Anticoagulation, hormones & menstrual bleeding

15e Nederlands Trombose Congres

Jenneke Leentjens, internist-vasculair geneeskundige – klinisch farmacoloog
Jenneke.leentjens@radboudumc.nl

Radboudumc

DISCLOSURES

(potentiële) belangenverstrengeling	None
Voor bijeenkomst mogelijk relevante relaties met bedrijven	*
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk … 	Synapse BV BMS-Pfizer, Astra Zeneca, Viatris All paid to institution

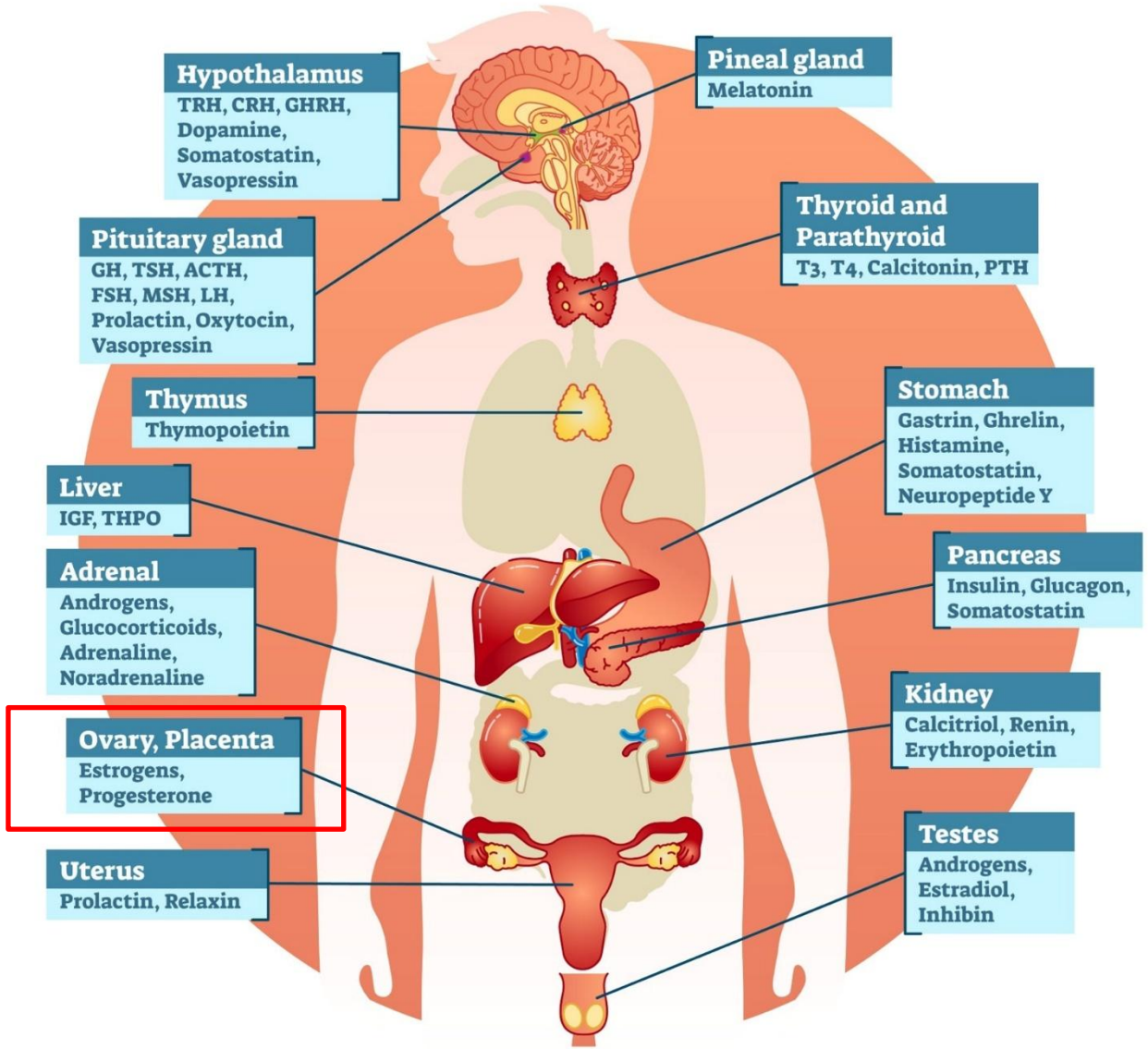
Content

- Hormones and venous thromboembolism (VTE) risk
- Anticoagulation and hormones
- Anticoagulation and menstrual bleeding

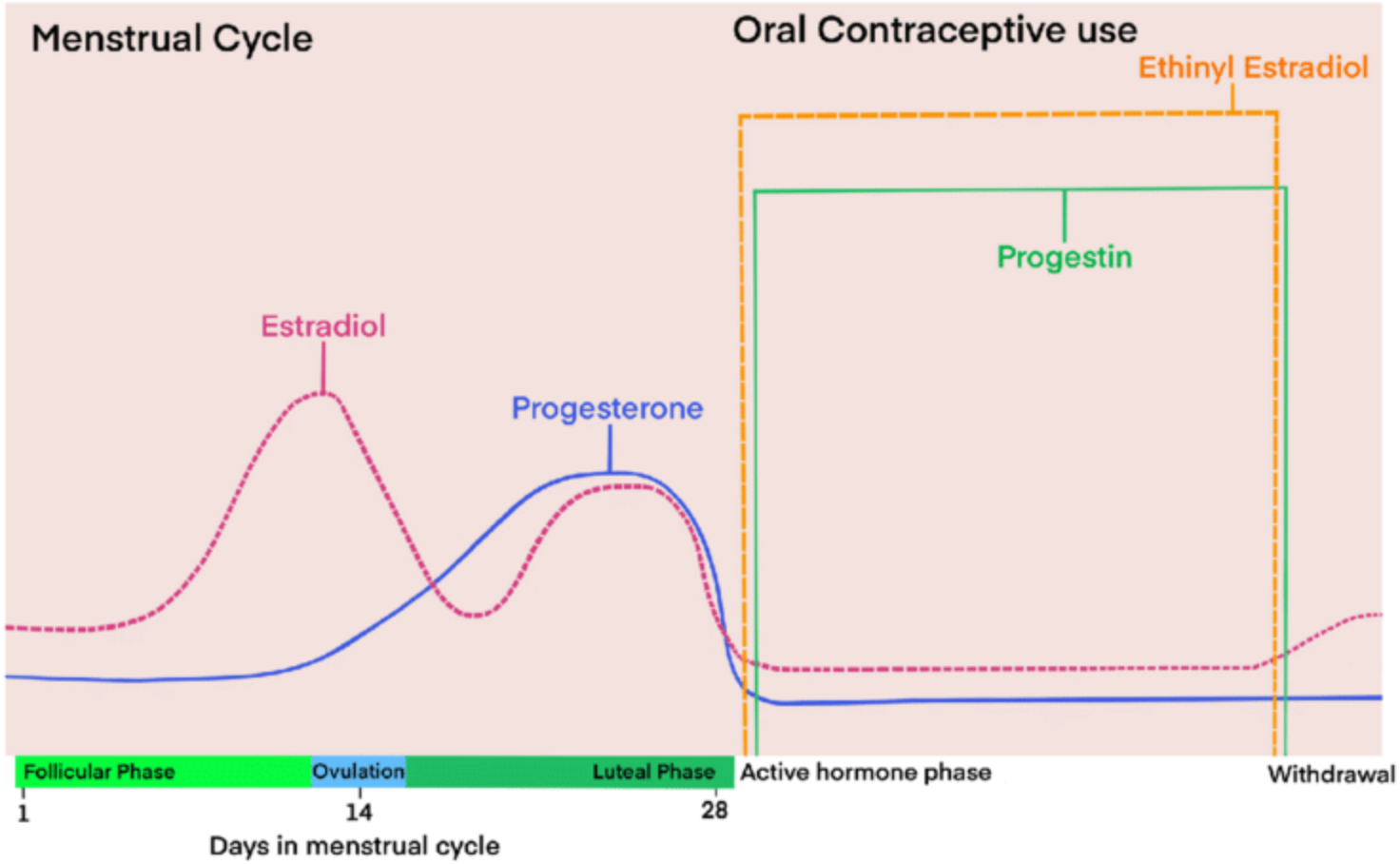
Content

- **Hormones and venous thromboembolism (VTE) risk**
- Anticoagulation and hormones
- Anticoagulation and menstrual bleeding

HORMONES



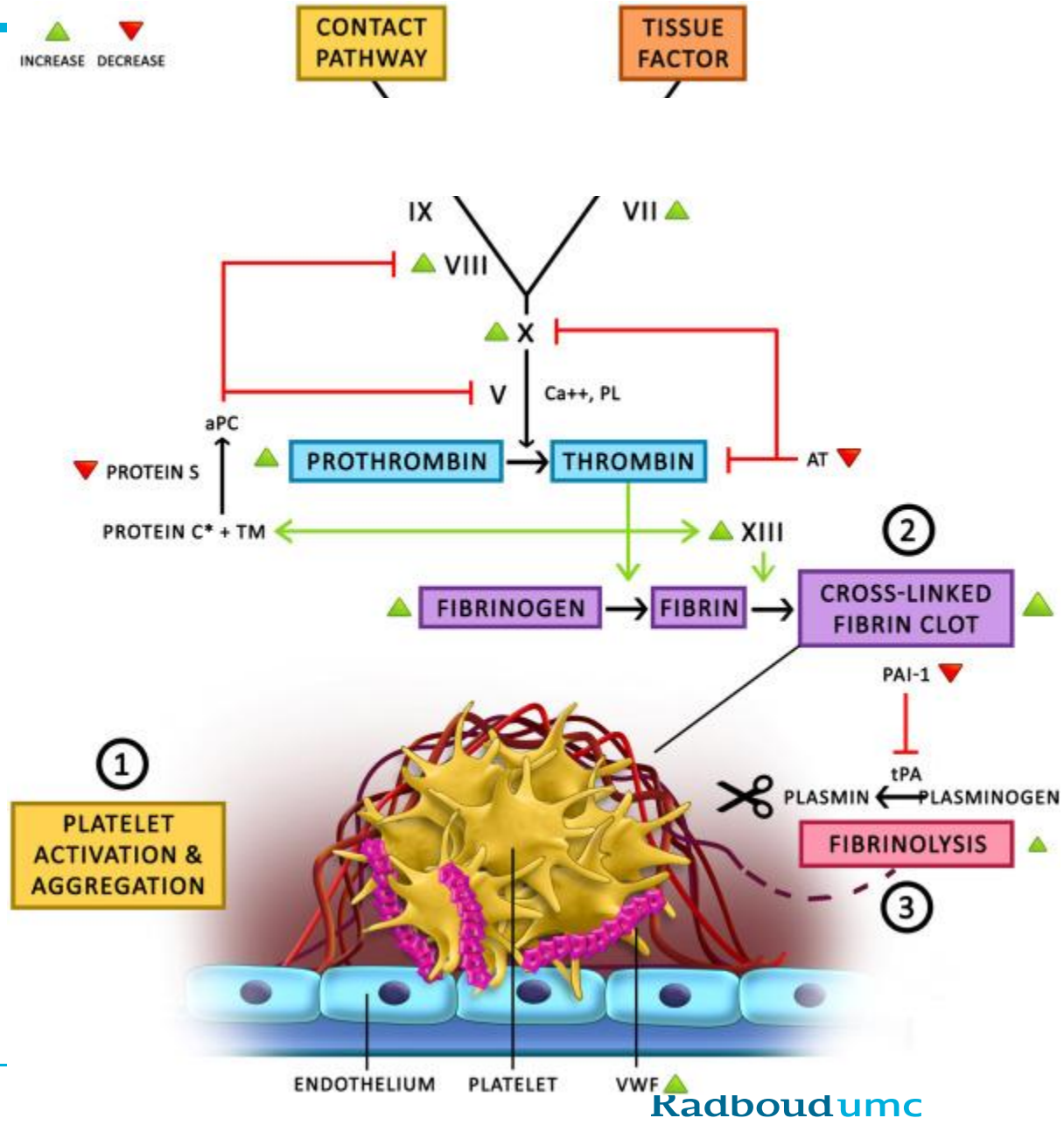
Human body hormones. Image Credit: VectorMine / Shutterstock


Menstrual Cycle
Oral Contraceptive use
Ethinyl Estradiol
Progestin
Estradiol
Progesterone
Follicular Phase
Ovulation
Luteal Phase
Active hormone phase
Withdrawal
1
14
28
Days in menstrual cycle

Hormones and VTE risk?

Estrogen

Progesterone – no increased risk in case of monotherapy



Radboudumc

WOOCLAP

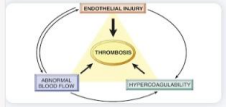

Exit
Radboud University
Neem deel aan dit Wooclap-evenement
1
Ga naar wooclap.com
2
Voer de code van het evenement in de bovenste banner in
Evenementcode
MHNKED
Antwoorden per sms inschakelen
Deelnamelink kopiëren

Question 1

Exit

Ga naar **wooclap.com** en gebruik de code **MHNKED**

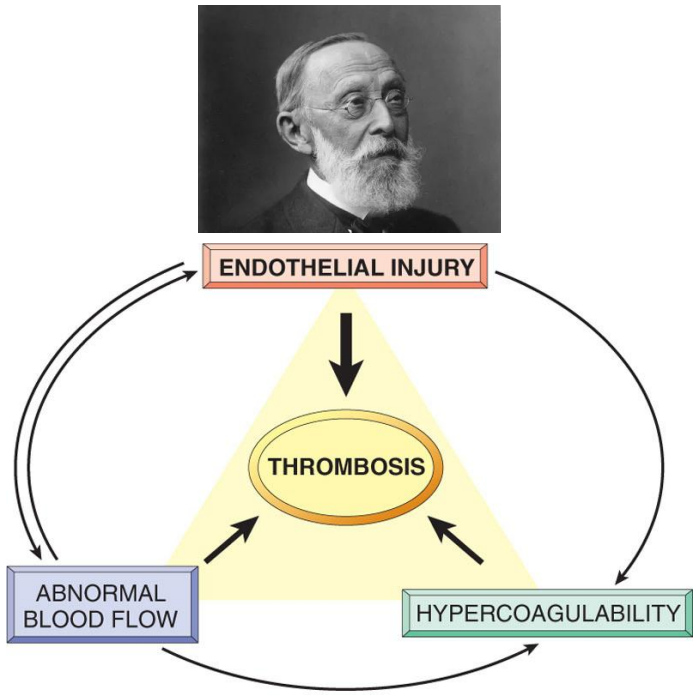
Radboud University



Rank the order from lowest (top) to highest (down) risk.

1. Malignancy
2. Obesity
3. Heterozygous G20210A prothrombin mutation
4. Pregnancy
5. Combined Oral contraceptive pills (COC)
6. Protein C deficiency

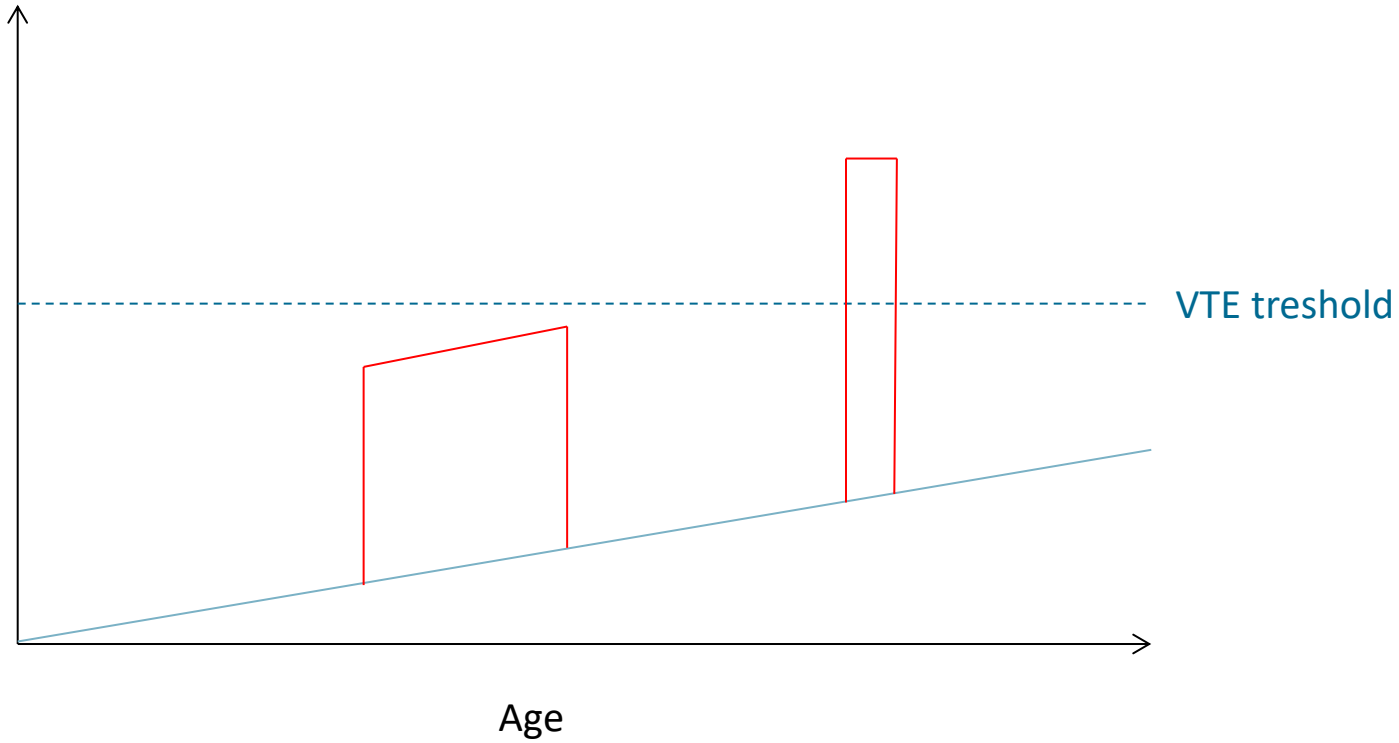
Venous thromboembolism riskfactors



VTE Risk factor	RR first VTE (95%CI)
Transdermal estrogen	1.0 (0.9–1.1) (1)
Testosterone	0.90 (95% CI, 0.73-1.12) (2)
Oral estrogens	2.22 (1.12-4.39) (1)
Heterozygous G20210A prothrombin mutation	2.35 (1.46-3.78)
First degree relative with VTE	2.38 (1.43-3.85) (3)
Obesity	2.6 (2.1-3.3) (4)
Long distance flight	2.8 (2.1-4.2) (5)
Heterozygous FVLeiden	2.7 (2,06-3.56) (2)
Oral contraception	3.5 (3-7) (8)
Oral estrogen and progesterone (HRT)	4.28 (2.49-7.34) (1)
Pregnancy	4.6 (2.7-7.9)
Protein S deficiency	5.98 (2.45-14.57 (5)
Protein C deficiency	7.47 (2.81-19.81)(5)
Homozygous FVLeiden	11.5 (6.8-19.3) (6)
Malignancy	14.91 (8.9-24.95) (7)
Antithrombin deficiency	12.17 (5.45-27.17) (5)
Compound FVLeiden + G20210A prothrombin	20.0 (11.1-36.1) (6)
Major surgery	69.1 (63.1-75.6)
Puerperium	84 (31.7-222.6)

Van Bunderen, Leentjens et al, haemastologia 2022

VTE – a multicausal disease



Transient riskfactor, eg oral contraception

Translated from Cannegieter & Hylckama Vlieg; J Thromb Haemost 2013

OAC and VTE risk with age

Table 2 | Absolute risk of venous thrombosis associated with oral contraceptive use by age category

Age category	Incidence of venous thrombosis in non-users of oral contraceptives (I_0) per 10 000 person-years*	Relative risk (95% CI) of oral contraceptive use†	Incidence of venous thrombosis in oral contraceptive users (I_1) per 10 000 person-years‡
<30 years	1.2	3.1 (2.2 to 4.6)	3.7
30-40 years	2.0	5.0 (3.8 to 6.5)	10.0
40-50 years	2.3	5.8 (4.6 to 7.3)	13.3

*I_0 is based on incidences published by Naess et al.[30]
†Non-users of oral contraceptives are used as the reference category.
‡$I_1 = I_0 \times$ relative risk.

Hylckama Vlieg et al, MEGA study, BMJ 2009

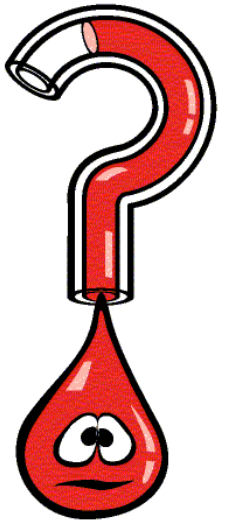
Safe alternatives?

Hormone preparations	Progesterone	Estrogen (mcg) (multiple numbers indicate multiphasic/extended formulations)	Effectiveness*	VTE risk
Progestin only pills	Norethindrone	None	93.0%	No increased risk
	Drospirenone	None		
LNG IUD	Levonorgestrel	None	99.7%	No increased risk
Implant†	Etonogestrel	None	99.9%	No increased risk
Injectable ("Depo")	Medroxyprogesterone	None	96.0%	OR 2.2 (1.3-4.0)‡
Vaginal ring	Segesterone	Ethinyl estradiol (13 mcg/day)	93.0%	6.5-fold (4.7-8.9) increased risk compared to non hormone users (mixed data compared to oral preparations)§
	Etonogestrel	Ethinyl estradiol (15 mcg/day)		
Transdermal patch¶	Levonorgestrel	Ethinyl estradiol (30 mcg/day)	93.0%	7.9-fold (3.5-17.7) increased risk compared to non hormone users (mixed data compared to oral preparations)§
	Norelgestromin	Ethinyl estradiol (30 mcg/day)		
4th Generation Progesterone COC	Dienogest	Estradiol valerate (3,2,2,1 mg)	93.0%	Similar/improved risk as 2nd generation progesterone COC
2nd Generation Progesterone COC	Levonorgestrel	Ethinyl estradiol (20, 10)	93.0%	OR 2.38 (2.18-2.59)**
		Ethinyl estradiol (20)		
		Ethinyl estadiol (30)		
		Ethinyl estradiol (20, 25, 30,10)		
		Ethinyl estradiol (30, 10)		
1st Generation Progesterone COC	Norethindrone acetate	Ethinyl estradiol (10,10)	93.0%	No data comparing 1st and 2nd generation, recommend lowest dose of estrogen for lowest risk of VTE
		Ethinyl estradiol (20)		
		Ethinyl estradiol (30)		
		Ethinyl estradiol (20,30,35)		
	Norethisterone††	-		
	Norethindrone	Ethinyl estradiol (35)		
	Ethynodiol diacetate	Ethinyl estradiol (35)		
		Ethinyl estradiol (50)‡‡		
	Norgestrel	Ethinyl estradiol (30)		
		Ethinyl estradiol (50)‡‡		
	Medroxyprogesterone††	-		
3rd Generation Progesterone COC	Norgestimate	Ethinyl estradiol (35)	93.0%	OR 2.53 (2.17-2.96)**
	Desogestrel	Ethinyl estradiol (20,0,10)	93.0%	OR 3.64 (3.00-4.43)**
		Ethinyl estadiol (30)		
	Gestodene††	-		OR 4.28 (3.66-5.01)**
4th Generation Progesterone COC	Drospirenone	Ethinyl estradiol (20)	93.0%	Similar risk as 3rd generation progesterone COC
		Ethinyl estradiol (30)		
		Estetrol (14.2 mg)		

Lavasseur et al, RPTH 2022

Take home messages part 1

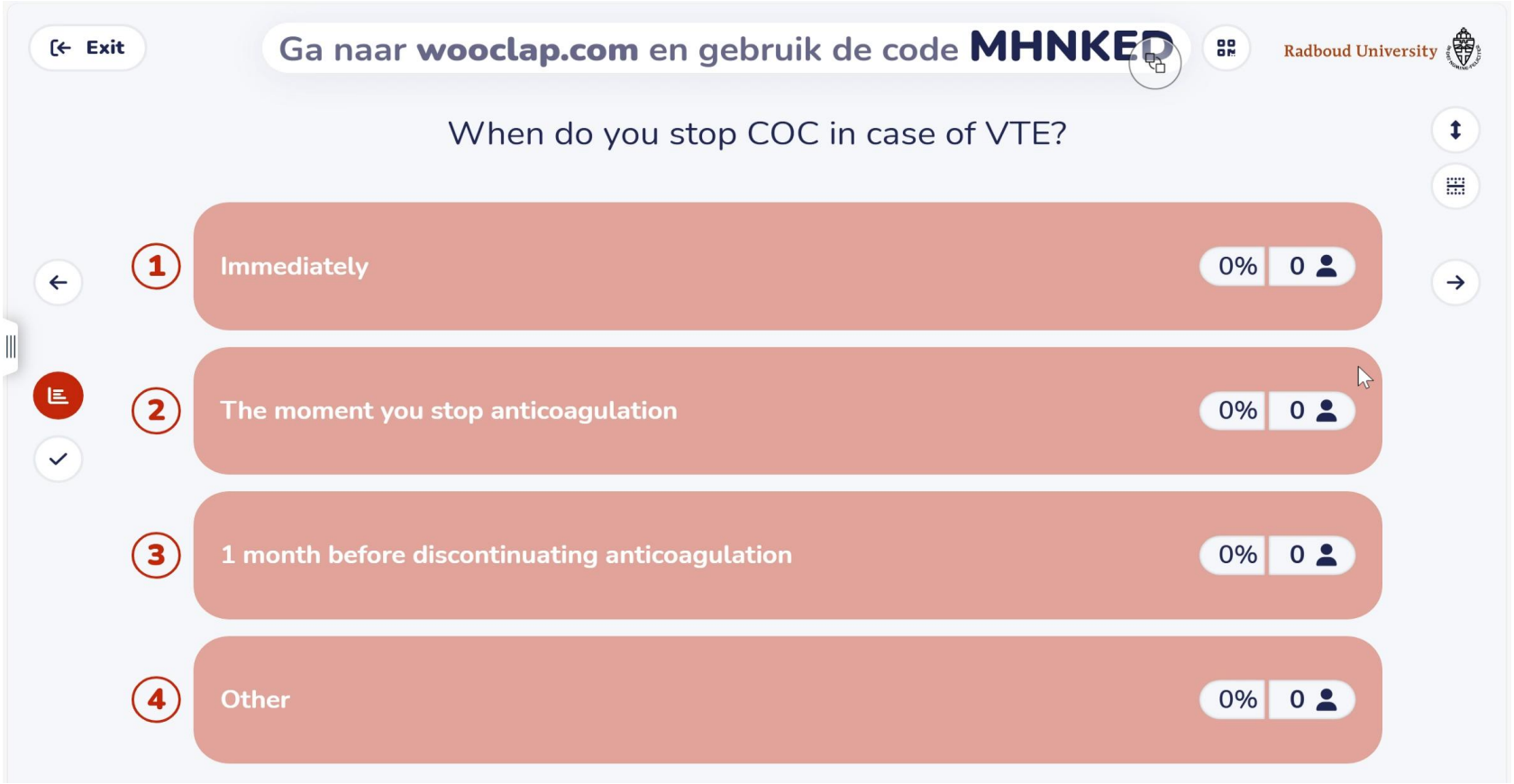
- Combined oral contraception increases VTE risk 3-7 fold
- Risk depends on type of COC, 2d generation is safest
- Absolute risk increases with age
- Several safe alternatives: IUD, implanon

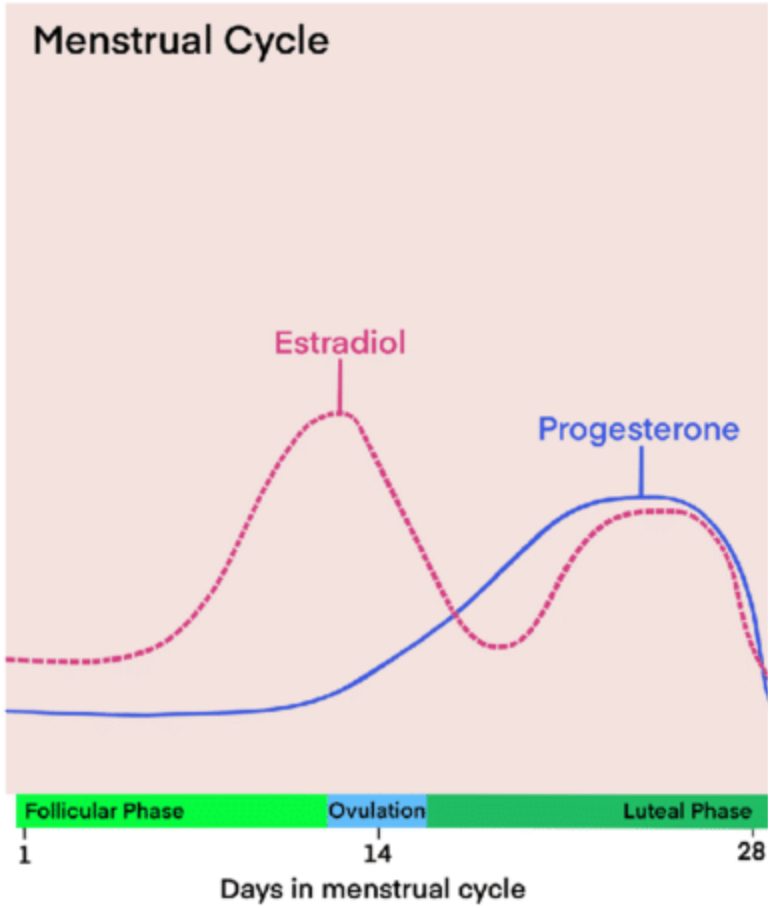


Content

- Hormones and venous thromboembolism risk
- **Anticoagulation and hormones**
- Anticoagulation and menstrual bleeding

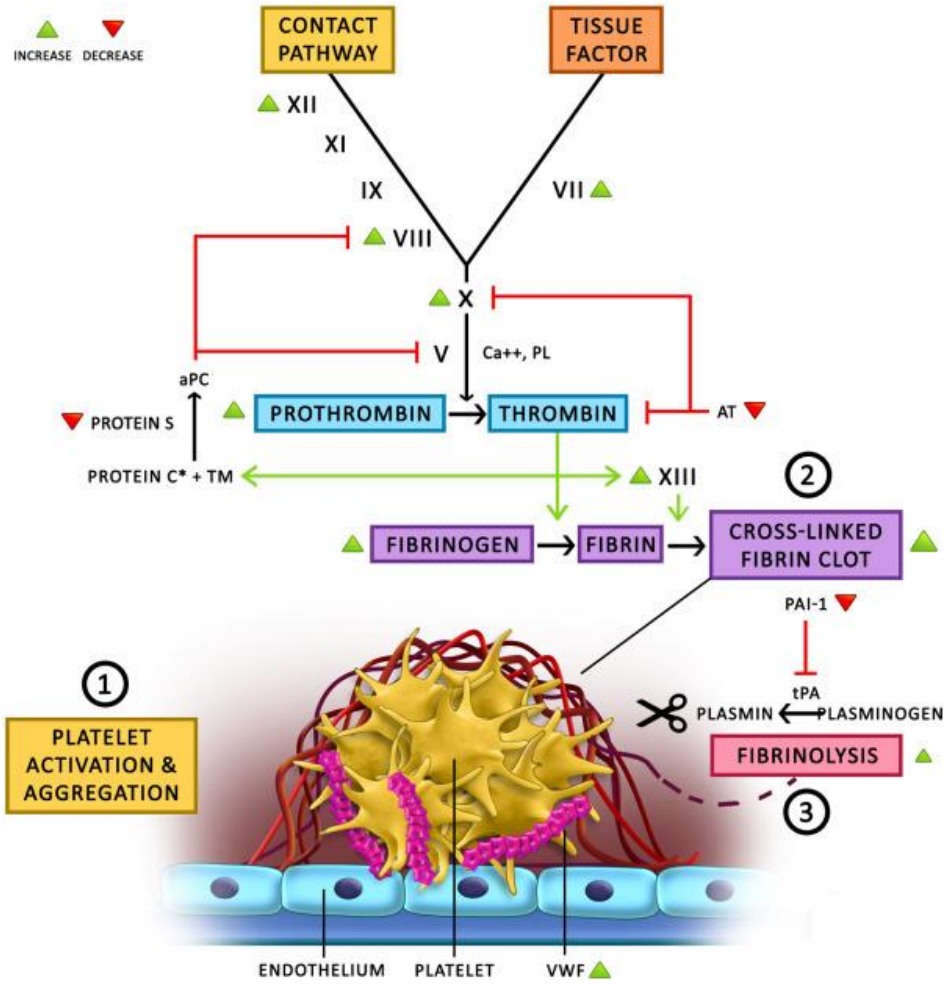
WOOCLAP


Exit
Ga naar wooclap.com en gebruik de code MHNKED
Radboud University
When do you stop COC in case of VTE?
1
Immediately
0%
0
2
The moment you stop anticoagulation
0%
0
3
1 month before discontinuating anticoagulation
0%
0
4
Other
0%
0


Menstrual Cycle
Estradiol
Progesterone
Follicular Phase
Ovulation
Luteal Phase
1
14
28
Days in menstrual cycle

Duration effect COC?

Stop anticoagulation 1 month after discontinuation COC, or in case of heavy breakthrough bleed



Content

- Hormones and venous thromboembolism risk
- Anticoagulation and hormones
- **Anticoagulation and menstrual bleeding**

Heavy menstrual bleeding (HMB)

Heavy menstrual bleeding (HMB) occurs in

- Up to 40 % of women in the general population
- Up to 70% of women using anticoagulation

Pad Saturation	Points per Item
	1
	5
	20
Tampon Saturation	
	1
	5
	10
Small clots (yes/no)	1
Large clots (yes/no)	5

Received: 7 April 2021 | Revised: 22 June 2021 | Accepted: 23 June 2021

DOI: 10.1002/rth2.12570

ILLUSTRATED REVIEW

Menstruation, anticoagulation, and contraception: VTE and uterine bleeding

Bethany Samuelson Bannow MD[1] | Claire McLintock MD[2] | Paula James MD, FRCPC[3]

Abnormal Uterine Bleeding

Normal menstrual cycle

- Cycle length: 28 (21-35) days
- Duration of bleeding: 2-7 days
- Median blood loss: 53mL/cycle

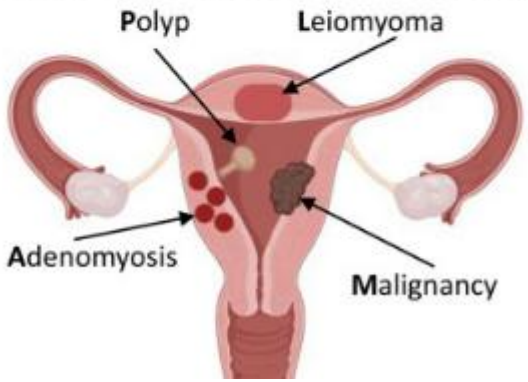
Heavy menstrual bleeding (HMB):

- >80mL menstrual blood loss (MBL)/cycle
- excessive menstrual blood loss that interferes with a woman's physical, social, emotional, or material quality of life.

Abnormal uterine bleeding (AUB) includes:

- Heavy menstrual bleeding
- Intermenstrual bleeding
- Postmenopausal bleeding
- Bleeding after sex
- Menstrual cycle <24 days or >38 days
- Irregular periods (cycle length varies by >7-9 days)

Structural causes of AUB: PALM[5]



Non-structural causes of AUB: COEIN[5]

Coagulopathy

Ovulatory

Endometrial

Iatrogenic

Anticoagulation and HMB

HMB/AUB effects:
- 30% of women at some point
- 70% of women on warfarin

Which medicine should I take?

Observational studies of rivaroxaban have demonstrated[6]:
- Prolonged menstrual bleeding >8 days (27%)
- Unscheduled contact with a provider for vaginal bleeding (41%)
- Medical or surgical interventions for vaginal bleeding (25%)
- Adaptation of anticoagulant treatment (15%)

Incidence of Major or Clinically Relevant Nonmajor Uterine Bleeds in Randomized Controlled Trials of Direct Oral Anticoagulants[7,8]

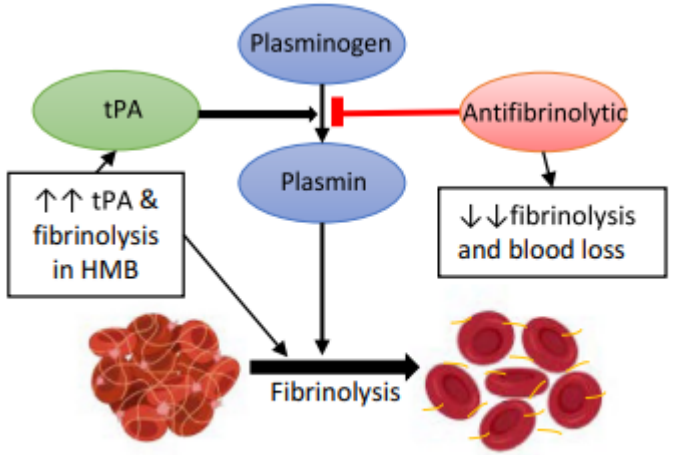
Drug	Incidence	OR (vs warfarin)
Rivaroxaban	9.5%	2.1
Edoxaban	9.0%	1.26
Apixaban	5.4%	1.18
Dabigatran	5.9%	0.59

Additional Approaches to Menstrual Management

Tranexamic acid is effective for the treatment of HMB

- 40% reduction in menstrual blood loss
- Improved quality of life
- Contraindicated in the setting of acute thrombosis
- Not studied in women on anticoagulation or with a history of VTE

Fibrinolysis and Menstrual Bleeding

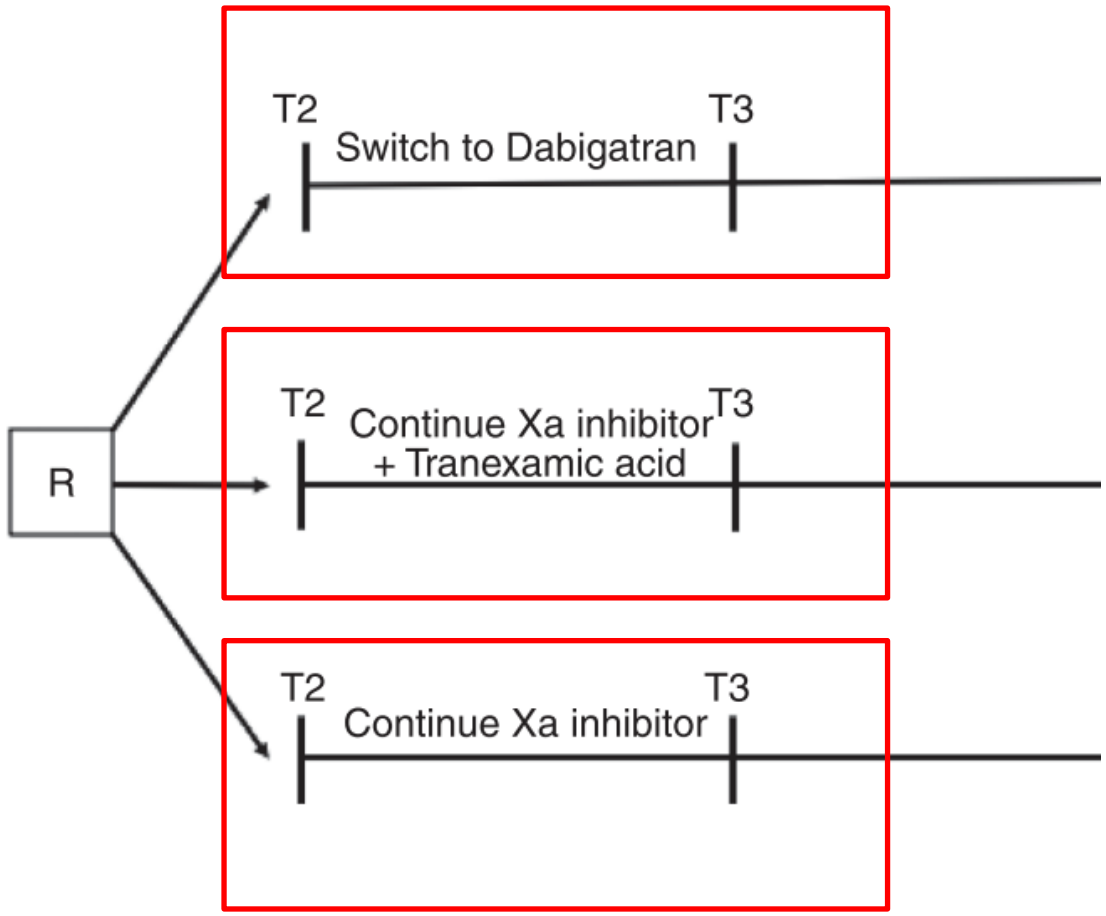


Does type of DOAC matter for women with HMB?

- MEDEA study, target n=120

Inclusion criteria

- Premenopausal women
- Age ≥ 18 years
- Anticoagulant treatment with a factor Xa inhibitor, either apixaban, edoxaban, or rivaroxaban
- Indication for anticoagulant treatment > 3 months after inclusion
- Heavy menstrual bleeding and a PBAC score > 150
- Use of adequate contraceptive methods during study participation (this is advised to any woman on factor Xa inhibitors during fertile ages, regardless of study participation)

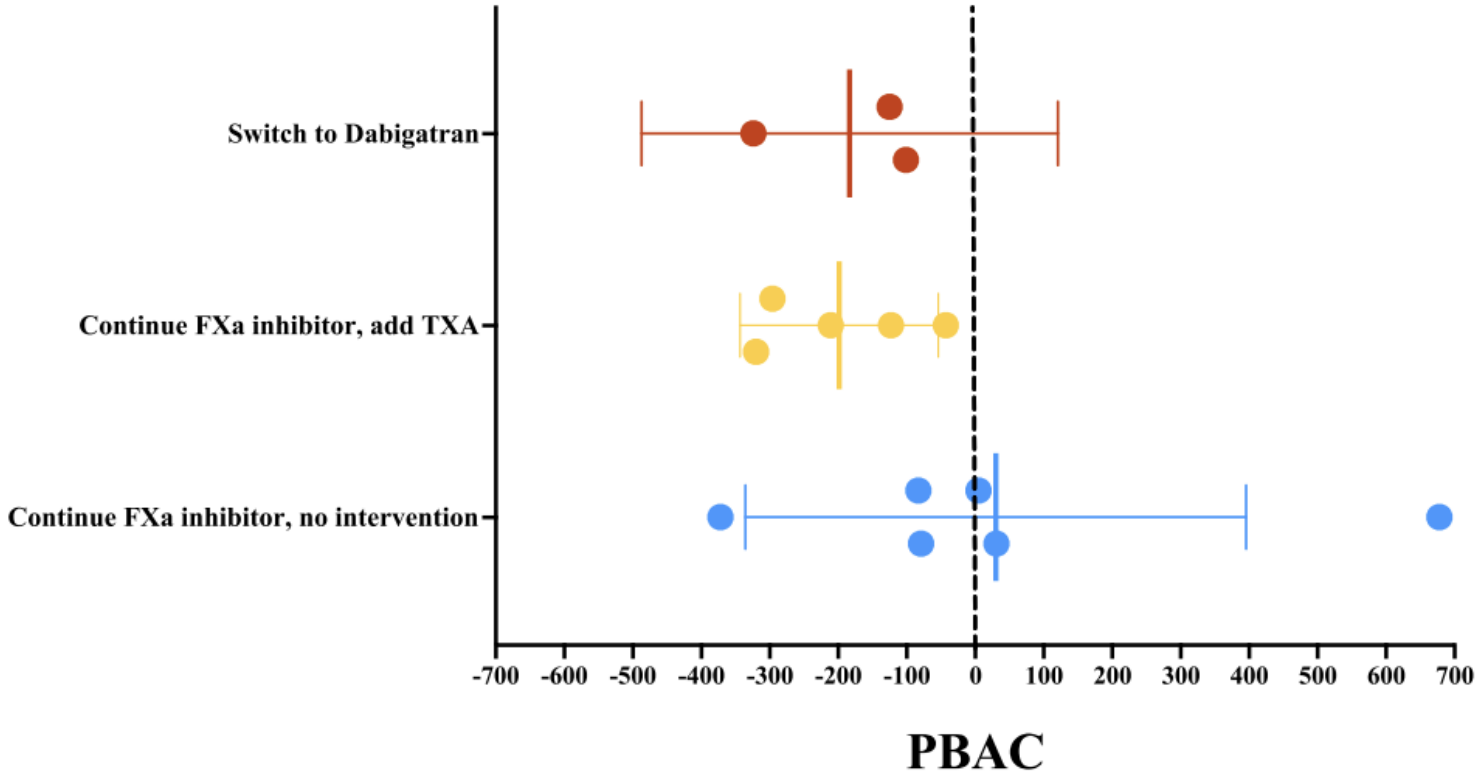


Hamulyák, RPTH 2022

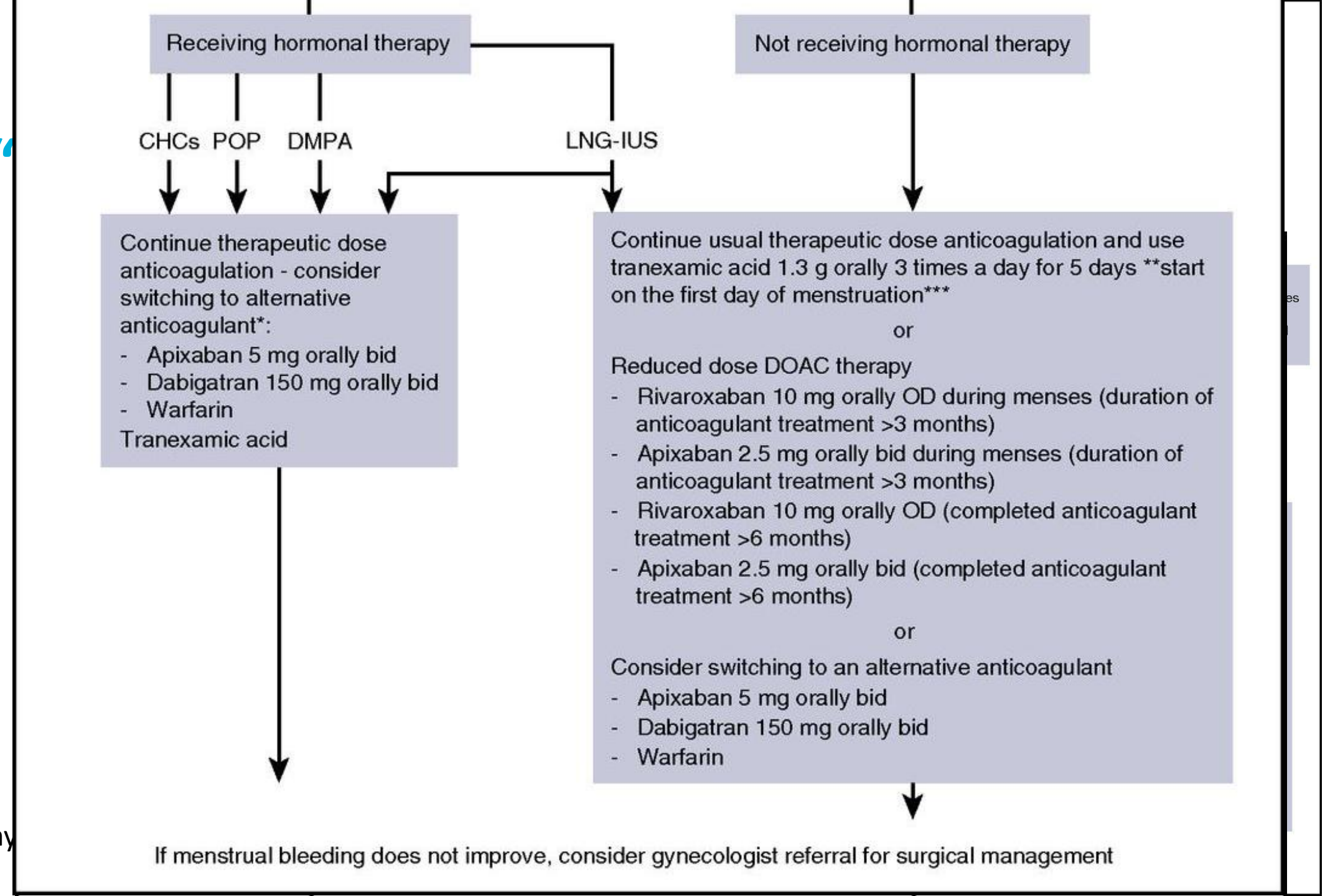
A premature end for Medea

24 women screened
16 women included

- Apixaban n=5
- Rivaroxaban n= 10
- Edoxaban n=1



Hamulyák, RPTH 2024


Receiving hormonal therapy
Not receiving hormonal therapy
CHCs
POP
DMPA
LNG-IUS
Continue therapeutic dose anticoagulation - consider switching to alternative anticoagulant*:
- Apixaban 5 mg orally bid
- Dabigatran 150 mg orally bid
- Warfarin
Tranexamic acid
Continue usual therapeutic dose anticoagulation and use tranexamic acid 1.3 g orally 3 times a day for 5 days **start on the first day of menstruation***
or
Reduced dose DOAC therapy
- Rivaroxaban 10 mg orally OD during menses (duration of anticoagulant treatment >3 months)
- Apixaban 2.5 mg orally bid during menses (duration of anticoagulant treatment >3 months)
- Rivaroxaban 10 mg orally OD (completed anticoagulant treatment >6 months)
- Apixaban 2.5 mg orally bid (completed anticoagulant treatment >6 months)
or
Consider switching to an alternative anticoagulant
- Apixaban 5 mg orally bid
- Dabigatran 150 mg orally bid
- Warfarin
If menstrual bleeding does not improve, consider gynecologist referral for surgical management

Take home messages part 2

- You don’t have to stop COC in patients on OAC
- Stop OAC +/- 1 month after stopping COC
- Talk about (M)MB with your patient
- In case of HMB don’t hold anticoagulation but switch to “lower risk OAC” and/or add tranexaminic acid, consider referral to gynaecologist.