THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM (VTE) IN SPECIAL POPULATIONS

Cristhiam M. Rojas-Hernandez, MD
Assistant Professor of Hematology

CONTENT

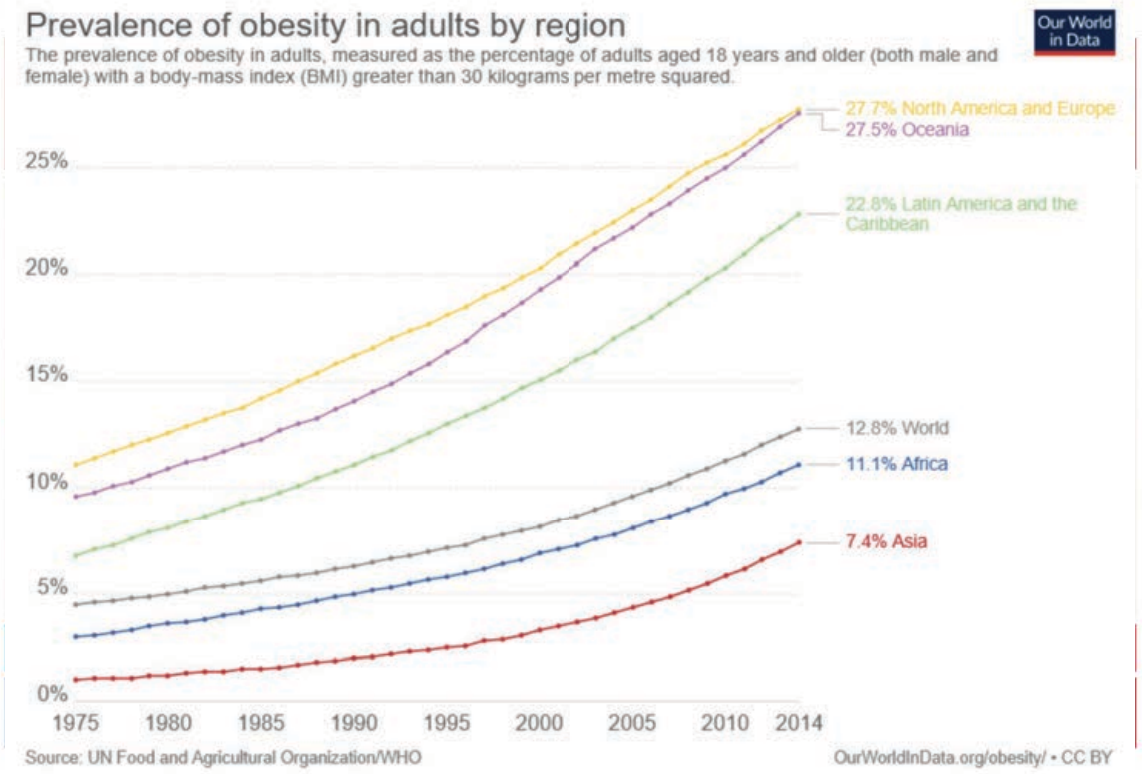
- Special populations:
  Extreme body weight, renal failure and pregnancy

- Review of guideline-recommendations for VTE in special populations
  - Dose adjustment of parenteral anticoagulation (heparin products)
  - Evidence for oral anticoagulants

- New evidence for areas of uncertainty
  - The use of new anticoagulation strategies

2019
MASCC/ISOO
Annual Meeting
Supportive Care in Cancer
21-23 JUNE
SAN FRANCISCO

EXTREME BODY WEIGHT AND RISKS FOR VTE AND VTE-TREATMENT RELATED-COMPLICATIONS



- Obesity increases the risk of venous thromboembolic complications by 2.5 fold (US DHHS)
- Excess body weight increases also the risk of recurrent VTE (Austrian registry on recurrent VTE)
- In obese patients receiving parenteral anticoagulation with heparin products, the rates of hemorrhage appear to be higher.
- Clinical prediction algorithms for long term anticoagulant related-bleeding indicate that body weight influences the risk.

- Obese patients are under-represented in clinical trials.

Hannah Ritchie and Max Roser (2019) - "Obesity & BMI". *Published online at OurWorldInData.org.* Retrieved from: 'https://ourworldindata.org/obesity' [Online Resource]
The American journal of medicine. 2005 Sep 1;118(9):978-80

Archives of internal medicine. 2008 Aug 11;168(15):1678-83
American heart journal. 2003 Jul 1;146(1):33-41

2019 MASCC/ISOO Annual Meeting Supportive Care in Cancer 21-23 JUNE SAN FRANCISCO

GUIDELINE STATEMENTS FOR THE USE OF ANTICOAGULANTS IN EXTREME BODY WEIGHT PATIENTS

Guideline/ Society	Year of publication	Heparin/LMWH Quality of evidence Recommendation	DOAC Quality of evidence Recommendation
ACCP	2012	**VTE prophylaxis and treatment: Weak** ▪ Non-controlled cohort studies ▪ Pharmacokinetics studies	
Guidance statement *Journal of thrombosis and Thrombolysis*	2016	▪ **Dose adjustment by actual body weight** ▪ **Dose capping should be avoided** ▪ **LMWH + obesity: Twice daily regime for treatment dose** ▪ **For body weight < 40 kg: UFH is preferred** ▪ **No routine use of anti-Xa level**	
ASH	2018		
ISTH	2016		**AF/VTE/arthroplasty prophylaxis: Moderate** ▪ Randomized control studies ▪ Pharmacokinetics studies ▪ **Standard DOAC dosing for BMI ≤ 40 kg/m^2 and weight ≤ 120 kg**

Chest. 2012;141(2 Suppl):e419S-7236S

Journal of Thrombosis and Haemostasis. 2016 Jun;14(6):1308-13

Journal of thrombosis and thrombolysis. 2016 Jan 1;41(1):165-86

Blood advances. 2018 Nov 27;2(22):3257-91

EXTREME BODY WEIGHT AND VTE MANAGEMENT: NEW EVIDENCE FOR CLINICAL OUTCOMES AND THE USE OF DOAC

Di Nisio et al. 2016: Subanalysis of EINSTEIN DVT/PE studies

- RCT open label comparing rivaroxaban versus LMWH/VKA for acute proximal lower extremity DVT/PE.
- BMI ≥ 30 (N=1630), BMI ≥ 35 (861)
- Comparison of recurrent thrombosis and bleeding outcomes by body weight and BMI group levels:
  ≤ 50Kg versus 50-100 kg versus > 100kg
  BMI: < 25 versus 25-29 versus 30-34
- The risk (HR) for recurrent VTE and clinical relevant bleeding was similar across groups at 21 days and at completion of study.

Beyer-Westendorf et al. 2018: The prospective Dresden DOAC registry

- Multicenter prospective registry enrolling consecutive patients started on DOAC with follow up-phone interviews. N=3432
- BMI categories as per WHO classification (< 18.5, 18.5-24.9, 25-29.9, 30-34.9, ≥35)
- BMI < 18.5 (0.5%), BMI 30-34.9 (21.3%), BMI 35-39.9 (7.2%), BMI ≥ 40 (2.9%)
- No indication that elevated BMI is associated with a lack of NOAC effectiveness (CV outcomes) or safety (major bleeding)
- BMI < 18.5: higher rates of CV outcomes and major bleeding.

Kushnir et al. 2019: Single center analysis of VTE/AF morbidly obese adult patients (BMI ≥ 40)

- Retrospective analysis, single center study. VTE (N=366), AF (N=429)
- BMI ≥ 50 (24%)
- Apixaban (N=150), Rivaroxaban (N=326), VKA (319)
- The recurrent VTE, stroke and major bleeding outcomes were not different across groups.

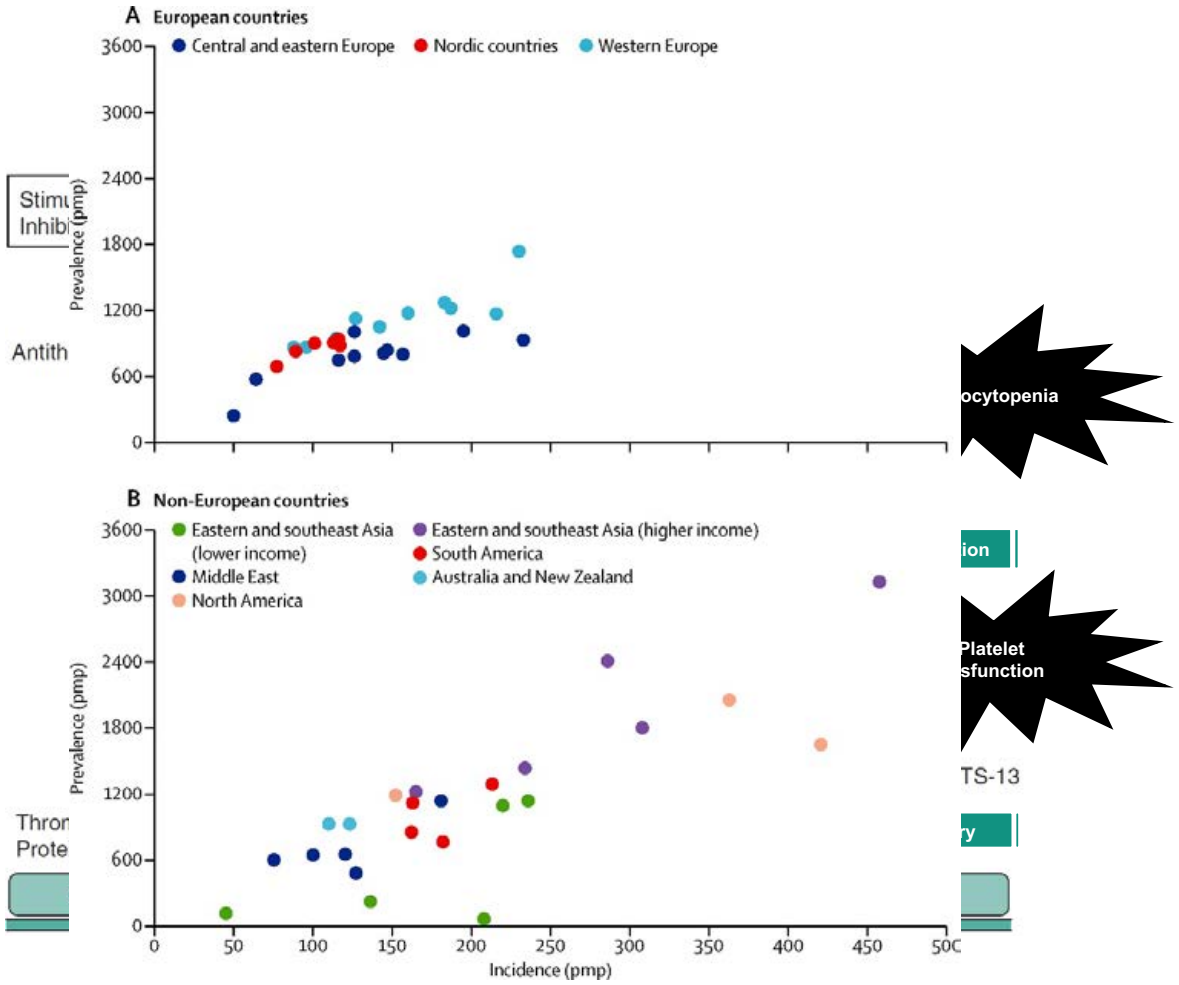
Thrombosis and haemostasis. 2016;116(10):739-46
International journal of cardiology. 2018 Jul 1;262:85-91.
The Lancet Haematology. 2019 May 24

EXTREME BODY WEIGHT AND VTE MANAGEMENT: CONCLUSIONS

1. For those patients requiring parenteral anticoagulation with low molecular heparins, the dose should be adjusted according to the actual body weight.
2. Routine use of anti-Xa levels to adjust dosage of low molecular weight heparins is not recommended.
3. When selecting oral anticoagulants, risks and benefits as well as patient-preferences need to be discussed.
4. Direct oral anticoagulants have now available data to support their use in obese patients.
5. Data are still needed for the use of direct oral anticoagulants in underweight (BMI < 18.5) and extremely obese patients (BMI > 40)

2019
MASCC/ISOO
Annual Meeting
Supportive Care in Cancer
21-23 JUNE
SAN FRANCISCO

RENAL DISEASE AND RISKS FOR VTE AND VTE-TREATMENT RELATED-COMPLICATIONS



- Renal disease is related to an increased risk of VTE (2-8 fold)
- Patients with severe renal failure (< 30mL/min) have 2-4 fold increment in the risk of major bleeding during anticoagulation treatment.
- Renal failure + VTE: Increased risk of fatal outcomes

  Severe renal failure: 6.6% fatal PE

  1.2% fatal bleeding
- Severe renal failure is a consistent exclusion criteria in VTE clinical trials.

The Lancet. 2016 Jul 16;388(10041):294-306
Journal of the American society of Nephrology. 2008 Jan 1;19(1):135-40

Am J Kidney Dis. 2011;58:746-755.
The American journal of medicine. 2006 Dec 1;119(12):1073-9

2019 MASCC/ISOO Annual Meeting Supportive Care in Cancer 21-23 JUNE SAN FRANCISCO

GUIDELINE STATEMENTS FOR THE USE OF ANTICOAGULANTS IN PATIENTS WITH RENAL FAILURE

Guideline/ Society	Year of publication	Heparin/LMWH Quality of evidence Recommendation	DOAC Quality of evidence Recommendation
ACCP	2012 2016	**VTE prophylaxis/treatment: Weak** ▪ Pharmacokinetics studies ▪ Non-controlled cohort studies ▪ Post hoc analysis	**VTE prophylaxis/treatment: Moderate** ▪ Randomized control studies ▪ Pharmacokinetics studies **Weak evidence for use in CrCl impairment (< 30 mL/min)** ▪ **Dose adjustment according to Cr Cl**
Guidance statement *Journal of thrombosis and Thrombolysis*	2016	▪ **Cockcroft-Gault method to estimate Cr Cl** ▪ **Cr Cl < 30 mL/min: anti-Xa activity monitoring and/or dose reduction (enoxaparin 1 mg per kg daily)** ▪ **Avoid LMWH if CrCl < 20 mL/min or RRT**	
ASH	2018	▪ **Cr Cl < 30 mL/min: No anti-Xa activity monitoring Follow adjustments in product labeling**	▪ **No specific recommendations on dose adjustment**

Chest. 2012;141(2 Suppl):e419S-7236S

Chest. 2016 Feb 1;149(2):315-52

Journal of thrombosis and thrombolysis. 2016 Jan 1;41(1):165-86

Blood advances. 2018 Nov 27;2(22):3257-91

2019 MASCC/ISOO Annual Meeting Supportive Care in Cancer 21-23 JUNE SAN FRANCISCO

RENAL DISEASE AND VTE MANAGEMENT: DOSE ADJUSTMENT OF ORAL ANTICOAGULANTS

Jurisdiction	VKA (Warfarin)	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Venous thromboembolism (treatment)					
United States	No dose adjustment	GFR > 30: 150 mg BID **GFR 15–30: 75 mg BID** **ESRD: contraindicated**	GFR ≥ 30: 15 mg BID for 21 d, then 20 mg QD **GFR < 30: contraindicated**	10 mg BID for 7 d, then 5 mg BID **No dose adjustment**	GFR > 50: 60 mg QD **GFR 15–50 OR weight ≤ 60 kg OR P-gp inhibitors: 30 mg QD**
Europe	No dose adjustment	GFR > 50: 150 mg BID **GFR 30–50: 110 mg BID if high bleeding risk** **GFR < 30: contraindicated**	**Same as United States**	**GFR > 15: same as US** **ESRD: contraindicated**	GFR > 50: 60 mg QD **GFR 15–50 OR weight ≤ 60 kg OR P-gp inhibitors: 30 mg QD** **ESRD: contraindicated**

Semin Thromb Hemost. 2018 Jun;44(4):353-363

END STAGE RENAL DISEASE AND DOSE ADJUSTMENT OF ORAL ANTICOAGULANTS: NEW EVIDENCE

Gollamudi et al. 2018: Safety of Apixaban in Patients with CKD Stage V and ESRD with VTE

- Case control study (N=9,000 patients) from 26 integrated US healthcare systems (1/6 US population)
- Cases: renal disease stage V or ESRD on apixaban for VTE (N=990)
- Controls: ESRD on VKA for VTE (N=8110)
- Primary endpoint: 30-day and 90-day bleeding rates (excluded history GIB, ICH, AF, trauma, cancer, cirrhosis)
- Pooled bleeding rates (GI and ICH) favored apixaban (absolute difference 18% and 19%)
- Use of VKA, antiplatelets; uncontrolled hypertension, AA ethnicity, age >65 were associated with risk of bleeding.

Reed et al. 2018: Safety and effectiveness of apixaban compared to warfarin in dialysis patients

- Retrospective study (N=164 patients), single center of ESRD patients on anticoagulation (VTE/AF/prophylaxis)
- Comparison of VKA versus apixaban for overall bleeding rate and recurrent thrombotic events.
- Lower bleeding rates with apixaban (16% difference for major bleeding): 0.31 event per person year.
- Similar recurrent thrombotic events.

Blood 2018 132:2523

Research and practice in thrombosis and haemostasis. 2018 Apr;2(2):291-8

2019
MASCC/ISOO
Annual Meeting
Supportive Care in Cancer
21-23 JUNE
SAN FRANCISCO

RENAL DISEASE AND VTE MANAGEMENT: CONCLUSIONS

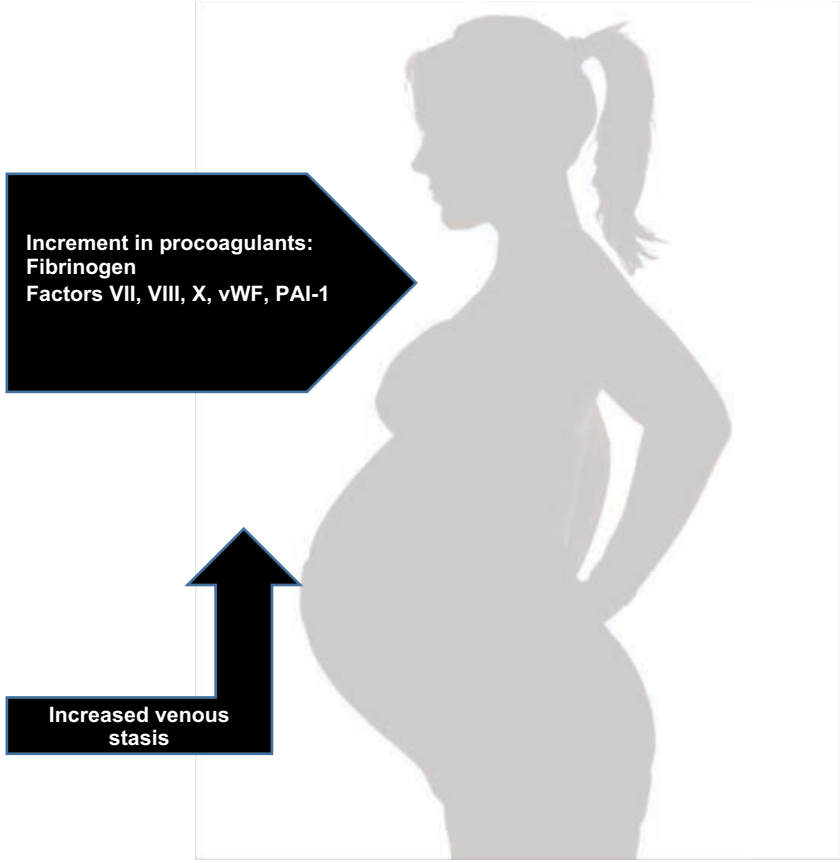
1. For those patients requiring parenteral anticoagulation with low molecular heparins and estimated creatinine clearance < 30 mL/min, dose reduction is advised and anti-Xa level monitoring for dose adjustment may be needed.

2. Avoid the use of low molecular heparins in patients requiring hemodialysis.

3. The appropriate dose adjustment of direct oral anticoagulants is unknown for patients with severe renal dysfunction, including patients requiring hemodialysis.

2019
MASCC/ISOO
Annual Meeting
Supportive Care in Cancer
21-23 JUNE
SAN FRANCISCO

PREGNANCY AND RISKS FOR VTE AND VTE-TREATMENT RELATED-COMPLICATIONS



- VTE during pregnancy occurs in ~ 1/1,000 deliveries.
- 40% of VTE occurs during the first trimester.
- VTE is the leading cause of maternal mortality.

- Most of the bleeding complications during VTE treatment develop after delivery.

- Due to placental transfer, many of the conventional anticoagulation options are contraindicated.

American journal of obstetrics and gynecology. 2001 Jan 1;184(2):104-10

Thrombosis and haemostasis. 2007;97(02):186-90

2019
MASCC/ISOO
Annual Meeting
Supportive Care in Cancer
21-23 JUNE
SAN FRANCISCO

GUIDELINE STATEMENTS FOR THE USE OF ANTICOAGULANTS DURING PREGNANCY

Guideline/ Society	Year of publication	Heparin/LMWH Quality of evidence Recommendation	DOAC Quality of evidence Recommendation
ACCP ANZJOG SOGC RCOG ACOG ASH ESC	2012 2012 2014 2015 2018 2018 2018	**VTE prophylaxis: Weak-Moderate** ▪ Observational studies (C-section) ▪ Small prospective studies (C-section) ▪ Randomized controlled studies (prior VTE) **VTE treatment: Moderate** ▪ Randomized controlled studies	**VTE prophylaxis/Treatment: Weak** ▪ Case report ▪ Pharmacovigilance repository
		▪ **LMWH Prophylaxis +/- pneumatic compression devices** **Thrombophilia carrier without family history VTE: Postpartum** **Prior history of VTE: Postpartum** **History of unprovoked: Antepartum-postpartum** **Family history VTE + homozygous FVL/ antithrombin III deficiency/compound thrombophilia: antepartum-postpartum** **Prior history of VTE+thrombophilia: antepartum-postpartum** **C-section with > 1 additional risk factors for VTE that will persist in the postpartum period** ▪ **Treatment: LMWH (body weight adjusted): once or twice daily** **Duration: 3 months (including 6 weeks post-partum)**	▪ **Avoid oral antiXa and thrombin inhibitors**
ASH	2018		
ISTH	2016		**Not recommended during pregnancy/lactation**

Chest. 2012;141(2 Suppl):e419S-7236S
ANZJOG. 2012;52:14–22
J Obstet Gynaecol Can 36(6):527–53
Obstetrics & Gynecology. 2018;132(1):1-17

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg37b/. Accessed 19 June 2019
Blood advances. 2018 Nov 27;2(22):3257-91
Journal of Thrombosis and Haemostasis. 2016, 14: 1673–1676

2019 MASCC/ISOO Annual Meeting Supportive Care in Cancer 21-23 JUNE SAN FRANCISCO

PREGNANCY AND VTE MANAGEMENT: REGISTRY FOR ORAL ANTICOAGULANT EXPOSURE

ISTH 2016: The international ISTH registry

http://www.surveygizmo.com/s3/2394649/International-registry-of-pregnancy-during-NOAC-use-Inclusion

VigiBase: The World Health Organization

- WHO global database of individual case safety reports of suspected adverse drug reactions.
- > 16 X 10^6 reports from 136 countries participation in the WHO International Drug Monitoring Program.
- 60 identified cases of exposure to DOAC during pregnancy and reported outcomes

  42 cases of abortion (43% had an alternative cause)

  8 cases of congenital abnormality (63% had an alternative cause)

  6 cases of fetal growth restriction (33% had an alternative cause)

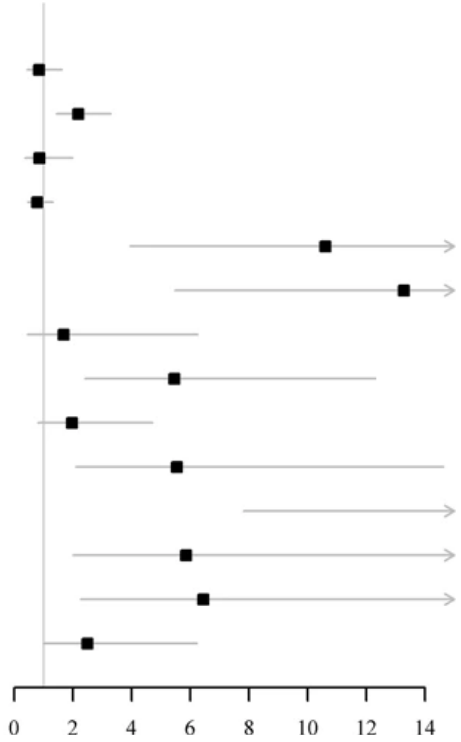
Journal of Thrombosis and Haemostasis. 2016, 14: 1673–1676

Scientific reports. 2019 May 10;9(1):7236.

2019
MASCC/ISOO
Annual Meeting
Supportive Care in Cancer
21-23 JUNE
SAN FRANCISCO

PREGNANCY AND VTE MANAGEMENT: REGISTRY FOR ORAL ANTICOAGULANT EXPOSURE

Variable	Reporting Odds Ratio	95% CI low	95% CI high	Outcome
Rivaroxaban vs All drugs	0.85	0.44	1.63	Spontaneous abortion - cases without alternative causes
Rivaroxaban vs All drugs	2.18	1.44	3.29	Spontaneous abortion - all cases
Rivaroxaban vs Warfarin	0.86	0.37	1.99	Spontaneous abortion - cases without alternative causes
Rivaroxaban vs Warfarin	0.79	0.47	1.32	Spontaneous abortion - all cases
Rivaroxaban vs All drugs	10.61	3.95	28.51	Intrauterine growth retardation - cases without alternative causes
Rivaroxaban vs All drugs	13.28	5.48	32.18	Intrauterine growth retardation - all cases
Rivaroxaban vs Warfarin	1.68	0.45	6.25	Intrauterine growth retardation - all cases
Apixaban vs All drugs	5.46	2.42	12.32	Spontaneous abortion - all cases without alternative causes
Apixaban vs Warfarin	1.97	0.82	4.72	Spontaneous abortion - all cases
Apixaban vs Warfarin	5.55	2.11	14.63	Spontaneous abortion - cases without alternative causes
Apixaban vs All drugs	19.04	7.82	46.36	Induced abortion - all cases without alternative causes
Apixaban vs Warfarin	5.86	2.01	17.06	Induced abortion - all cases
Apixaban vs Rivaroxaban	6.45	2.27	18.35	Spontaneous abortion - cases without alternative causes
Apixaban vs Rivaroxaban	2.50	1.01	6.23	Spontaneous abortion - all cases



Scientific reports. 2019 May 10;9(1):7236.

2019
MASCC/ISOO
Annual Meeting
Supportive Care in Cancer
21-23 JUNE
SAN FRANCISCO

PREGNANCY AND VTE MANAGEMENT: CONCLUSIONS

1. **Thrombotic risk stratification early on pregnancy is critical to provide adequate prophylaxis/treatment strategies for VTE.**

2. **Low molecular weight heparin(s) are the medication(s) of choice for prophylaxis and treatment of VTE.**

3. **Weight based dose regimes are preferred for treatment.**

4. **Due to maternofetal risks, oral anticoagulants are not recommended during pregnancy.**

2019
MASCC/ISOO
Annual Meeting
Supportive Care in Cancer
21-23 JUNE
SAN FRANCISCO