Hormonal Therapy, Thrombosis and Women's Health

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Anticoagulation FORUM

ANTICOAGULATION BOOTCAMP
THROMBOSIS CANADA
ANNUAL CONFERENCE
Saturday
November 1
2014
McMaster University
HEALTH SCIENCES

Faculty/Presenter Disclosure

- **Faculty:** Dr. Shannon Bates
- **Relationships with commercial interests:**
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- **This program has received financial support from** Alexion Canada, Leo Pharma, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Covidien, Novartis, Octapharma, BMS/Pfizer Alliance, Pfizer Canada Injectables, Aspen Pharmacare and Sanofi in the form of an Unrestricted Educational Grant
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- **<u>Potential for conflict(s) of interest</u>:**
  - Dr. Shannon Bates has received honoraria from Leo Pharma and Pfizer Canada
  - Leo Pharma distributes tinzaparin (Innohep) and Pfizer Canada distributes dalteparin (Fragmin), both products that will be discussed in this program

Mitigating Potential Bias

- The content of Dr. Bates' presentation does not involve products distributed or manufactured by Leo Pharma, Pfizer Canada or Eli Lilly Canada

Objectives

- After this presentation, participants should be able to:
  - Consider the risks for venous thromboembolism (VTE) associated with different hormonal therapies used for contraception and hormone replacement therapy (HRT)
  - Provide an approach to the management of women at risk of VTE who require hormonal therapy

Epidemiology of VTE in Women

Age (y)	Risk in General Population / Year
<20	1/100,000
20-40	1/10,000 → pregnancy, contraception
40-80	1/1,000 → hormone replacement
>80	1/100

1. Nordstrom M. J Intern Med 1992
2. Naess IA. J Thromb Haemost 2007

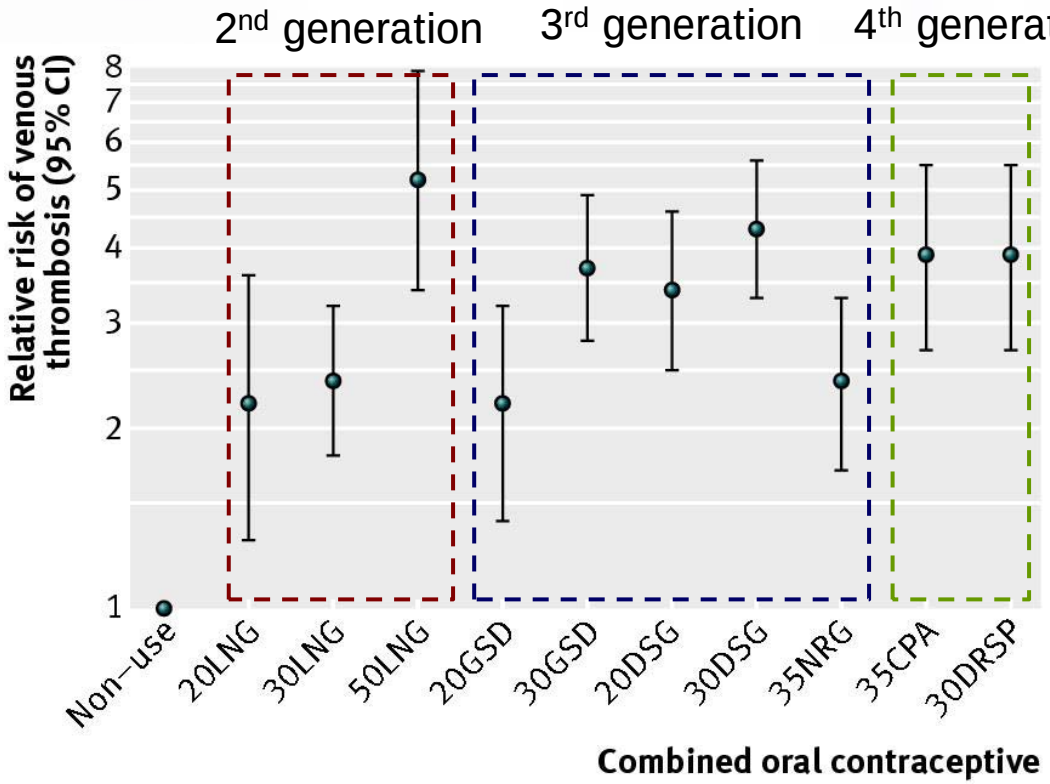
Combined Oral Contraceptives (COC)

Formulation	Estrogen	Progesterone
1st generation oral	Ethinyl estradiol (50-150µg)	+/- Norethindrone
2nd generation oral	Ethinyl estradiol (35-50 µg)	Levonorgestrel Norethindrone Norgestrel
3rd generation oral	Ethinyl estradiol (35-50 µg)	Desogestrel Gestodene Norgestimate
4th generation oral	Ethinyl estradiol (30-35 µg)	Drosperenone
Oral	Ethinyl estradiol (35 µg)	Cytoproterone acetate
Transdermal	Ethinyl estradiol (20 µg)	Norelgestromin
Vaginal ring	Ethinyl estradiol	Etonogestrel

Progesterone-only Contraceptives

Formulation	Progesterone
Injectable	Medroxyprogesterone
Implantable	Etonogestrel
Intrauterine	Levenogestrel
Oral	Norethisterone

COC and VTE Risks



LNG: levonorgestrel
GSD: gestodene
DSG: desogestrel
NRG: norgestimate
CPA: cytoproterone acetate
DRSP: drosperinone

Cochrane Database of Systematic Reviews. 3 MAR 2014 DOI: 10.1002/14651858.CD010813.pub2
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010813.pub2/full#CD010813-fig-0004

Non-Oral Hormonal Contraceptives

Type	Adjusted RR (95% CI)	Incidence /10,000 exposure years
Non-use	1.00 (reference)	2.05
COC: 30-40µg estrogen + levonogestrel	3.21 (2.70-3.81)	6.22
Patch	7.90 (3.54-17.65)	9.71
Vaginal Ring	6.48 (4.69-8.94)	7.75
Implant	1.40 (0.58-3.38)	1.70
Levonogestrel IUD	0.57 (0.41-0.81)	1.38

*Adjusted for age, calendar year and education

Lidegaard O. BMJ 2012

Combined Contraceptives and VTE

Group	Estimated VTE Risk / Year
Non-users	2/10,000
Levonogestrel Norethisterone Norgestimate	5-7/10,000
Drospirenone Gestodene Desogestrel Cytoproterone acetate	9-12/10,000
Etonogestrel Norelgestromin	6-12/10,000
Pregnancy (antepartum) Postpartum	5-20/10,000 40-65/10,000

EMA. http://www.ema.europa/eu

FDA. http://www.fda.gov/Drugs/DrugSafety/ucm299305

Frequent Questions

- Is an inherited thrombophilia truly an absolute contraindication to combined oral contraceptives?
- Are all progestin-only contraceptives safer?
- What about agents containing cytoproterone acetate?
- Are combined oral contraceptives truly contraindicated in women with VTE who are receiving adequate anticoagulant therapy?

Hereditary Thrombophilias: General Observations

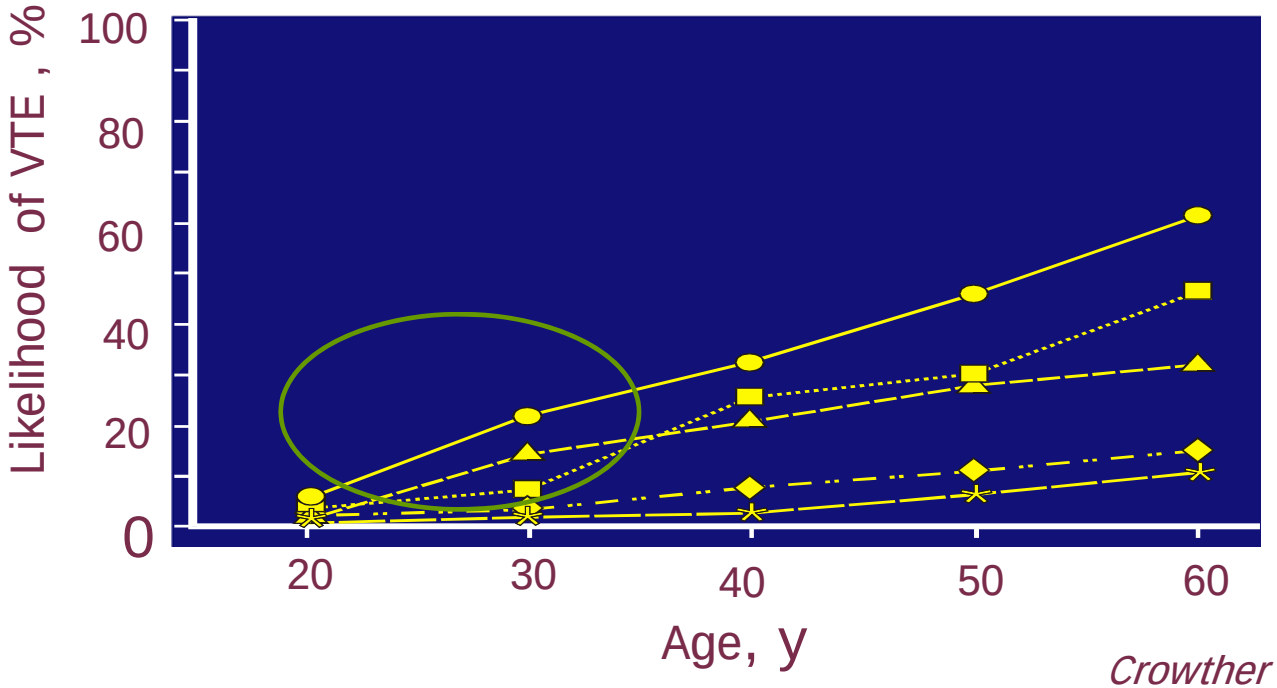
Frequency		Severity		
		Risk	Homozygous	VTE Risk by 60 yrs
Group I ↓ AT, Protein C, Protein S	< 1%	+++	Often lethal	> 50%
Group II FV Leiden/APCR Prothrombin mutation	1–5%	+	Not lethal	< 10%

all approximates

Crowther M. Ann Intern Med 2004

Thrombosis Risk: Thrombophilia & Age

Age (y)	Risk in General Population / Year
<20	1/100,000
20-40	1/10,000
40-80	1/1,000
>80	1/100



↓ Antithrombin
↓ Protein C
↓ Protein S
Factor V Leiden
No thrombophilia

Crowther M. Ann Intern Med 2003

Avoidance of Familial COC-Related VTE

Thrombophilia	VTE Risk on COC/y (%)	To Prevent 1 VTE N to Avoid COC	N to Test
Population (age 20 y)			
No FHx	0.04	3333	None
Positive FHX	0.08	1667	None
AT/PC/PS			
Deficient	4.3	28	56
Non-deficient	0.7		
FV Leiden/Prothrombin			
With mutation	0.5	333	666
Without mutation	0.2		

(Assume baseline VTE risk of 0.01%/y; RR of VTE with OCP use=4 and RR of VTE with positive FHX=2)

Middeldorp S. Hematol 2011

VTE in Women with FVL and/or PGM 20210A

	COC	LNG-IUD	Copper IUD	Condom
Incidence of 1st VTE per 100 pill-years	0.55	0.25	0.25	0.25
VTE cases per 100,000 pill-years	550	250	250	250
Contraceptive failure rate per 100 women-years	0.2	0.7	1.4	12
Unintended pregnancies per 100,000 women-years	200	700	1400	12 000
Incidence of VTE per 100 pregnancy-years	2.8	2.8	2.8	2.8
Additional VTE cases	6	20	40	336
Total number of VTE	556	270	290	586

Van Vlijmen EFW, et al. Blood 2011

Is Progestin-Only Contraception Safer?

- Meta-analysis: 8 observational studies (3,052 pts)

Agent	Risk	Notes/Comments
All progestin-only	RR: 1.03 (95% CI, 0.76-1.39)	
Progestin-only pill	RR: 0.9 (95% CI, 0.57-1.45)	
Progestin IUD	RR: 0.61 (95% CI, 0.24-1.53)	2 studies only
Injectable progestin	RR: 2.67 (95% CI, 1.29-5.53)	2 studies only

* Comparator: non-users

Mantha S. BMJ 2012

Cytoproterone Acetate Containing COCs

- Approved in Canada for treatment of moderate to severe acne unresponsive to other treatments
  - Health Canada Review (April 2014)
    - Published data and review of Canada Vigilance database
    - Benefits continue to outweigh risks when used as authorized
- SOGC Position Statement
  - Risk of VTE is very low and comparable to that of other combined hormonal contraceptives
    - For most women, the benefits outweigh
    - VTE risk should be considered as part of patient assessment
    - Patients should be counselled about signs and symptoms of VTE and need to seek attention should they occur

Health Canada. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/review-examen/diane-35-eng.php
http://sogc.org/media_updates/position-statement-diane-35-and-risk-of-venous-thromboembolism-vte/

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Suggested Prescriber/Counselling Checklist for DIANE-35 (cyproterone acetate/ethinyl estradiol) and its generics

DIANE-35 (cyproterone acetate and ethinyl estradiol) is indicated for the treatment of women with severe acne, unresponsive to oral antibiotic and other available treatments, with associated symptoms of androgenization, including seborrhea and mild hirsutism.

Note: **DIANE-35 is NOT indicated for the purposes of contraception.**

This suggested checklist can assist you when prescribing **DIANE-35** (cyproterone acetate/ethinyl estradiol) and its generics. Please see the Canadian Product Monograph (PM) for full prescribing information on indications, warnings and precautions, and adverse events (http://www.bayer.ca/files/DIANE-35-PM-ENG-11FEB2014-169560.pdf).

If any of the criteria below is checked YES, DO NOT prescribe DIANE-35

Health Canada Santé Canada

ismp CANADA
Institute for Safe Medication Practices Canada
L'Institut pour l'utilisation sécuritaire des médicaments du Canada

Canadian Pharmacists Association
Association des Pharmaciens du Canada

Canadian Dermatology Association
Association canadienne de dermatologie

If any of the criteria below is checked YES, DO NOT prescribe DIANE-35

MEDICAL CONDITIONS/MEDICATIONS	YES	NO
Concomitant use with another hormonal contraceptive	☐	☐
History of or actual thrombophlebitis or thromboembolic disorders	☐	☐
History of or actual cerebrovascular disorders	☐	☐
History of or actual myocardial infarction or coronary arterial disease	☐	☐
History of cholestatic jaundice, previous or existing liver tumours or active liver disease	☐	☐
Smoker AND age > 35 years	☐	☐
Known or suspected carcinoma of the breast or estrogen-dependent neoplasia	☐	☐
Pregnancy is suspected or diagnosed	☐	☐
Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields	☐	☐
Severe diabetes with vascular changes	☐	☐
History of migraine with aura	☐	☐
Very high blood pressure e.g., systolic > 160 or diastolic > 100 mmHg	☐	☐
Very high blood lipids	☐	☐

THE FOLLOWING POTENTIAL ADDITIONAL RISK FACTORS HAVE BEEN DISCUSSED WITH THE PATIENT:			
☐	Smoking	☐	Age over 35 years
☐	Hypertension	☐	Diabetes
☐	Migraine	☐	Obesity BMI > 30 kg/m2
☐	Major surgery or a period of prolonged immobilization		

PATIENT HAS BEEN COUNSELLED TO SEEK MEDICAL ATTENTION IF THE FOLLOWING SYMPTOMS OCCUR:	
☐	Sudden unexplained breathlessness or rapid breathing; severe pain in the chest which may increase with deep breathing; sudden cough without an obvious cause (which may bring up blood) – indicating potential pulmonary embolism.
☐	Severe pain or swelling in either leg that may be accompanied by tenderness, warmth or changes in the skin colour such as turning pale, red or blue which may indicate a deep vein thrombosis.
☐	Chest pain, often acute, but may include just discomfort, pressure, heaviness, upper body discomfort, radiating to back, jaw, throat, or arm together with feelings of indigestion or choking, sweating, nausea, vomiting or dizziness. These symptoms could indicate a heart attack.
☐	Face, arm or leg weakness or numbness, especially on one side of the body; trouble speaking or understanding; sudden confusion; sudden loss of vision or blurred vision; severe headache/migraine that is worse than normal. This may indicate a stroke.

Hormonal Contraception in Women Receiving Treatment for VTE

- No published trials with clinical outcomes assessing the risk of recurrent VTE in this patient population[1]
- Theoretically, VTE risk should be dramatically reduced while on therapeutic doses of anticoagulation
  - e. g. Pregnancy
- ISTH SSC Guidelines (unprovoked or hormonal VTE)[2]
  - Discontinue hormone therapy before stopping anticoagulants
  - Effective alternative contraception in premenopausal women
  - Suggest hormonal therapy can be continued in selected patients if there is a strong clinical indication

1. *Culwell KR, Curtis KM. Contraception 2009;80:337-345*
2. *Baglin T. J Thromb Haemost 2012;10:698-702*

Take Home Message
Contraception & VTE : Patient-Centered Approach

- Patient risk stratification
  - Family VTE history and/or type of thrombophilia
  - Additional risk factors (obesity; age >35 y; tobacco use)
- Patient counselling regarding risks, efficacy, and tolerability of contraceptive options
  - Use absolute risks specific to contraception type
  - Including pregnancy
- Involvement of the patient in informed decision making
  - Consider patient preferences
  - Consider likelihood of adherence
  - Counselling about signs and symptoms of thrombosis and need to seek medical attention should they occur

Trenor CC III. Pediatrics 2011. *Van Vlijmen EF. Blood 2011*

Hormone Replacement Therapy (HRT)

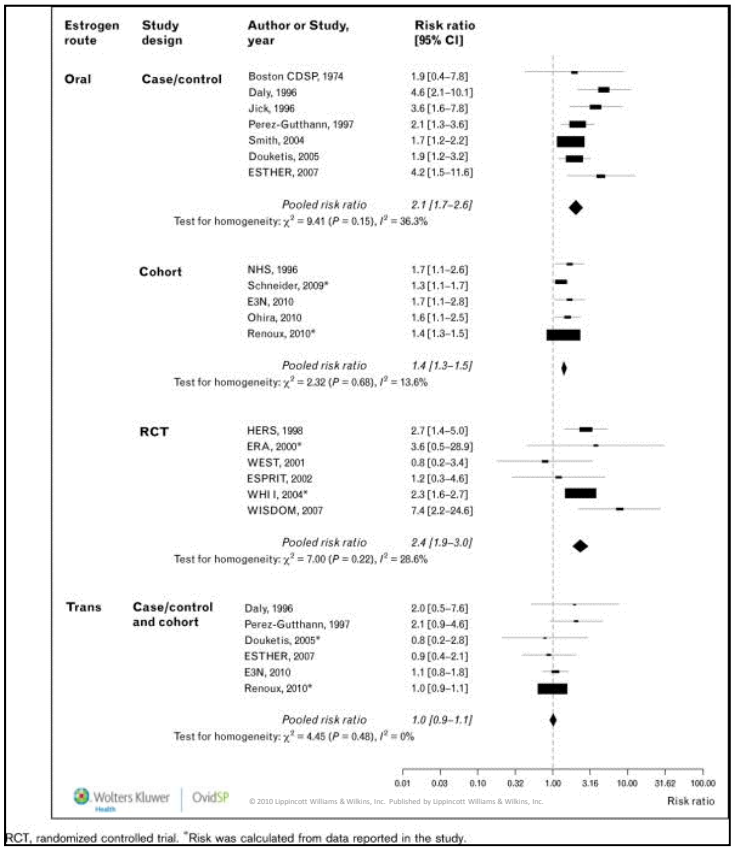
- Is HRT-related VTE management still relevant?
  - Most effective therapy for climateric symptoms
    - 25% of all women have these symptoms
    - 5% have debilitating symptoms
  - OB/GYN panels endorse short-term use for symptomatic patients

HRT: Risk of VTE

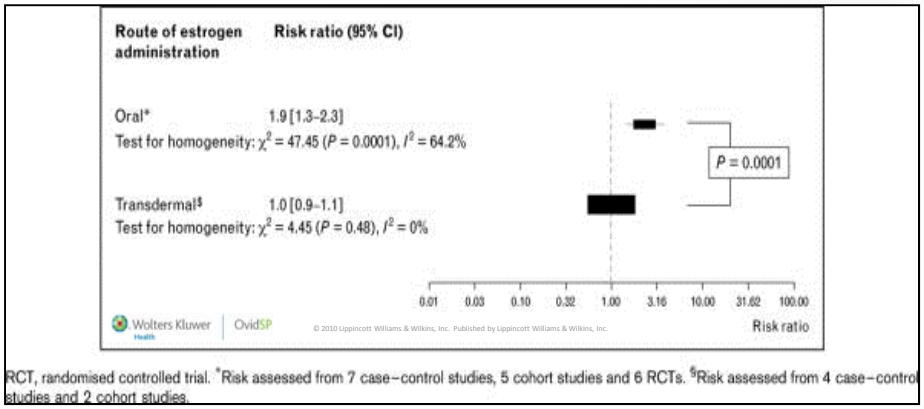
Study	VTE Risk (Risk Estimate; 95% CI) Oral Combined Estrogen & Progestin
Observational Studies	
Daley	5.3 (1.9-14.6)
Jick	2.4 (0.8-7.3)
Varas-Lorenzo	5.0 (1.5-16.7)
Perez-Gutthann	2.2 (1.4-3.5)
Douketis	2.7 (1.4-5.1)
Scarabin	3.6 (1.9-7.0)
Randomized Trials	
HERS	2.7 (1.4-5.0)
WHI	2.9 (1.5-5.6)

1. Daly E. Lancet 1996
2. Jick H. Lancet 1996
3. Varas-Lorenzo C. Am J Epidemiol 1998
4. Perez-Gutthann S. BMJ 1997
5. Douketis J. J Thromb Haemost 2005
6. Scarabin PY. Lancet 2003
7. Hulley S. JAMA 1998
8. WHI. JAMA 2002

HRT: Oral and Transdermal Estrogen



RCT, randomized controlled trial. *Risk was calculated from data reported in the study.



RCT, randomised controlled trial. *Risk assessed from 7 case–control studies, 5 cohort studies and 6 RCTs. §Risk assessed from 4 case–control studies and 2 cohort studies.

VTE Risk (RR, 95% CI)

Oral Estrogen (case-control)
OR: 1.9 (95% CI, 1.3-2.3)

Transdermal Estrogen
OR: 1.0 (95% CI, 0.9-1.1)

Olie V, Canonico M, Scarabin P-Y. Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. Curr Opinion i Hematol. 2010;17(5):457-463.

Combined Oral HRT: Thrombophilia

VTE Risk & Factor V Leiden Mutation

	Risk Estimate (95% CI)	
Study	**FVL absent**	**FVL present**
Lowe	4.1 (1.3-13.3)	13.3 (4.3-41.0)
Rosendaal	3.2 (1.7-6.0)	15.5 (3.7-77.0)
Herrington	3.3 (1.4-9.4)	14.1 (2.7-72.4)
Douketis	3.2 (1.2-8.6)	17.1 (3.7-78)
WHI	2.2 (1.5-3.5)	6.7 (3.1-14.5)

1. Lowe G. Thromb Haemost 2000
2. Rosendaal F. Br J Haematol 2002
3. Herrington D. Arterioscler Thromb Vasc Biol 2002
4. Douketis J. Clin Appl Thromb Hemost 2011
5. Cushman M. JAMA 2004
6. Curb J. Arch Intern Med 2006

Transdermal HRT: Thrombophilia

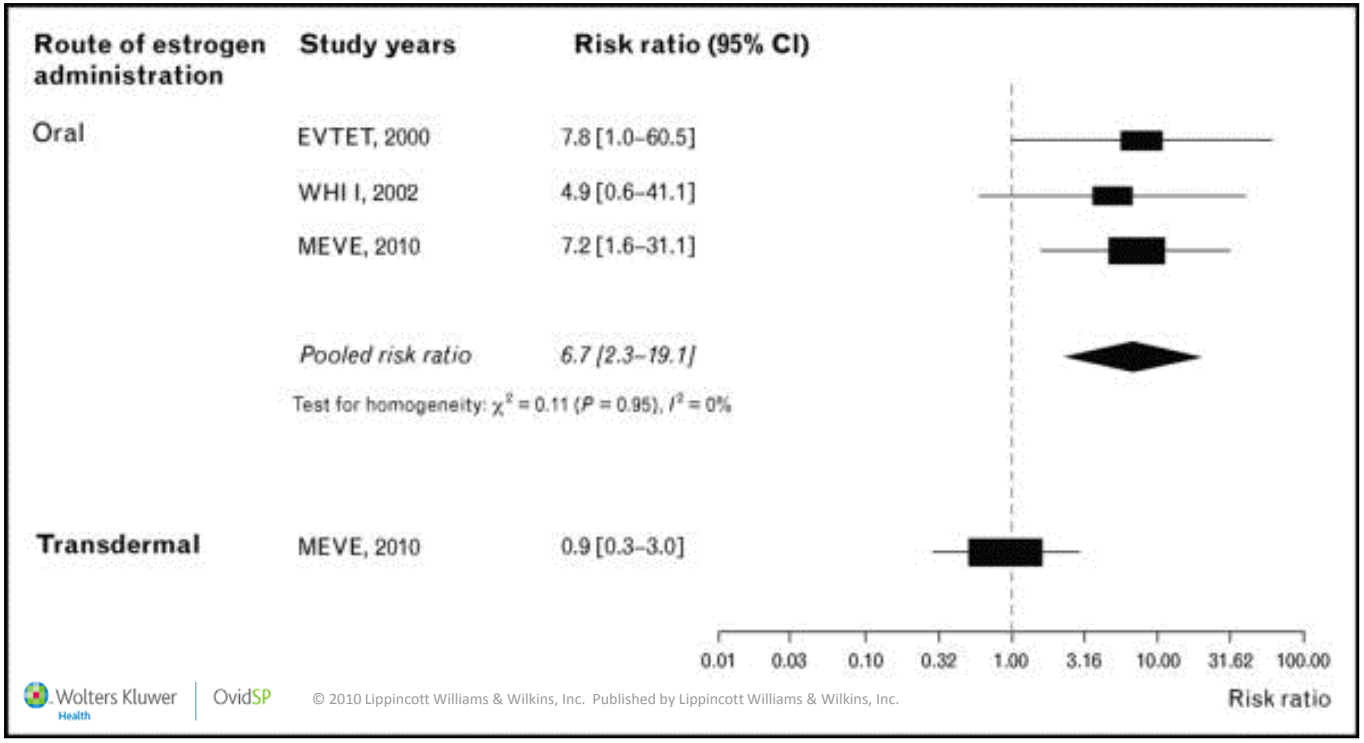
VTE Risk & Thrombophilia

Risk Estimate (95% CI)

Thrombophilia	No HRT	Oral HRT	Transdermal HRT
Factor V Leiden	2.6 (1.3-5.4)	16.4 (4.3-62)	4.6 (1.6-13.8)
Prothrombin gene	6.4 (2.5-16.4)	N/A	3.3 (1.1-10.2)

Straczek C. Circulation 2005

HRT: Prior VTE



Olie V, Canonico M, Scarabin P-Y. Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. Curr Opinion i Hematol. 2010;17(5):457-463.

Take Home Message
HRT & VTE: Patient-Centered Approach

- Patient risk stratification (age, VTE history, thrombophilia)
- Counselling regarding VTE risks
  - Combined oral HRT: ↑ risk 2-5 fold; transdermal: smaller ↑
  - Use absolute risks

	Estimated VTE Risk (%/yr)		
	No HRT	**E + P**	**Transdermal**
Age 40y	0.1	0.4	Similar to no HRT
Age 40y + Factor V Leiden	0.5	1.5	Similar to no HRT
Age 80y	1	4 or higher	Similar to no HRT
Prior VTE	2.3	10.7	Similar to no HRT

- Involve the patient in informed decision making
  - Consider patient preferences
  - Counselling about signs and symptoms of VTE