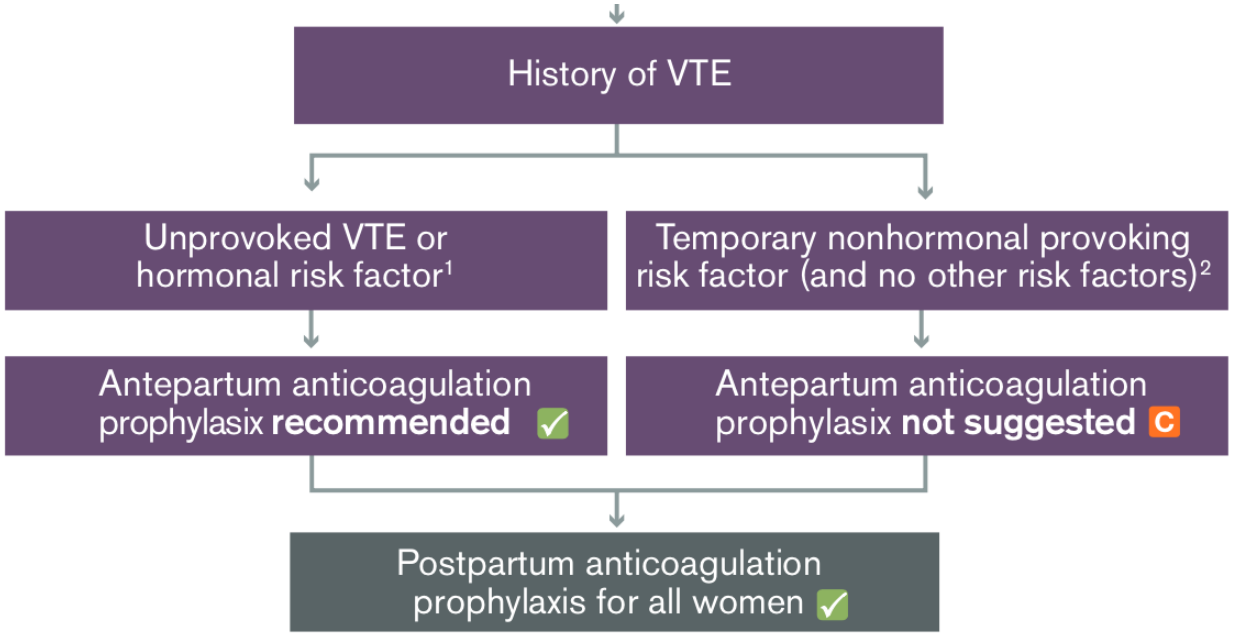






Bank, Thromb Res 2004, Schindewolf J Allergy Clin Immunol 2013, Schultinge Neth J Med 2013

Women not receiving long-term anticoagulant therapy



Bates et al: ASH Pocket guide for the clinician November 2019

Unresolved issues: dosing of LMWH

- Guidelines (**ACCP 2012**)
- Prophylactic or intermediate dose LMWH (grade 2C)
- Extrapolating RRR of “only” 64% from orthopedic surgery

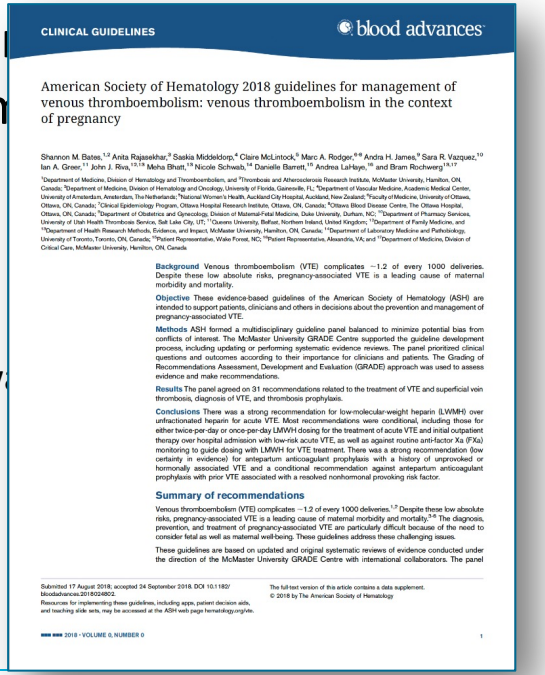
- Several treatment failures on low dose LMWH have been reported
- Antepartum and postpartum
- Up to 8% in high risk women

Sanson, Thromb Haemost 1990;
Leperq et al, BJOG 2001;
Pabinger et al, J Thromb Haemost 2005;
Voke, Br J Haematol 2008
Rozanski (abstract) ASH 2009;
Roeters van Lennep, J Thromb Haemost 2011
De Stefano, EHA abstract 2012

What do guidelines say?

American Society of Hematology 2018 guidelines for
venous thromboembolism: venous thromboembolism
pregnancy

Shannon M. Bates, Anita Rajasekhar, Saskia Middeldorp, Claire McLintock,
James, Sara R. Vazquez, Ian A. Greer, John J. Riva, Meha Bhatt, Nicole Schwa
LaHaye, and Bram Rochwerg



CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy

Shannon M. Bates,[1,2] Anita Rajasekhar,[3] Saskia Middeldorp,[4] Claire McLintock,[5] Marc A. Rodger,[6-8] Andra H. James,[9] Sara R. Vazquez,[10] Ian A. Greer,[11] John J. Riva,[12,13] Meha Bhatt,[13] Nicole Schwab,[14] Danielle Barrett,[15] Andrea LaHaye,[16] and Bram Rochwerg[16,17]

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Background Venous thromboembolism (VTE) complicates ~1.2 of every 1000 deliveries. Despite these low absolute risks, pregnancy-associated VTE is a leading cause of maternal morbidity and mortality.

Objective These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians and others in decisions about the prevention and management of pregnancy-associated VTE.

Methods ASH formed a multidisciplinary guideline panel balanced to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline development process, including updating or performing systematic evidence reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess evidence and make recommendations.

Results The panel agreed on 31 recommendations related to the treatment of VTE and superficial vein thrombosis, diagnosis of VTE, and thrombosis prophylaxis.

Conclusions There was a strong recommendation for low-molecular-weight heparin (LWMH) over unfractionated heparin for acute VTE. Most recommendations were conditional, including those for either twice-per-day or once-per-day LMWH dosing for the treatment of acute VTE and initial outpatient therapy over hospital admission with low-risk acute VTE, as well as against routine anti-factor Xa (FXa) monitoring to guide dosing with LMWH for VTE treatment. There was a strong recommendation (low certainty in evidence) for antepartum anticoagulant prophylaxis with a history of unprovoked or hormonally associated VTE and a conditional recommendation against antepartum anticoagulant prophylaxis with prior VTE associated with a resolved nonhormonal provoking risk factor.

Summary of recommendations

Venous thromboembolism (VTE) complicates ~1.2 of every 1000 deliveries.[1,2] Despite these low absolute risks, pregnancy-associated VTE is a leading cause of maternal morbidity and mortality.[3-6] The diagnosis, prevention, and treatment of pregnancy-associated VTE are particularly difficult because of the need to consider fetal as well as maternal well-being. These guidelines address these challenging issues.

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the McMaster University GRADE Centre with international collaborators. The panel

Submitted 17 August 2018; accepted 24 September 2018. DOI 10.1182/bloodadvances.2018024802.

Resources for implementing these guidelines, including apps, patient decision aids, and teaching slide sets, may be accessed at the ASH web page hematology.org/vte.

The full-text version of this article contains a data supplement.

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Current (2018) ASH evidence synthesis

- All based on studies that did not formally assess bleeding risk

  - 3 very small RCTs (n=16, n=40, subgroup n=36)
  - Observational studies

Recommendation

- **For pregnant women who require prophylaxis, the panel suggests against intermediate-dose LMWH prophylaxis compared to standard-dose LMWH prophylaxis during the antepartum period *(conditional recommendation, very low certainty)***
- **The panel suggests either standard- or intermediate-dose LMWH prophylaxis during the postpartum period *(conditional recommendation, very low certainty)***

Remarks:

- *Very low certainty evidence suggesting unclear net health benefit for using intermediate dosing*
- However, difficult to make significant conclusions given limitations in evidence

- Favor standard-dose antepartum to minimize risks of bleeding or delayed epidural access
- Standard- or intermediate-dose reasonable for postpartum prophylaxis given increased thrombotic risk after delivery

What do we know about LMWH dosing?

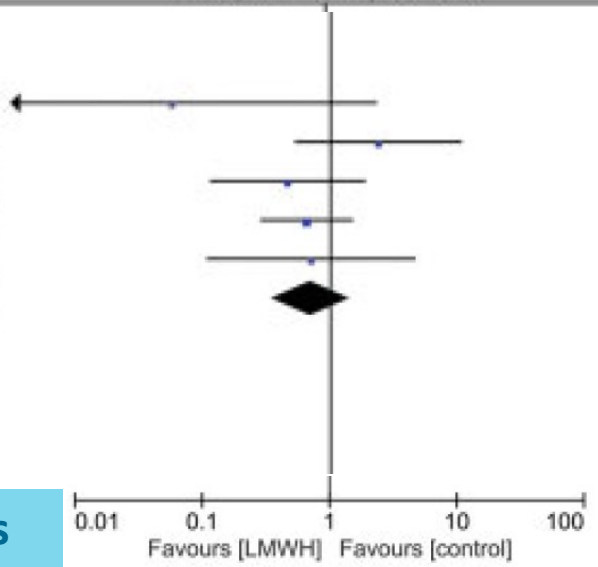
Even in the non-pregnant population:
NOT MUCH!

Intermediate LMWH vs no prophylaxis

Study or Subgroup	LMWH Events	LMWH Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
3.2.4 Acutely ill medical patients						
Ahuja 2016	0	50	4	50	0.6%	0.10 [0.01, 1.95]
Kakkar 2011	8	4174	4	4145	3.3%	1.99 [0.60, 6.61]
Lederle 2006	5	140	9	140	3.7%	0.54 [0.18, 1.65]
Leizorovicz 2004	15	1856	21	1850	8.6%	0.71 [0.36, 1.38]
Samama 1999	3	367	4	371	2.2%	0.76 [0.17, 3.40]
Subtotal (95% CI)		**6587**		**6556**	**18.4%**	**0.76 [0.44, 1.33]**
Total events	31		42			

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 4.66$, $df = 4$ ($P = 0.32$); $I^2 = 14\%$

Test for overall effect: $Z = 0.95$ ($P = 0.34$)



Although indirectly – RRR in same range as ANY prophylaxis LMWH dose

Eck, Semin Thromb Haemost 2019

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What do we know about LMWH dosing?

ASH VTE guidelines in the context of Pregnancy, 2018:

- More data are required regarding optimal intensity of LMWH prophylaxis in the antepartum and postpartum setting

The Highlow study

Objective

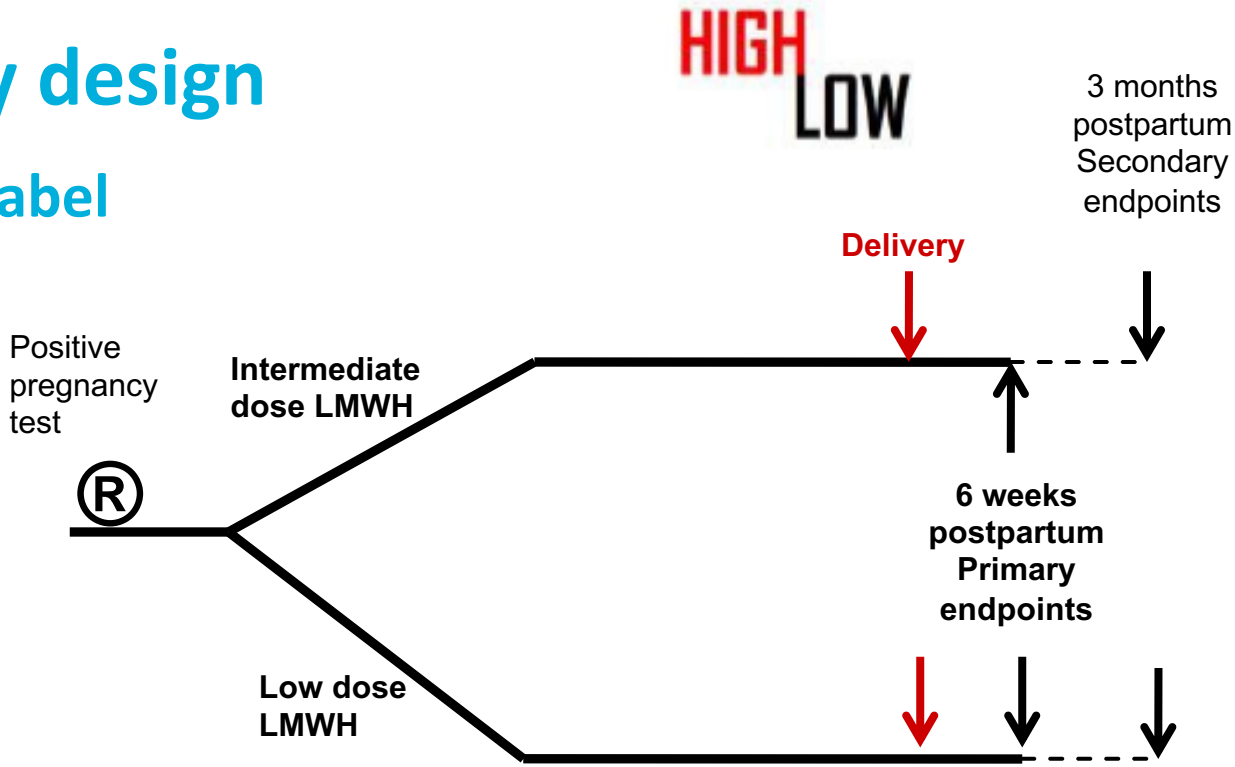
Efficacy and safety of intermediate dose LMWH versus low dose LMWH in pregnant women with a history of VTE

Hypothesis

Intermediate dose LMWH is superior in preventing recurrent VTE to low dose LMWH, with an acceptable safety profile

Study design

Open-label



www.highlowstudy.org

www.clinicaltrials.gov 01828697

8 countries, > 70 sites, > 1100 patients randomized (Recruitment closed November 2020)

Thrombosis Research 144 (2016) 62–68

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy: Rationale and design of the Highlow study, a randomised trial of two doses

Suzanne M. Bleker [a,*], Andrea Buchmüller [b], Céline Chauleur [c], Fionnuala Ní Áinle [d], Jennifer Donnelly [d], Peter Verhamme [e], Anne Flem Jacobsen [f], Wessel Ganzevoort [g], Martin Prins [h], Jan Beyer-Westendorf [i], Maria DeSancho [j], Stavros Konstantinides [k], Ingrid Pabinger [l], Marc Rodger [m,n], Hervé Decousus [b], Saskia Middeldorp [a]

Sample size considerations

Assumptions

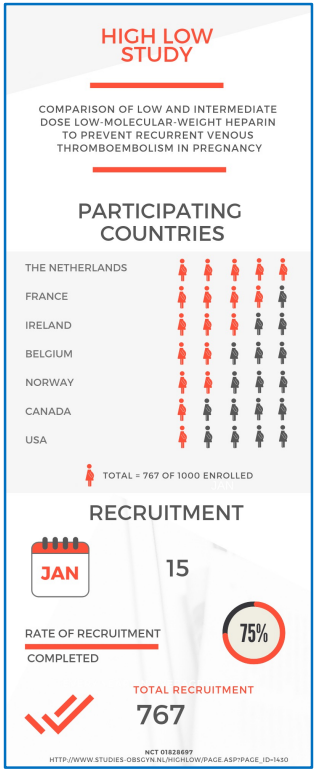
- 4-5% incidence in low group - 65% RRR high vs low
- 29 VTE events needed

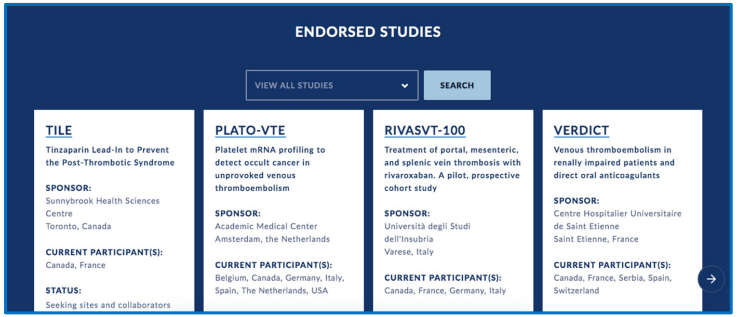
Incidence (%) in Low	Incidence (%) in intermediate group	Average Incidence (%)	Total nr of Patients
5,0	1,750	3,375	859
4,5	1,575	3,038	955
4,0	1,400	2,700	1.074
3,5	1,225	2,363	1.228

INVENT Network Members (9)

ENDORSED STUDY SUPPORT

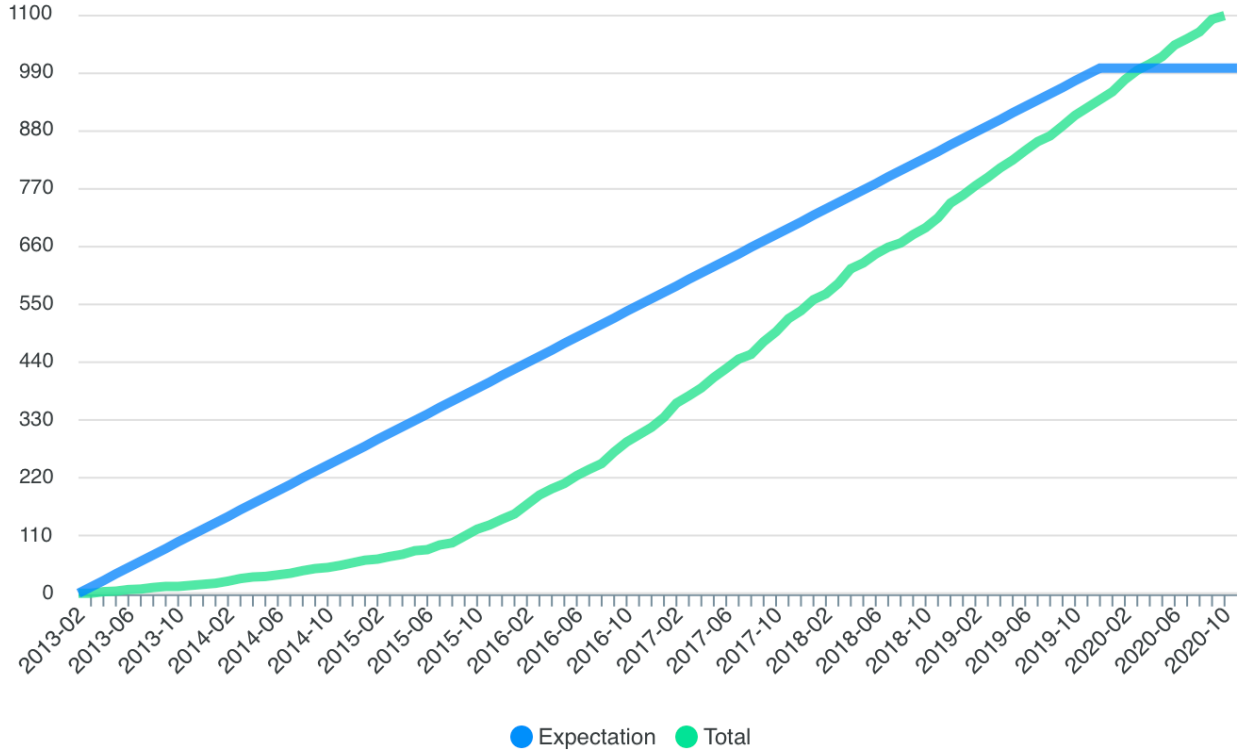
- Promotions
  - Website
  - Social Media
  - Booth at ISTH
  - Newsletter





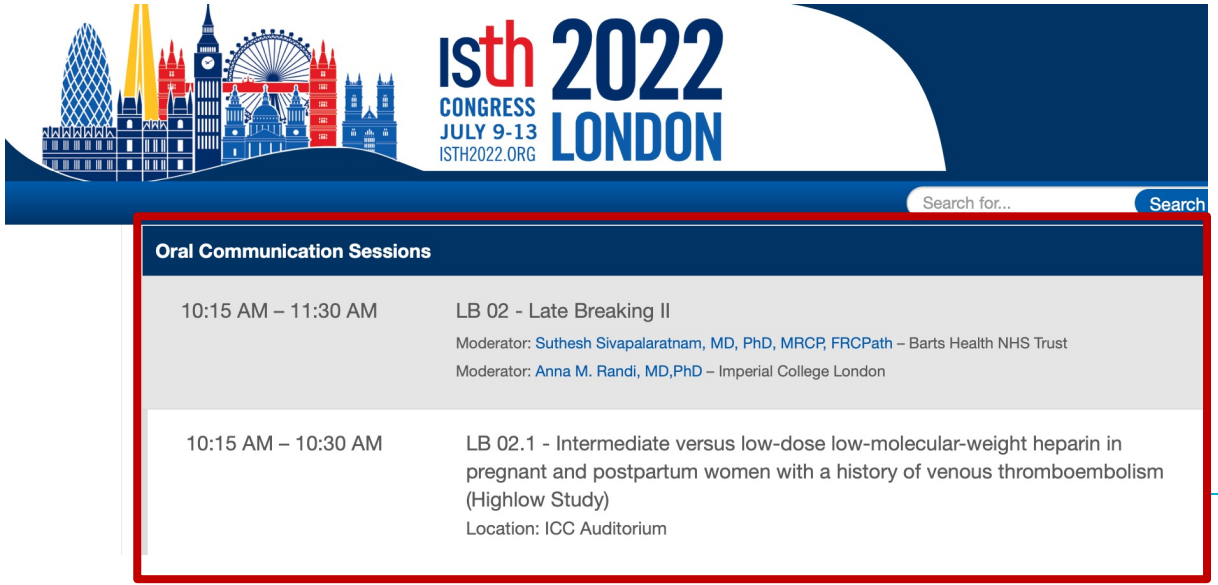
Event-driven sample size reached!

- 7.5 years
- >1100 women



Current status

- Submitted for publication, with > 70 authors from 70 centers
- Late Breaking Abstract Presentation on Wednesday July 13, 10:15



Outline

- Prevention of pregnancy-related VTE
- **Thrombophilia and pregnancy complications**

Antithrombotics for pregnancy complications

An approach based on trial evidence

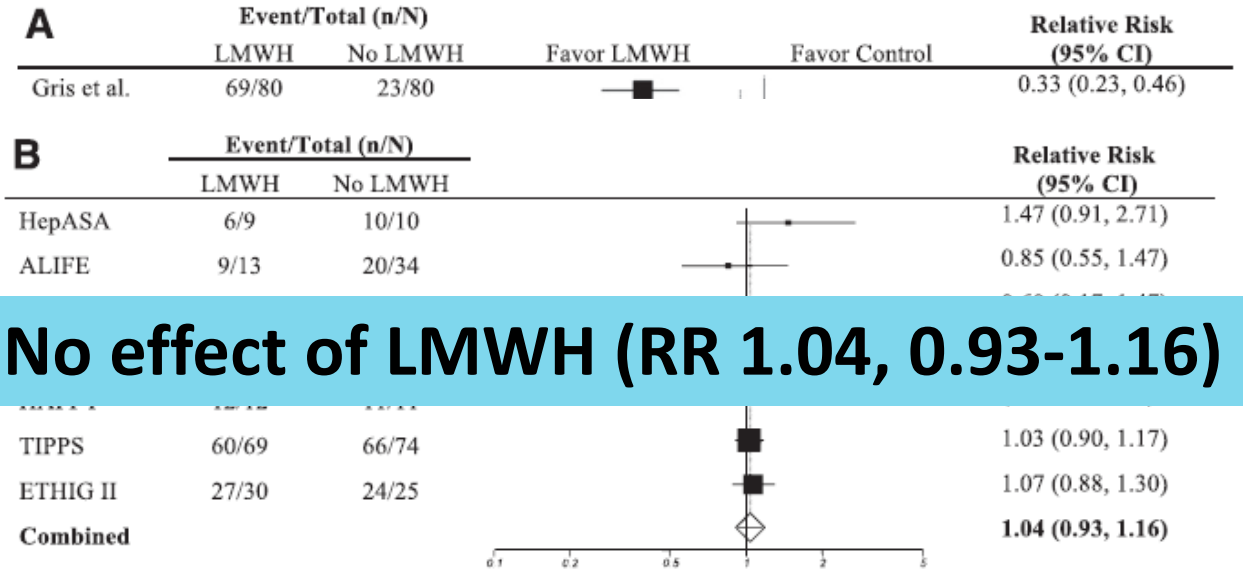
- Antiphospholipid syndrome (APS)
- **Inherited thrombophilia**

Outcomes

- Live birth
- (Recurrence of) preeclampsia, HELLP, SGA, abruption

Many trials without a no treatment or placebo comparator

LMWH in women with inherited thrombophilia and recurrent miscarriage – effect on miscarriage



A

	Event/Total (n/N)		Relative Risk (95% CI)
	LMWH	No LMWH	
Gris et al.	69/80	23/80	0.33 (0.23, 0.46)

B

	Event/Total (n/N)		Relative Risk (95% CI)
	LMWH	No LMWH	
HepASA	6/9	10/10	1.47 (0.91, 2.71)
ALIFE	9/13	20/34	0.85 (0.55, 1.47)
TIPPS	60/69	66/74	1.03 (0.90, 1.17)
ETHIG II	27/30	24/25	1.07 (0.88, 1.30)
Combined			**1.04 (0.93, 1.16)**

Favor LMWH | Favor Control

0.1 0.2 0.5 1 2 5

No effect of LMWH (RR 1.04, 0.93-1.16)

Skeith, Blood, 2016

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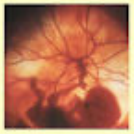
More evidence underway

ALIFE2 trial www.alife2trial.org

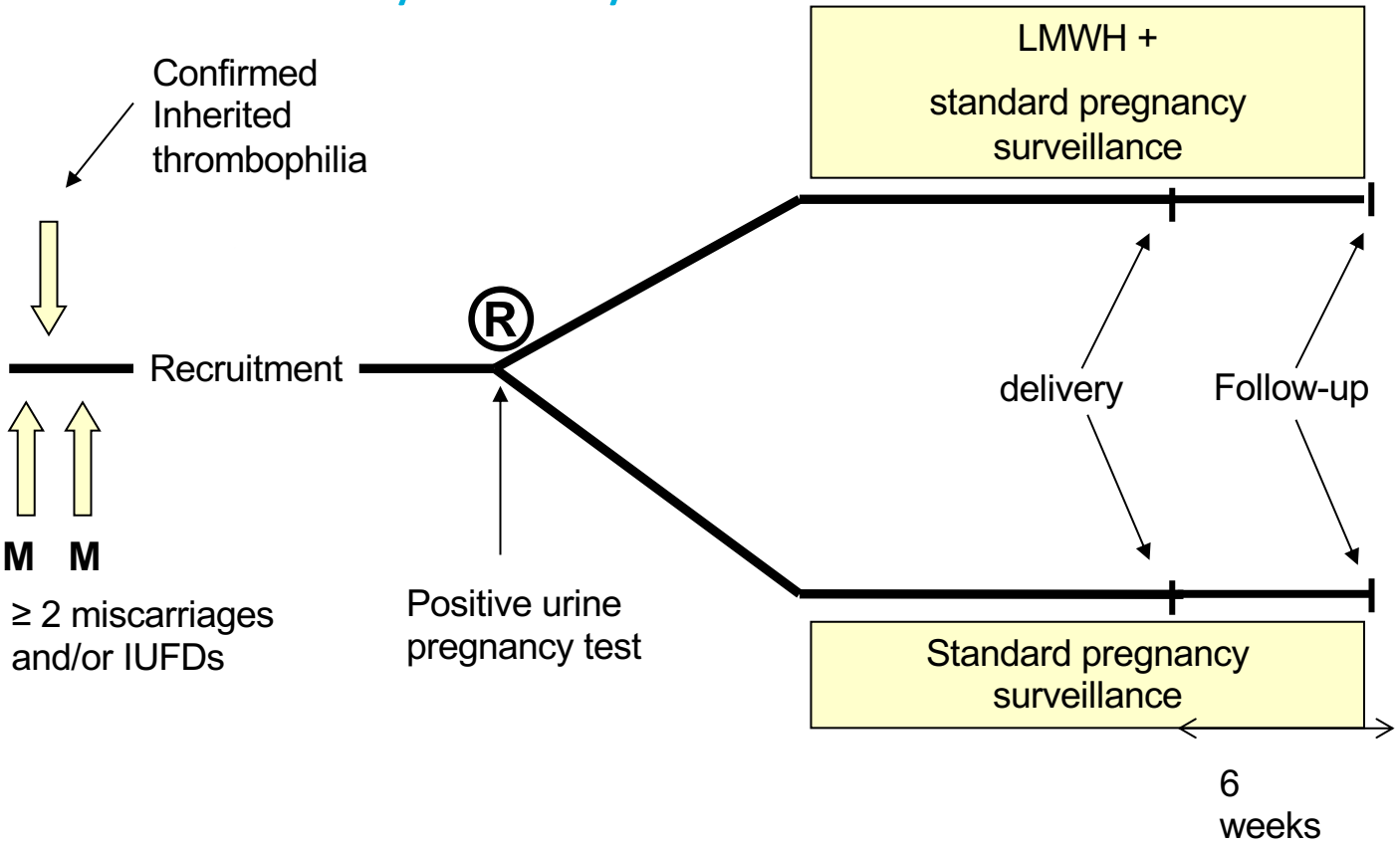
- 2 or more miscarriages
- Inherited thrombophilia
- LMWH vs no LMWH
- Multi-center
- Recruitment closed 2021
- Results expected 2022



ALIFE2

ALIFE2 Study design

Primary efficacy outcome: Live birth



Take home points

- The optimal thrombosis prophylaxis dose in pregnancy and postpartum women is uncertain – but Highlow will provide answers!
- ALIFE2 will show us whether LMWH is out or in in women with inherited thrombophilia and recurrent miscarriage
- **Randomized controlled trials with LMWH in pregnancy can be done**

Our patients deserve randomized trials

- 10 months of injections
- It better be optimal!

From a Highlow participant – used with permission