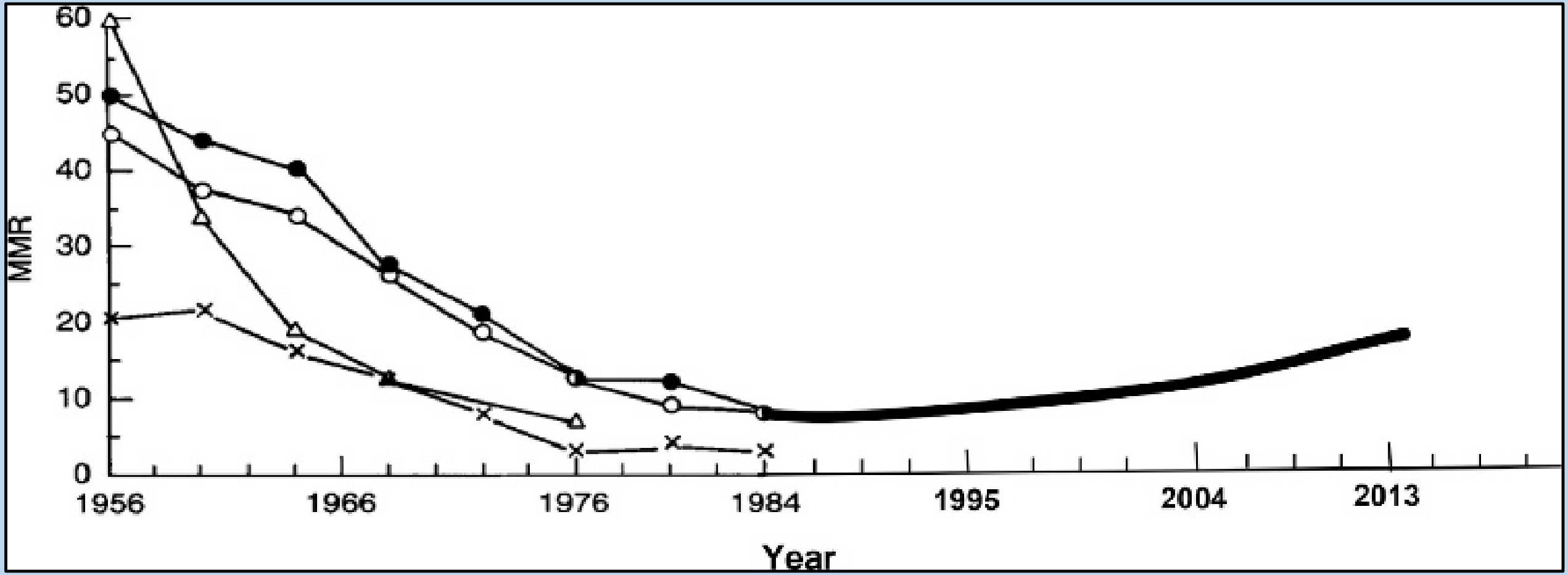
Anticoagulation in Pregnancy

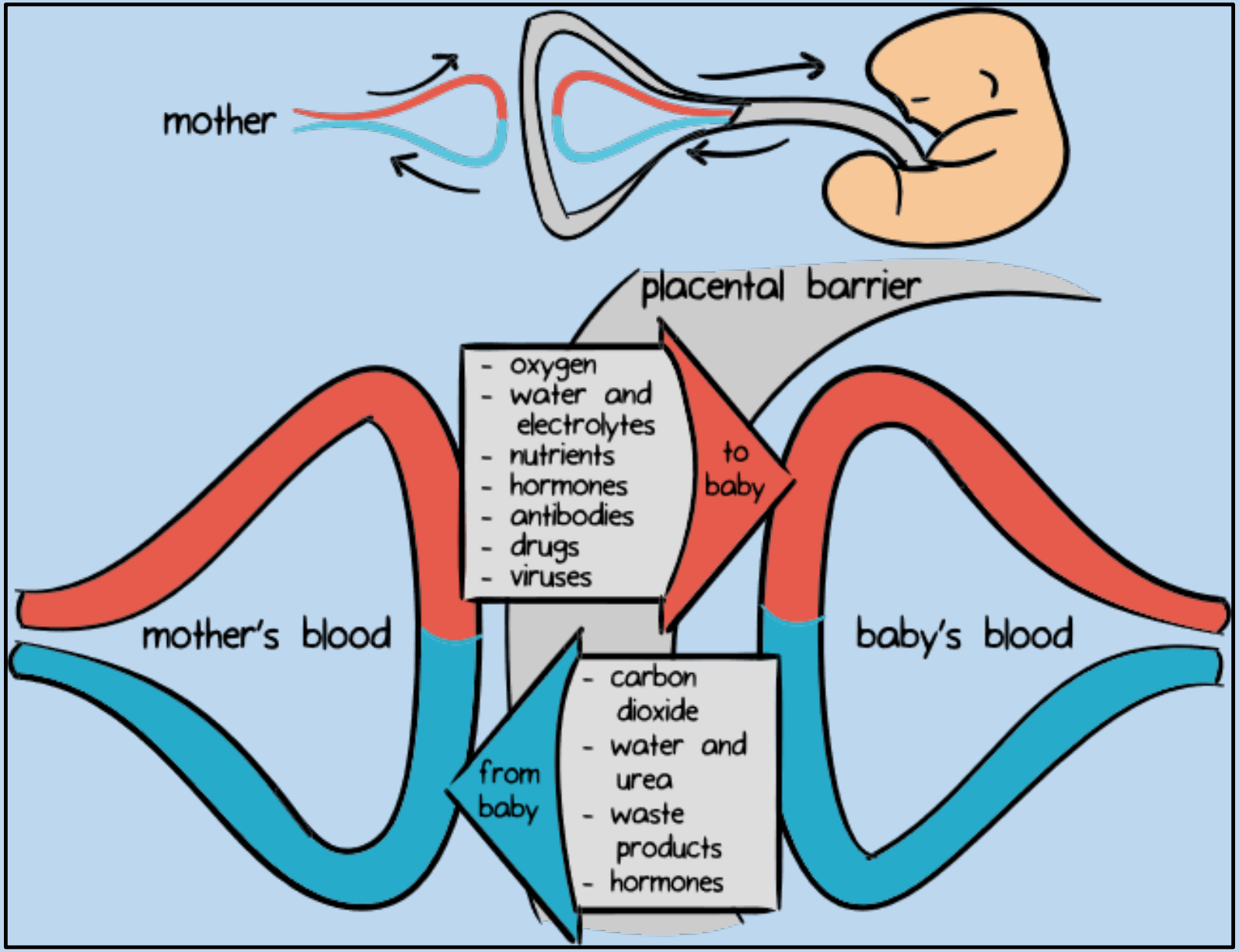
Saurabh Rajpal, MBBS, MD
Assistant Professor
The Ohio State University

May 12th, 2019

No Disclosures

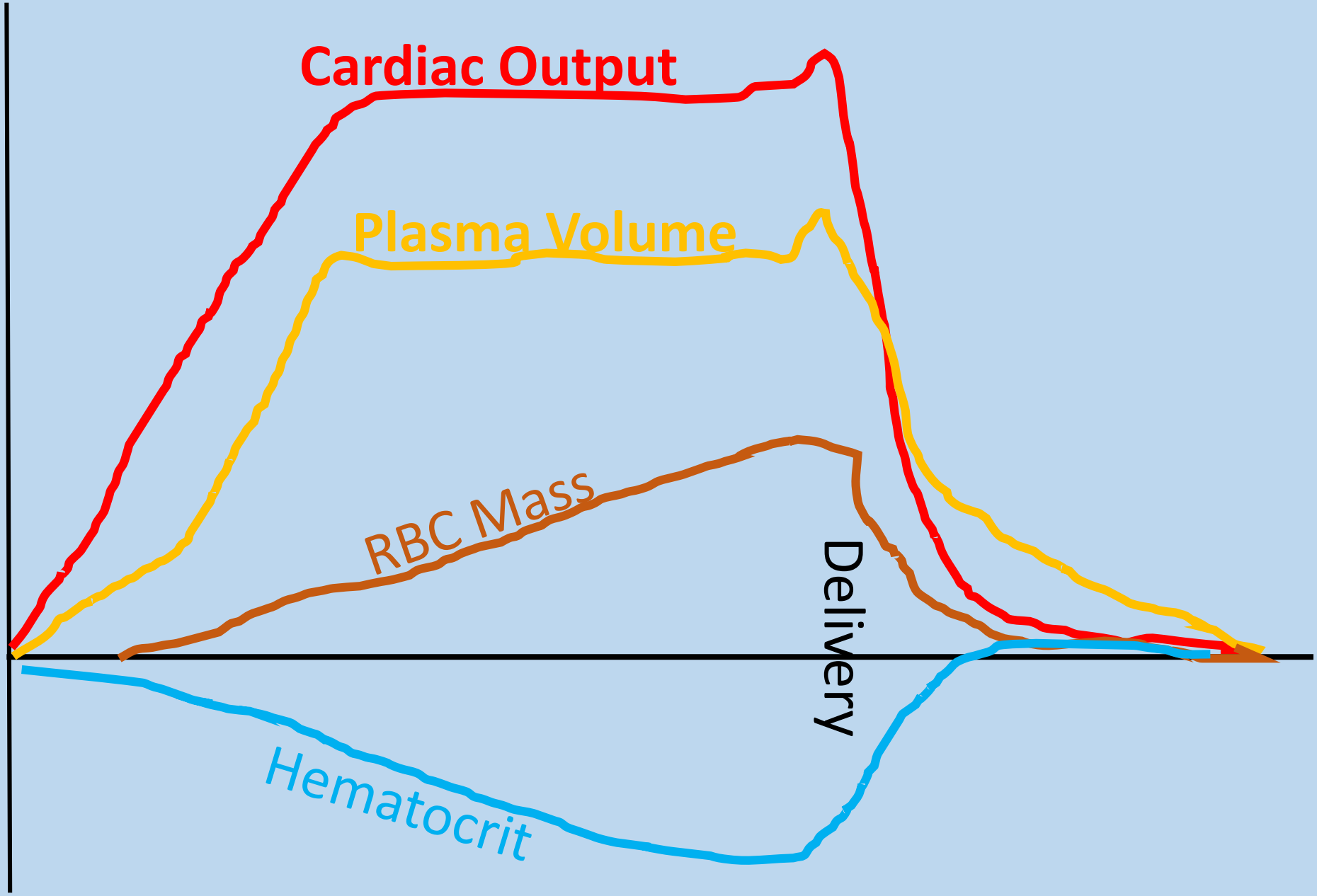
Rise in Pregnancy-Related Mortality





https://www.khanacademy.org/test-prep/nclex-rn/rn-reproductive-system-physiology/rn-pregnancy/a/physiology-of-pregnancy

Physiologic Changes During Pregnancy



Pregnancy is a Pro-coagulant State

Procoagulant

Anticoagulant

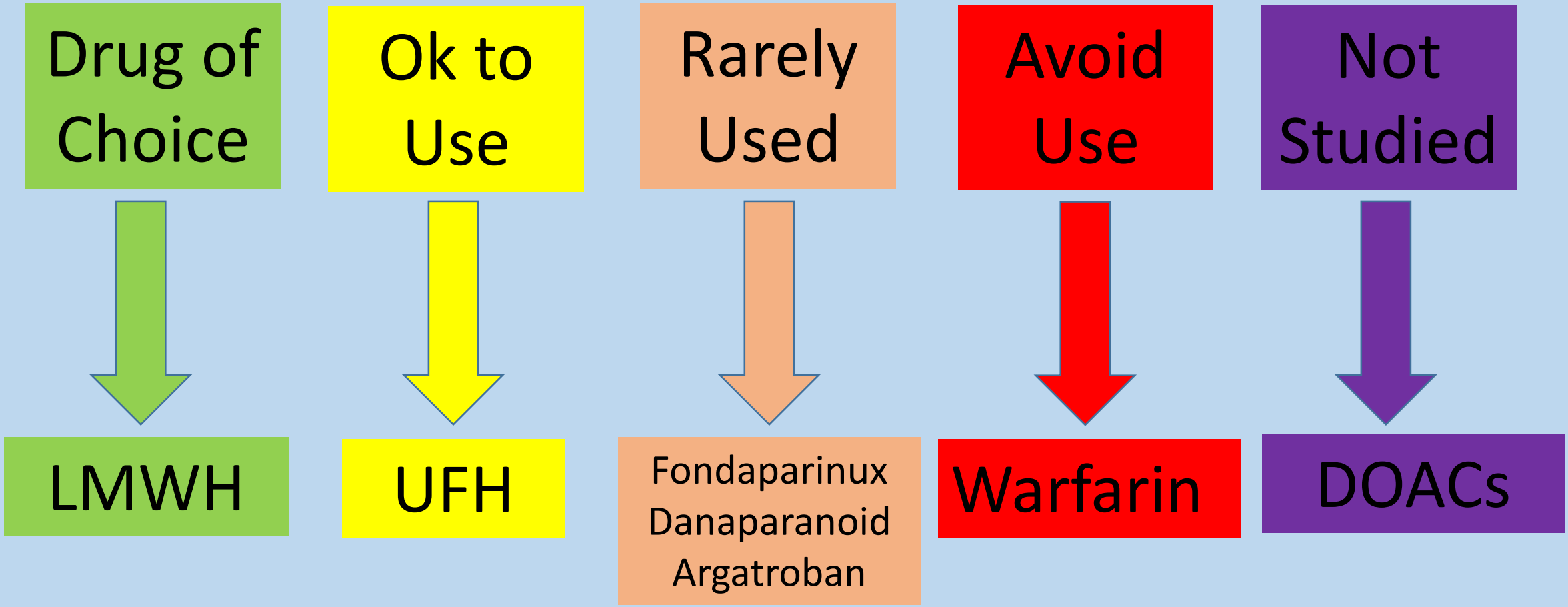
The risk is highest in the immediate post-partum period and slowly decreases back to pre-pregnancy levels by 8 to 12 weeks post-partum

Placental hormones
Inhibition of fibrinolysis

Need for Anticoagulation in Pregnancy

- Prosthetic Heart Valves
- DVT/PE (Venous Thromboembolism)
- Inherited Thrombophilias
- Atrial Fibrillation
- Peripartum Cardiomyopathy and Preexistent DCM
- Women with History of Fetal Loss

Anticoagulants in Pregnancy



Anticoagulants in Pregnancy

	Pre-conception	1st Trimester	2nd /3rd Trimester	Post Partum
Warfarin	Teratogenic	Embryopathy	Fetopathy/ Bleeding	Bleeding
UFH	-	-	Fetopathy/ Bleeding	Bleeding
LMWH	-	-	Bleeding	Bleeding

Warfarin Embryopathy

- 0.6–10%
- Limb defects/Nasal hypoplasia
- 0.45–0.9% - low-dose

Fetopathy

- Ocular defects
- CNS abnormalities Intracranial haemorrhage

LMWH in Pregnancy

TABLE 1. COMPARATIVE STUDIES OF ANTI-Xa and ANTI-IIa ACTIVITIES OF THE MOTHERS AND THEIR RELATED FETUSES 3 HOURS AFTER THE LMWH INJECTION (Mean and standard deviation).

	Mothers (n=5)	Fetuses (n=5)
anti-Xa activity (IU/ml)	0,175 ± 0,07	< 0,01*
anti-IIa activity (IU/ml)	< 0,1	< 0,1*

Forestier F et al. Thromb Res 1984; 34:557

LMWH in Pregnancy

- Drug Of Choice: ~~Embryopathy/Fetopathy~~
- Dosage: Early pregnancy body weight
  - Enoxaparin 1 mg/kg body weight BID
  - Dalteparin 100 IU/kg body BID
- Monitoring: 4–6 h peak anti-Xa - 0.6–1.2 IU/mL

LMWH in Pregnancy

- Risk of recurrent VTE - 1.15%
- Major bleeding - 1.98%
- Markedly lower
  - Heparin-induced thrombocytopenia
  - Heparin-induced osteoporosis (0.04%)
- Dosing less frequent

UFH in Pregnancy

- Low Cost
- Need for rapid reversal is important

  Delivery or Perioperatively
- Severe Renal Insufficiency
- Acute Massive PE
- Risk of Osteoporosis

- LMWH switch to IV UFH 36h before IOL or CS
- Discontinue UFH 4–6h before
- Restart 6 h after

Mechanical Heart Valves (MHV) in Pregnancy

Valve Thrombosis
First Trimester

Venous Thromboembolism
Postpartum

- Transition from warfarin to heparins
- Changing pharmacokinetics
- Unidentified homeostatic factors
- Warfarin discontinued by patient

MHV in Pregnancy - Challenging Situation

- Teratogenic effects of anticoagulants
- Dosing complexities
- Management around labor
- Teratogenic effects during conception

ROPAC Registry

	Mechanical Valves n=212 (%)	No Prosthetic Valve n= 2906 (%)	P Value
Maternal Mortality	1.4	0.2	0.025
Hospital Admission	36.7	24.5	<0.001
Thrombosis	6.1	0.4	<0.001
Hemorrhage	23.1	4.0	<0.001
Miscarriage<24 wks	15.6	1.7	<0.001
Miscarriage>24 wks	2.8	0.6	0.003

Van Hagen et al. Circulation 2015

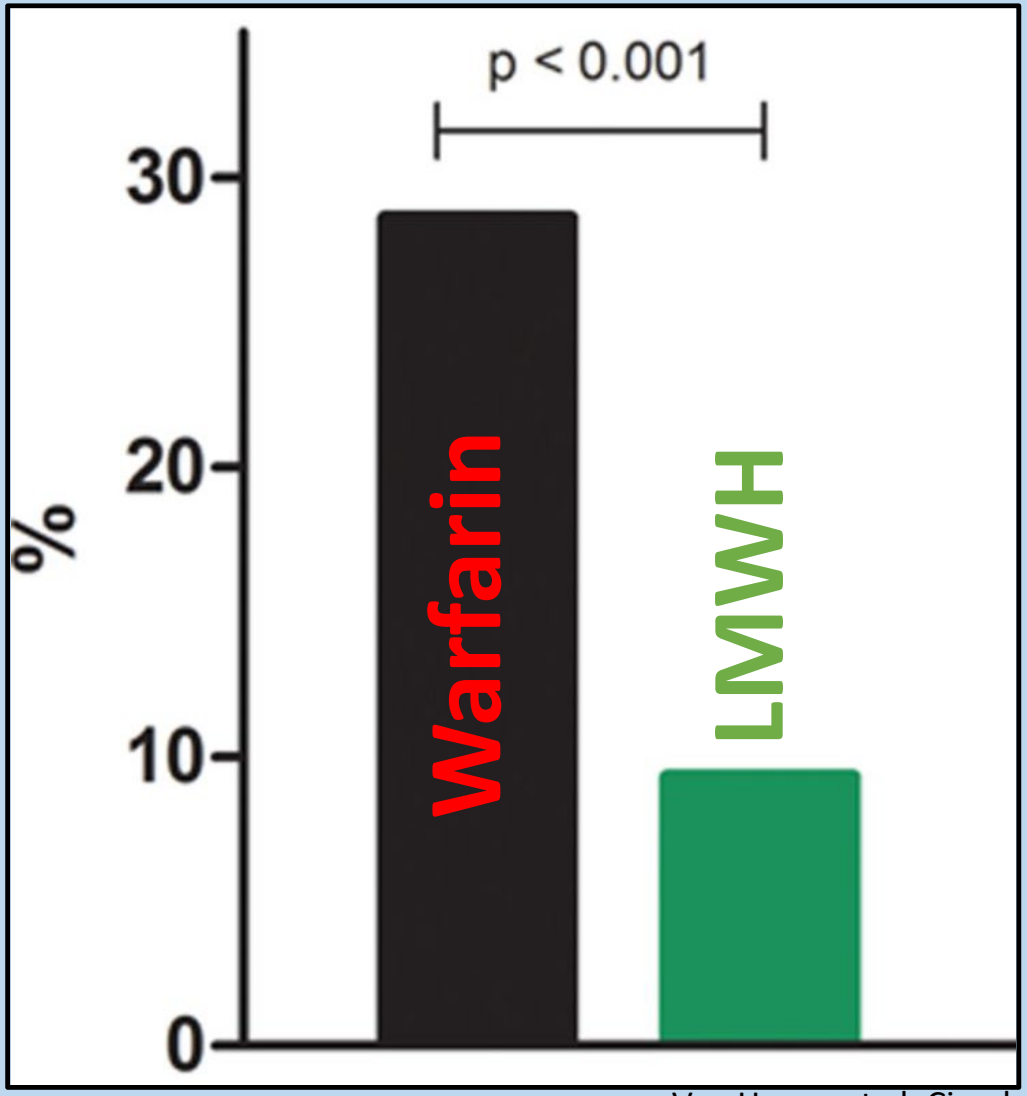
ROPAC Registry

	Mechanical Valves	Tissue Valve	No Prosthetic Valves
Live Mom and Baby	81%	97%	97.7%
Event Free Live Birth	58%	79%	71.1%

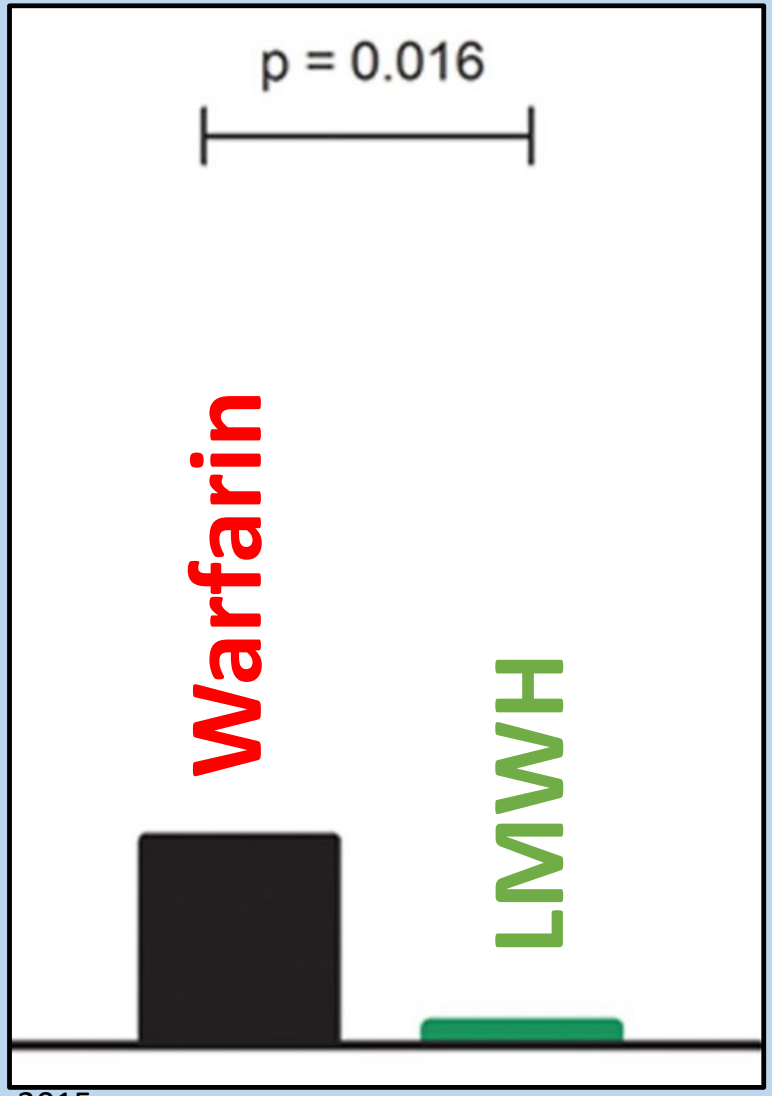
Van Hagen et al. Circulation 2015

Warfarin vs LMWH in First Trimester

Miscarriage <24 wks



Fetal Loss >24 wks



Van Hagen et al. Circulation 2015

Management of MHV in Pregnancy- Preconception Counseling

- Consider bioprosthetic valves
- Discuss risk profile
- Eliminate modifiable risk factors
  - Smoking
  - Atrial arrhythmia
- Start ASA

Management of MHV in Pregnancy

	1st Trimester	2nd & 3rd Trimesters	Peripartum
ACC/AHA	Warfarin if dose ≤ 5 mg/d (IIa) or Dose-adjusted LMWH* (IIb) or Dose-adjusted IV UFH† (IIb)	Warfarin + daily Aspirin (I)	Dose-adjusted IV UFH (I)
ESC	Warfarin if dose < 5 mg/d (IIa) or > 5 mg/d (IIb) Dose-adjusted LMWH (IIb) or Dose-adjusted IV UFH (IIb)	Warfarin (I)	Dose-adjusted LMWH or IV UFH (I)

Alshwabkeh et al. JACC 2016

Prosthesis thrombogenicity	Patient Related Risk Factors	
	None	≥1
Low	2.5	3
Medium	3.0	
High	3.5	4

- MVR
- TVE
- H/O TE
- Afib
- Any MS
- LVEF <35%

Low- Carbomedics, Medtronic Hall, ATS, or Medtronic Open-Pivot, St Jude Medical, On-X, or Sorin Bicarbon

High- Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Björk-Shiley and other tilting-disc valves; any pulmonary valve prosthesis.

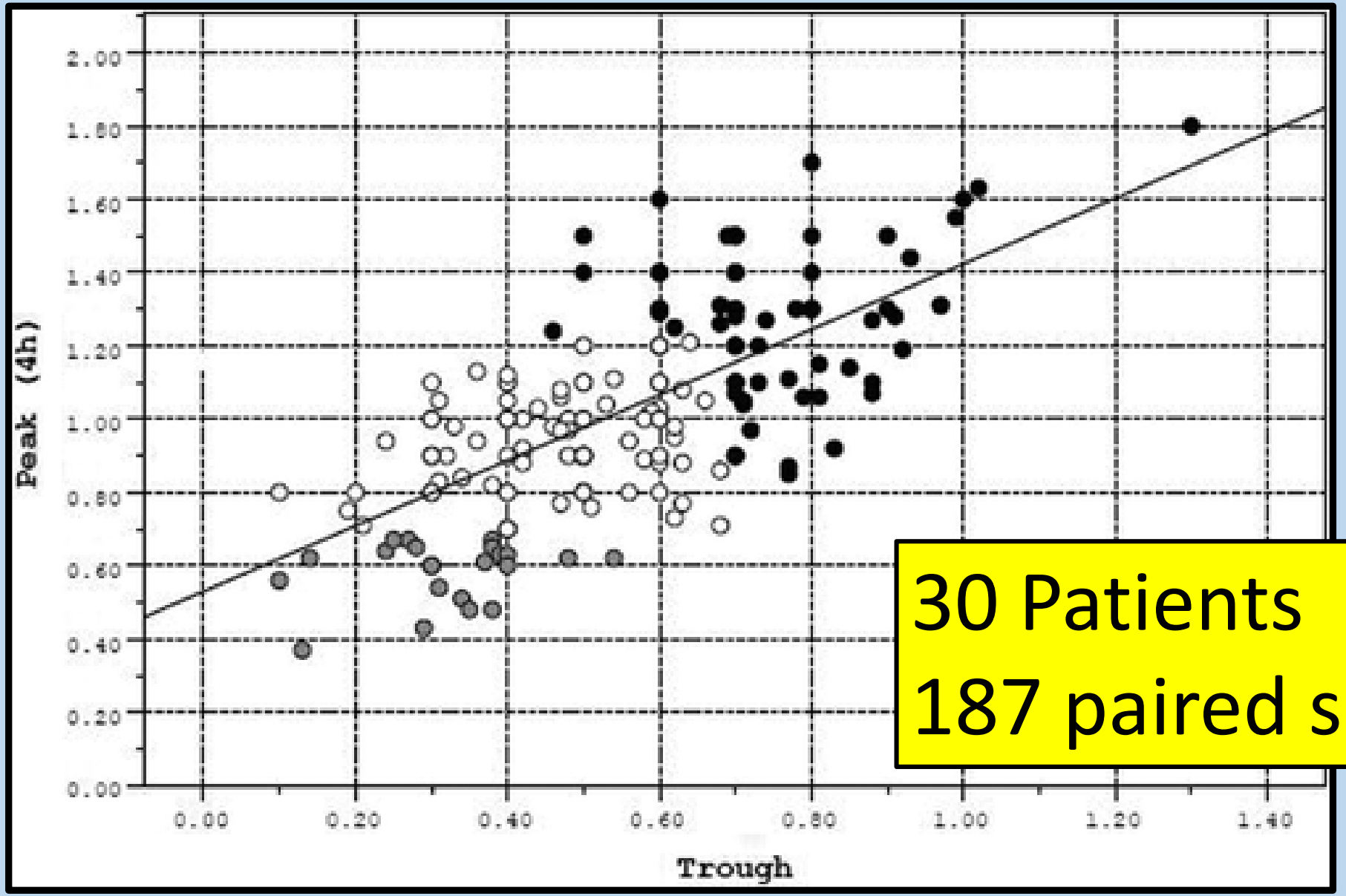
MHV in Pregnancy - Surveillance

- Pregnancy heart team in an expert center
- Anticoagulation - Weekly or every 2 weeks
- Clinical follow-up + echocardiography- monthly

Anticoagulation for MHV in Pregnancy

- ↑ maternal and fetal mortality
- ↑ thrombotic and hemorrhagic complications
- Most MVTs - first trimester
- All MVTs in women on some form of heparin
- Warfarin (even low dose) – miscarriage /fetal demise
- No regime safe

LMWH Peak and Trough



30 Patients
187 paired samples

Goland et al. J Cardiovasc Pharmacol Therap 2014

LMWH Monitoring with MHV in Pregnancy

Prosthesis thrombogenicity	Anti-Xa Peak	Anti-Xa Trough
Low	≤1.5	≥0.6
High	≤1.5	≥0.7

Goland et al. Cardiol Clin 2012

VTE During Pregnancy

- VTE is highest in post-partum period with rates- 0.5%
- In women with previous VTE, recurrence rates - 7.6%
- High index of suspicion + low threshold for investigation

Regitz-Zagrosek et al. EHJ 2018

Post-Partum Management VTE

- Heparin treatment should be restarted
  - 6 h after a vaginal birth and
  - 12 h after a caesarean delivery
- Warfarin may be started on the second day after delivery
- Atleast 3 months, or for 6 months if PE occurred later
- INR 2-3, 1–2 weekly check
- Warfarin safe for breastfeeding

Prevention of VTE During Pregnancy

- High-risk for VTE
  - prophylactic enoxaparin- 0.5 IU/kg daily or equivalent

- Previous unprovoked recurrent VTEs
- Previous VTE—unprovoked or estrogen-related
- Thrombophilia + FH VTE

Regitz-Zagrosek et al. EHJ 2018

Atrial Fibrillation In Pregnancy

- Not been systematically studied
- Some experts recommend anticoagulation if Afib>48hrs
- ESC guidelines- Same rules apply as Afib in non-pregnant
- Warfarin should not be given
- Cardiovert within 48 hrs to reduce TE risk

Regitz-Zagrosek et al. EHJ 2018
Goland et al. Cardiol Clin 2012

Mitral Stenosis- Suggested Indications for Anticoagulation in Pregnancy

- Atrial Fibrillation
- Prior thromboembolism
- Enlarged left atrium > 55 mm

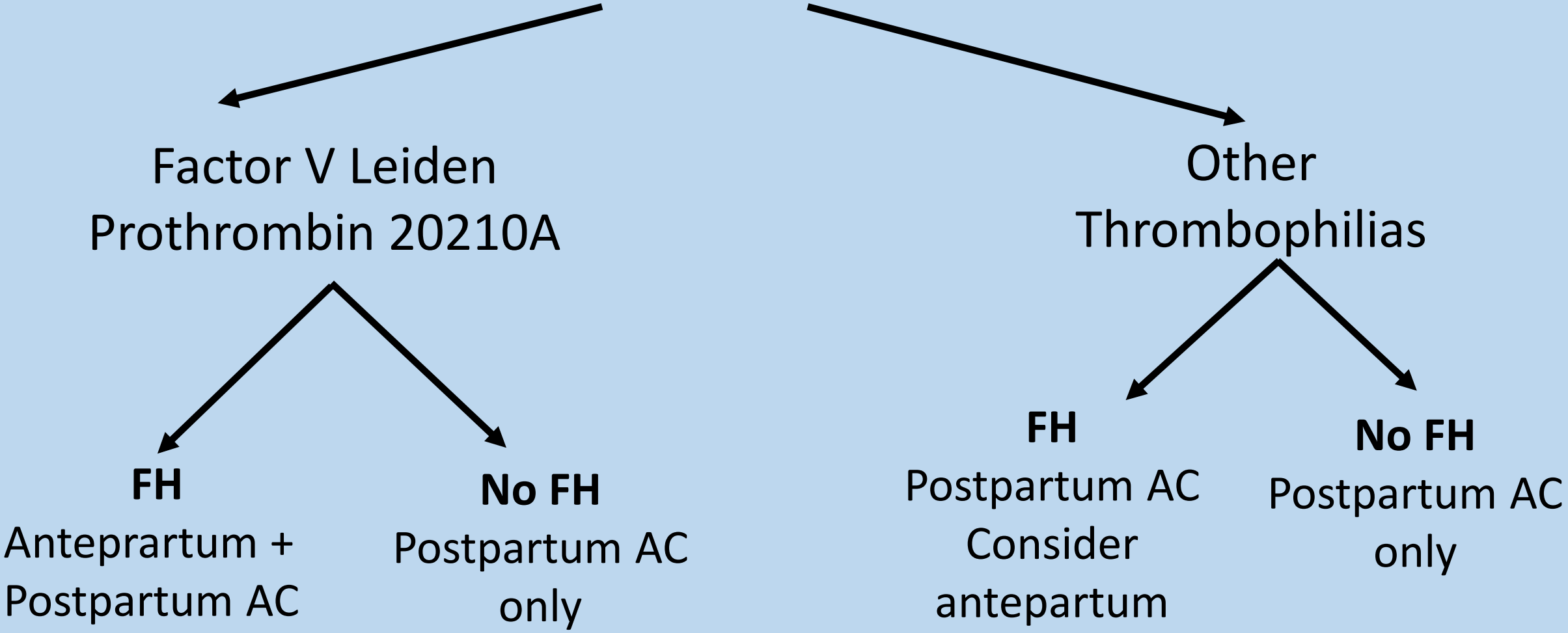
Goland et al. Cardiol Clin 2012

Peripartum Cardiomyopathy and Pre-existent Dilated Cardiomyopathy

- Atrial Fibrillation
- Prior thromboembolism
- LV thrombus
- Bromocriptine use for PPCM

Goland et al. Cardiol Clin 2012

Inherited Thrombophilias



Antepartum: LMWH or UFH

Post-partum: LMWH, UFH or Warfarin

Bates et al . Chest 2012

Some Other Scenarios

- Severe ovarian hyperstiumaulation syndrome
  - LMWH 3 months
- APLA - UFH or LMWH + ASA 81 mg
- At risk for preeclampsia- ASA 81 mg

Bates et al . Chest 2012

Neuraxial Anesthesia

- Not be done if patient anticoagulated - risk of spinal/ epidural hematoma
- >95 % CS and >65% VD in US
- Prophylactic LMWH- 12 hrs last dose
- Intermediate and Therapeutic LMWH – 24 hrs
- Prophylactic and therapeutic UFH – Once the aPTT has normalized
  - 6 hours after IV
  - 24 hours SQ

Gogarten W et al. Eur J Anaesthesiol 2010

Conclusion

- Pregnancy is a procoagulant state
- Anticoagulation -Increased maternal & fetal morbidity + mortality
- MHV - increased risk of valve thrombosis - first trimester
- LMWH is the drug of choice in pregnancy
- LMWH and UFH carry a high risk of MVT
- Warfarin lower risk of MVT but high risk of adverse fetal outcome
- Warfarin, LMWH and UFH are safe in post partum period
- DOACs have not been studied in pregnancy

Thank you