Reduced Risk of Venous Thromboembolism with Natural Estrogen-Based COCs Compared to Ethinylestradiol Pills

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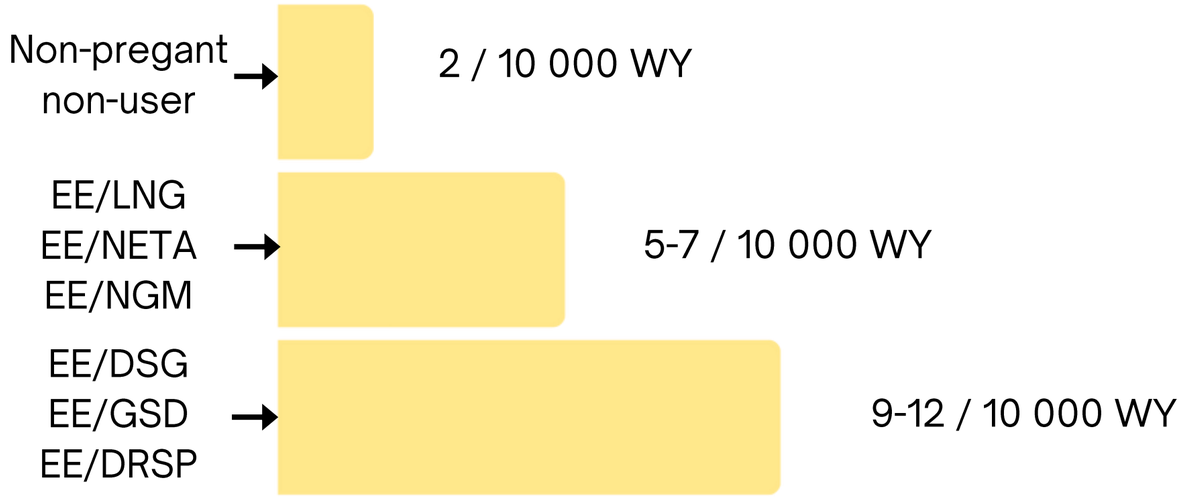
Combined oral contraceptives and VTE risk

Estimates risk of venous thromboembolism (VTE) with COCs



Annual number of COC associated VTE cases

22,000 cases / Year
Europe

16,000 cases / Year
USA

Three-year societal cost attributable to VTE

110,000 EUR / VTE case

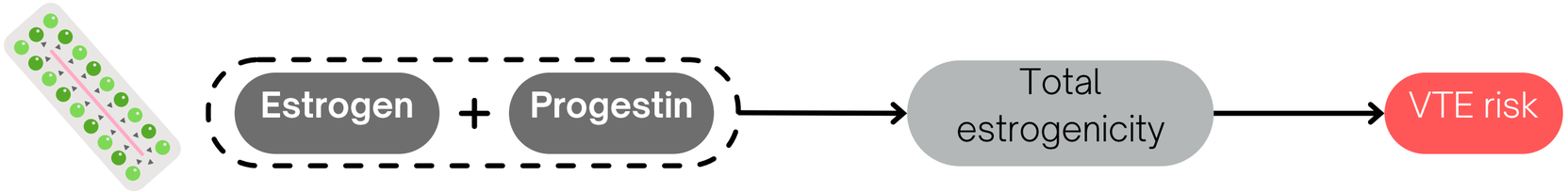
Direct and indirect yearly cost of COC associated VTE cases

2.5 billions EUR considering only a three-year

Clinical, social and economic management, a **burden** on **healthcare systems**

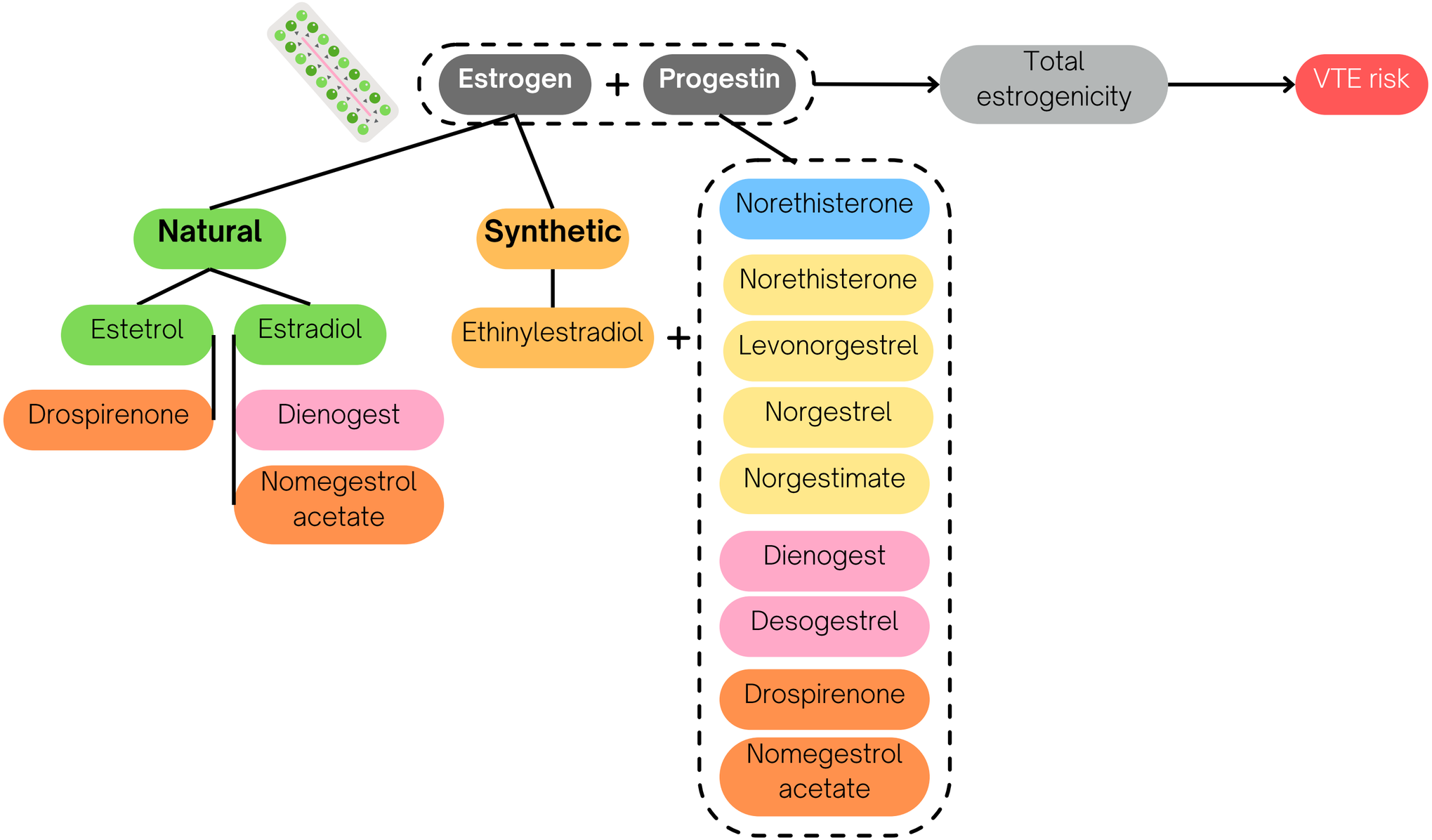
McDaid and al. 2017
Gustafsson and al. 2020 | Eur Heart J Qual Care Clin Outcomes

Combined oral contraceptives and VTE risk



Morimont, 2021 | Frontiers

Combined oral contraceptives and VTE risk



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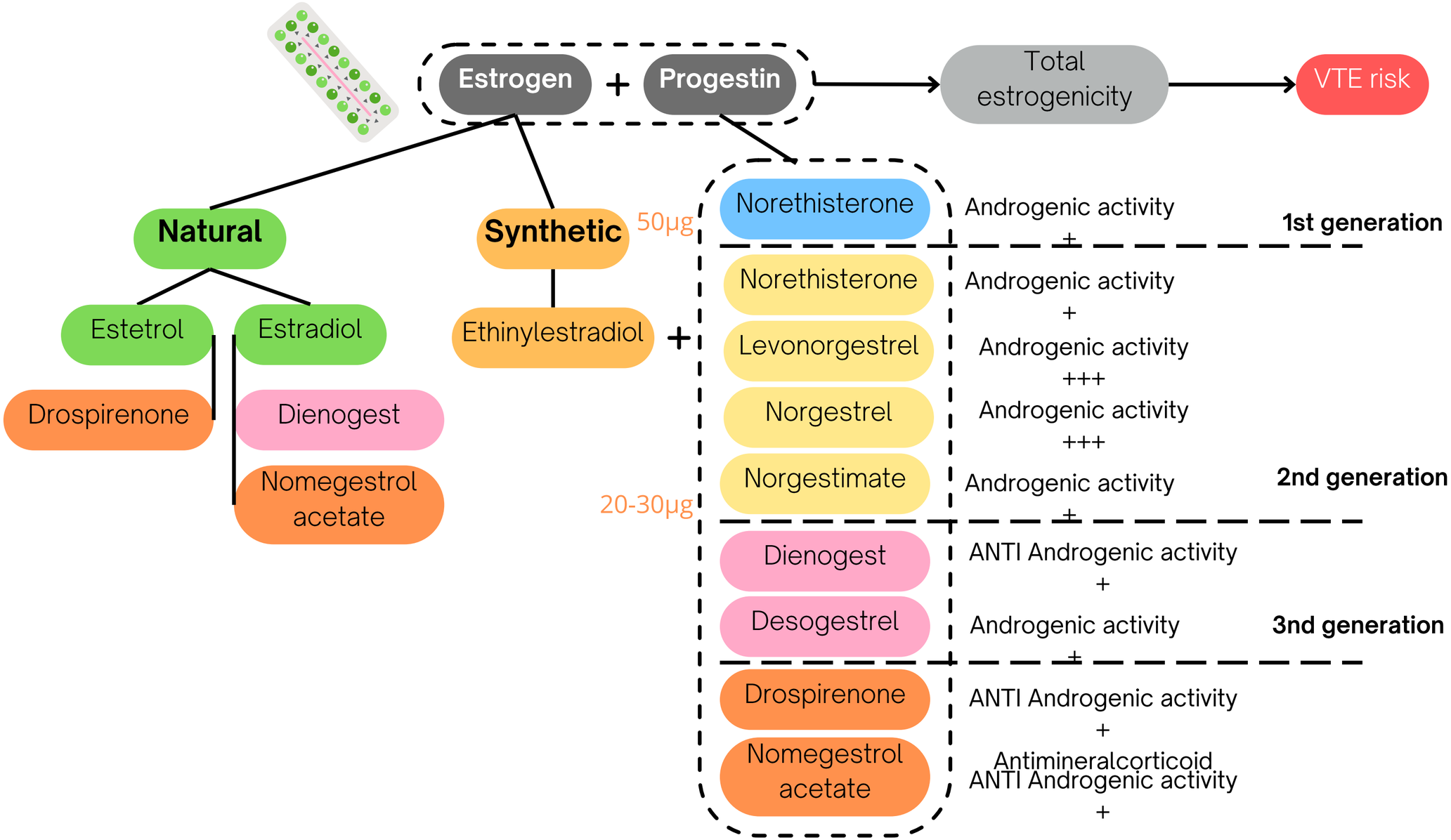

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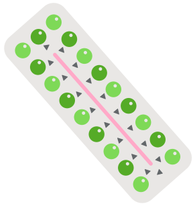

Estrogen + Progestin → Total estrogenicity → VTE risk

VTE risk ↑

Natural

- Estetrol
- Estradiol
- Drospirenone
- Dienogest
- Nomegestrol acetate

Synthetic

- Ethinylestradiol +

50µg

- Norethisterone — Androgenic activity ± — VTE risk ↑ — **1st generation**

20-30µg

- Norethisterone + Levonorgestrel — Androgenic activity + Androgenic activity +++
- Norgestrel — Androgenic activity +++
- Norgestimate — Androgenic activity ± — VTE risk ↑ — **2nd generation**
- Dienogest + Desogestrel — ANTI Androgenic activity + Androgenic activity ± — VTE risk ↑ — **3nd generation**
- Drospirenone + Nomegestrol acetate — ANTI Androgenic activity + Antimineralcorticoid ANTI Androgenic activity + — VTE risk ↑

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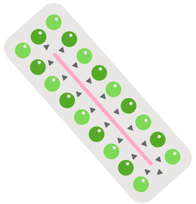
Combined oral contraceptives and VTE risk



Estrogen + Progestin → Total estrogenicity → VTE risk

VTE risk

Natural

- Estetrol
- Estradiol
- Drospirenone
- Dienogest
- Nomegestrol acetate

Synthetic

- Ethinylestradiol

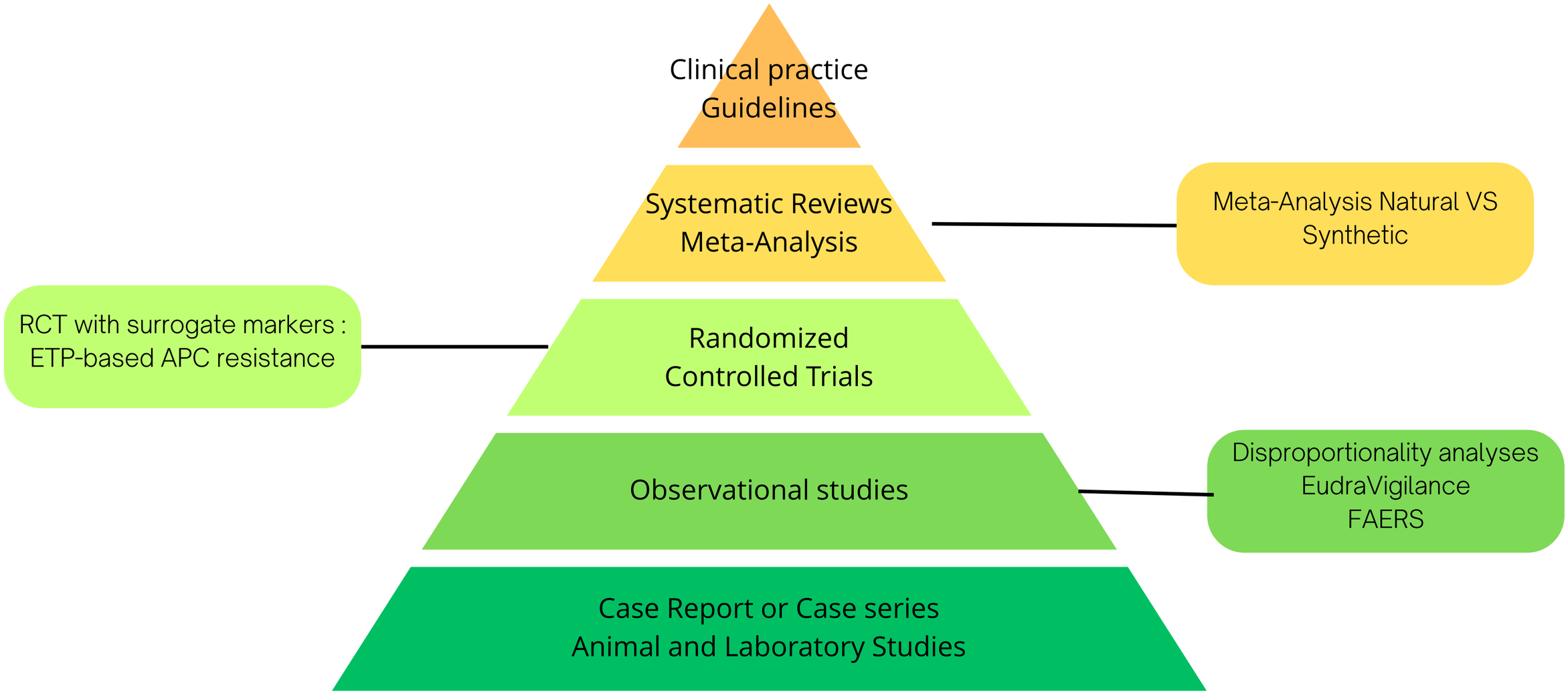
50µg + 20-30µg

Norethisterone	Androgenic activity ±	VTE risk 1st generation
Norethisterone + Levonorgestrel	Androgenic activity + Androgenic activity +++	VTE risk 2nd generation
Norgestrel	Androgenic activity +++	
Norgestimate	Androgenic activity ±	
Dienogest + Desogestrel	ANTI Androgenic activity + Androgenic activity ±	VTE risk 3nd generation
Drospirenone + Nomegestrol acetate	ANTI Androgenic activity + Antimineralcorticoid ANTI Androgenic activity +	VTE risk

Exert a **less pronounced effect on coagulation factors and the hemostatic system** compared to EE

Morimont, 2021 | Frontiers

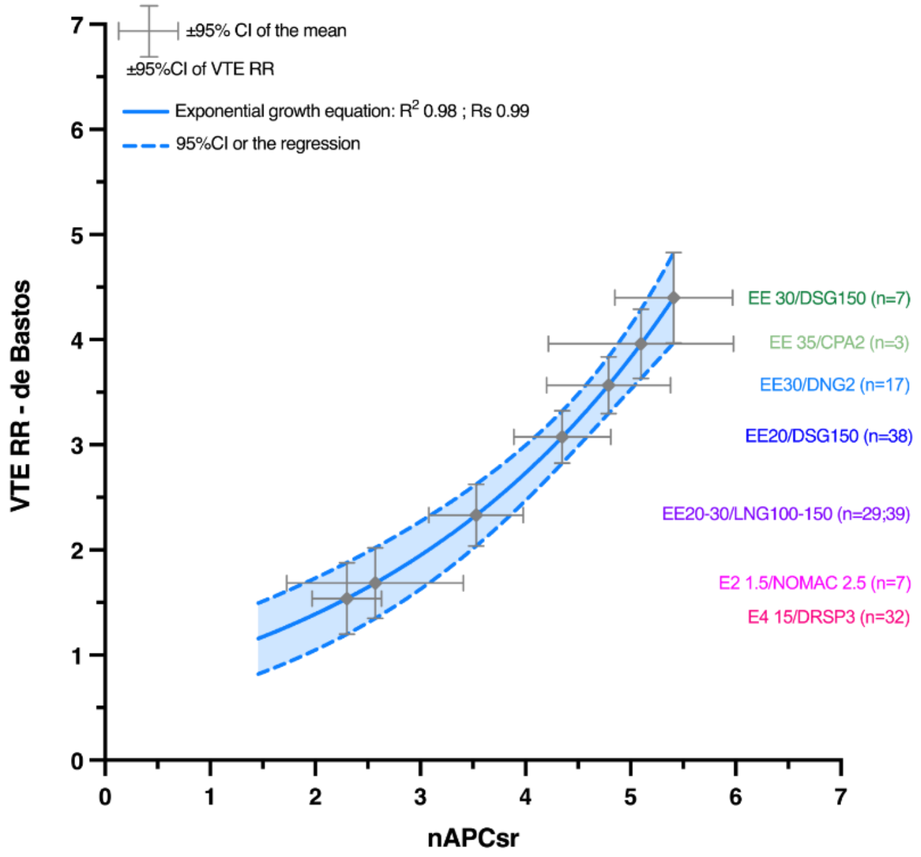
Natural estrogens: several levels of evidence



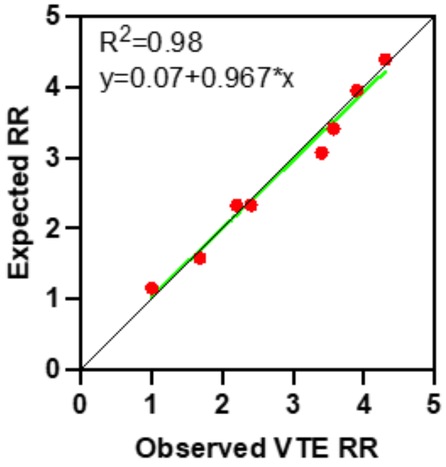
Didembourg M et al. Contraception. 2024.| Douxfils, J. et al. Contraception. 2020. 102(6): p. 396-402 | Morimont et al. Thromb Res. 2020. 193: p. 221-223. | Douxfils J, et al. Front Endocrinol

Natural estrogens: biological and observational studies

Biological data



- A higher risk of VTE is observed with pills that produce higher nAPCsr
- **Higher nAPCsr values are observed with EE/LNG <u>compared</u>** with COCs containing **natural estrogens**
- EE generates a prothrombotic environment contrary to E4 which demonstrates a **neutral profile on hemostasis**



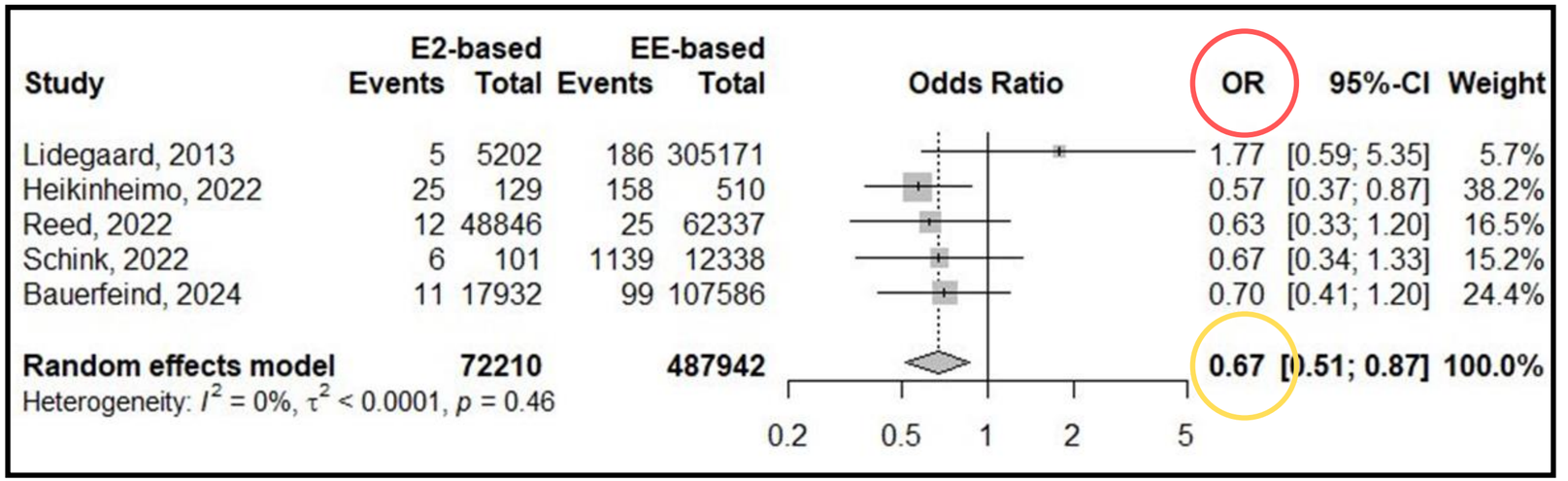
de Bastos, M., et al. Cochrane Database Syst Rev, Morimont et al. Thromb Res. 2020. 193: p. 221-223.

Natural estrogens: meta-analysis

Meta-Analysis
Natural VS Synthetic estrogen

E2-based VS EE-based

Assessment of the risk of VTE associated with COCs containing synthetic estrogens like ethinylestradiol (EE) versus natural estrogens like estradiol (E2).



Crude OR, without adjustment for confounding factors

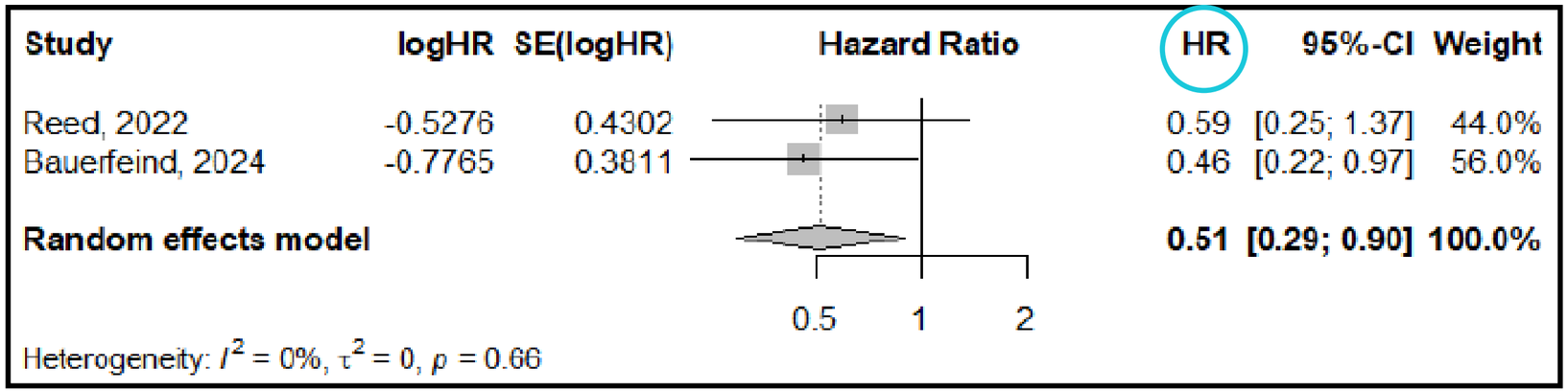
Significant 33% reduction in VTE risk among users of E2-based COCs compared to those using EE-based COCs.

Natural estrogens: meta-analysis

Meta-Analysis
Natural VS Synthetic estrogen

E2-based VS EE-LNG

Stratification analyses using adjusted hazard ratios (HR) of the main observational studies

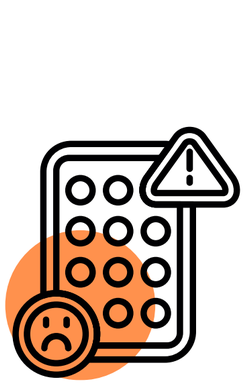


Adjusted HR, adjustment for confounding factors

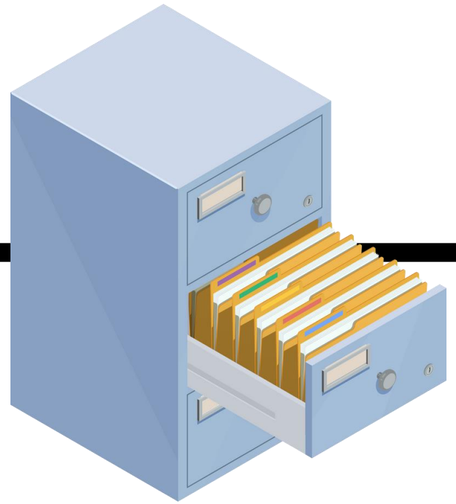
Stratification analyses using adjusted hazard ratios (HR) for ZEG studies showed a **49% reduced VTE risk of E2-based pills compared to EE/LNG**

Natural estrogens: pharmacovigilance data

Dispropotionality analysis



Adverse events



Database

Extraction of VTE events

VTE events

Numbers of Individual Case Safety Reports

Reporting Rate

Natural estrogens: pharmacovigilance data

Dispropotionality analysis

RR

$$\frac{\text{VTE events}}{\text{Numbers of Individual Case Safety Reports}}$$

PRR

$$\frac{A / A + B}{C / C + D}$$

A	Number with positive (bad) outcome	Number of VTE events for the selected drug
B	Number with negative (good) outcome	Number of ISCRs for the selected drug
C	Number with positive (bad) outcome	Number of VTE events for the comparator
D	Number with negative (good) outcome	Number of ISCRs for the comparator

Natural estrogens: pharmacovigilance data

Dispropotionality analysis

RR

$$\frac{\text{VTE events}}{\text{Numbers of Individual Case Safety Reports}}$$

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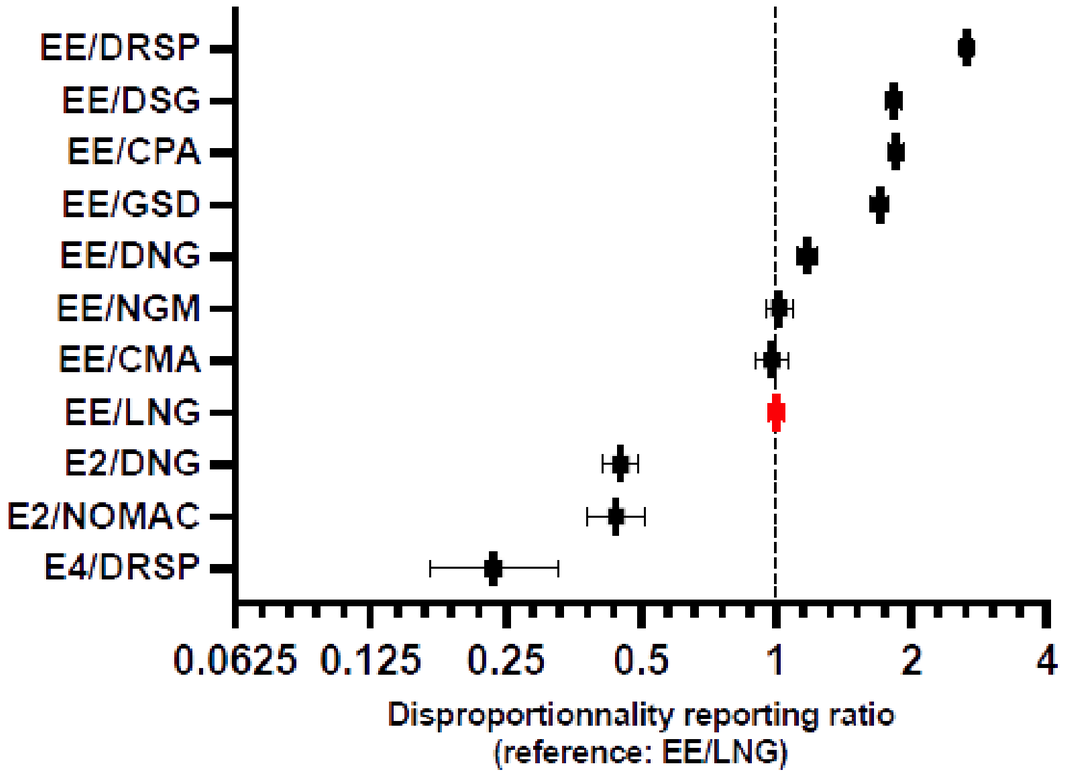
Therapeutic class OR EE/LNG

Natural estrogens: pharmacovigilance data

EudraVigilance



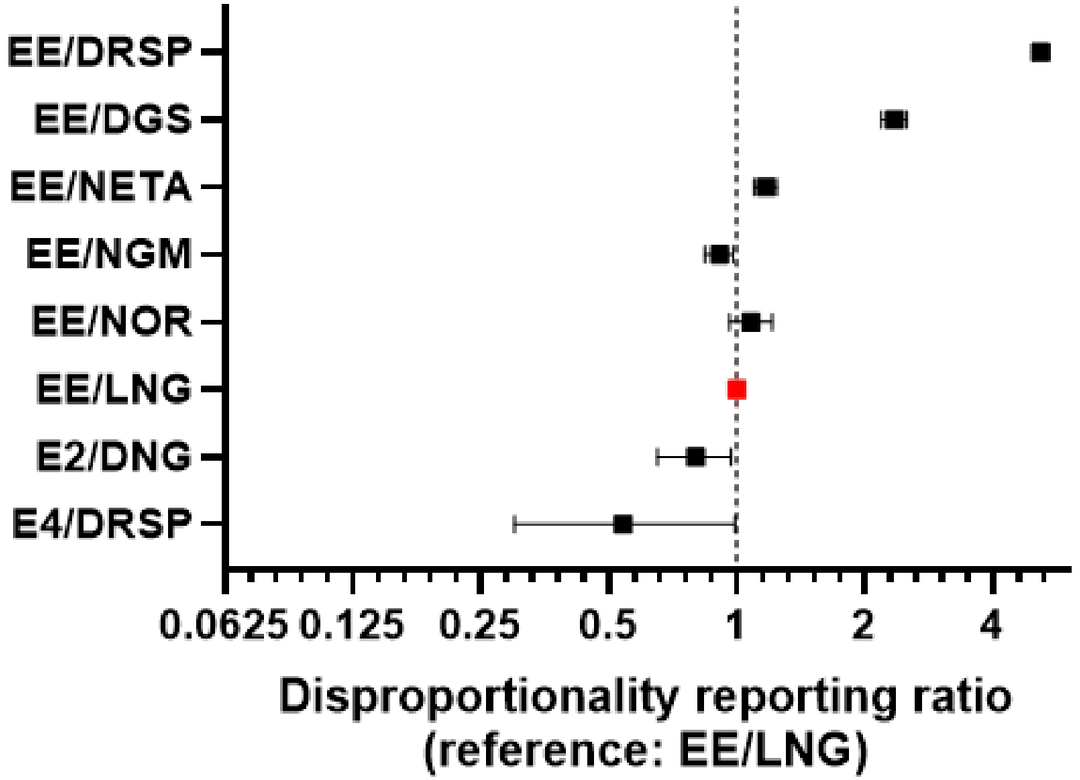
LOWEST VTE RISK COMPARED TO CLASS

LOWER VTE RISK COMPARED TO EE/LNG

Didembourg M et al. Contraception. 2024.

Natural estrogens: pharmacovigilance data

FAERS

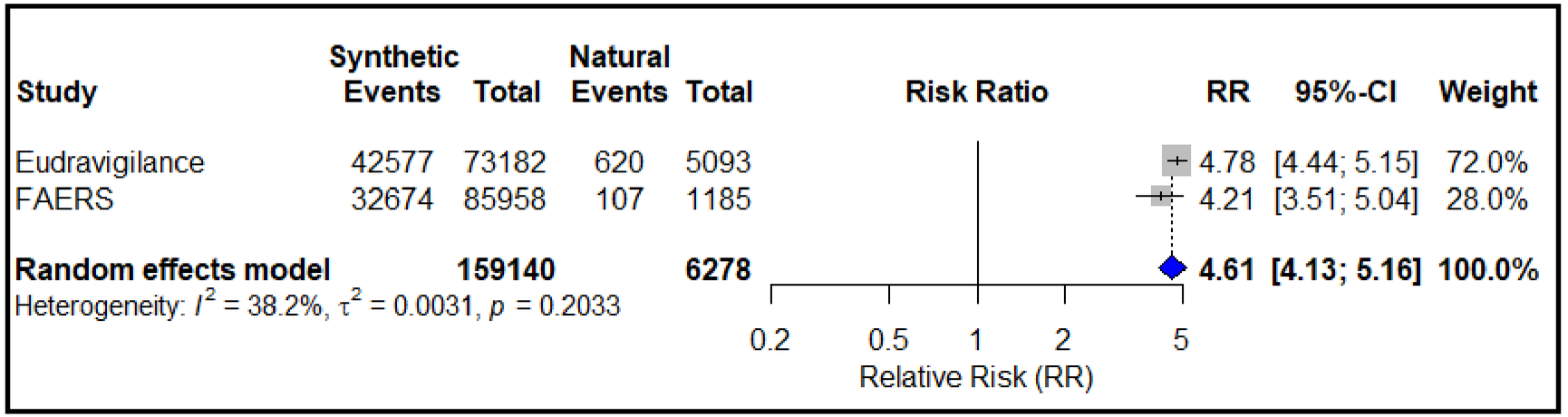


LOWEST VTE RISK COMPARED TO CLASS

LOWER VTE RISK COMPARED TO EE/LNG

Natural estrogens: pharmacovigilance data

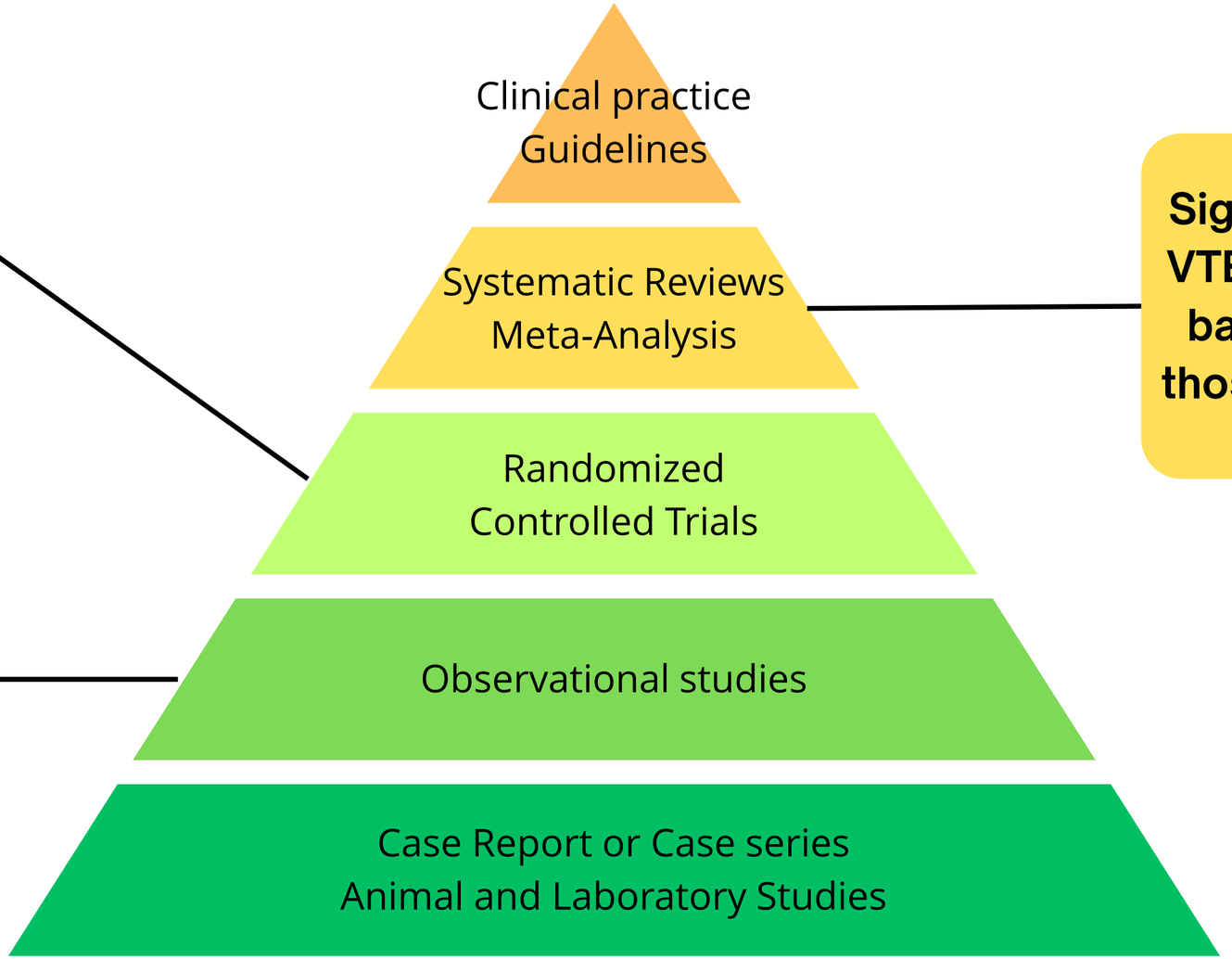
Meta-analysis of EudraVigilance and FAERS database



Natural estrogens: towards a safer alternative

Higher nAPCsr values are observed with EE/LNG compared with COCs containing natural estrogens

Lower VTE risk with natural estrogens, compared to EE-based COCs, particulary EE/LNG



Significant 33% reduction in VTE risk among users of E2-based COCs compared to those using EE-based COCs.

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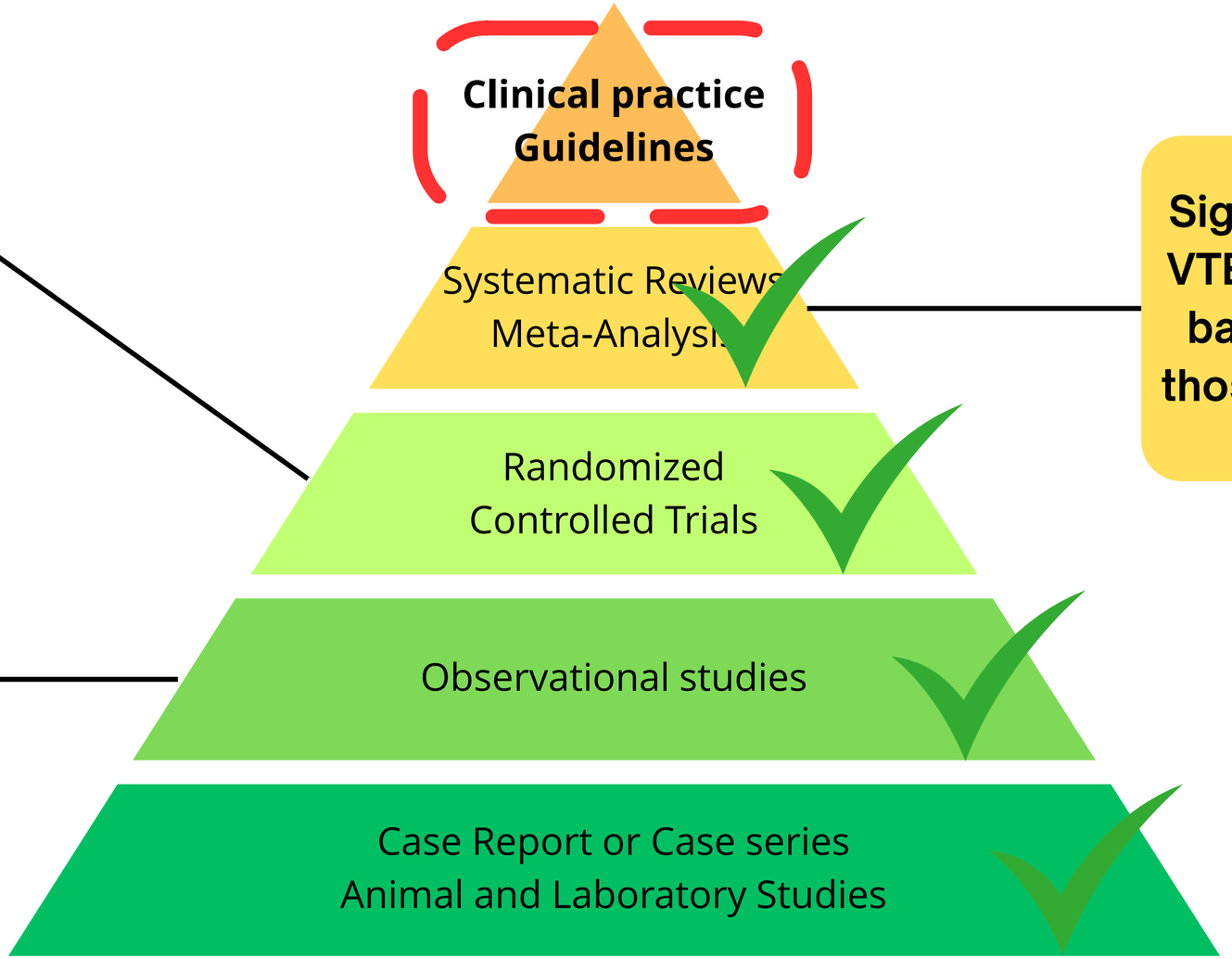
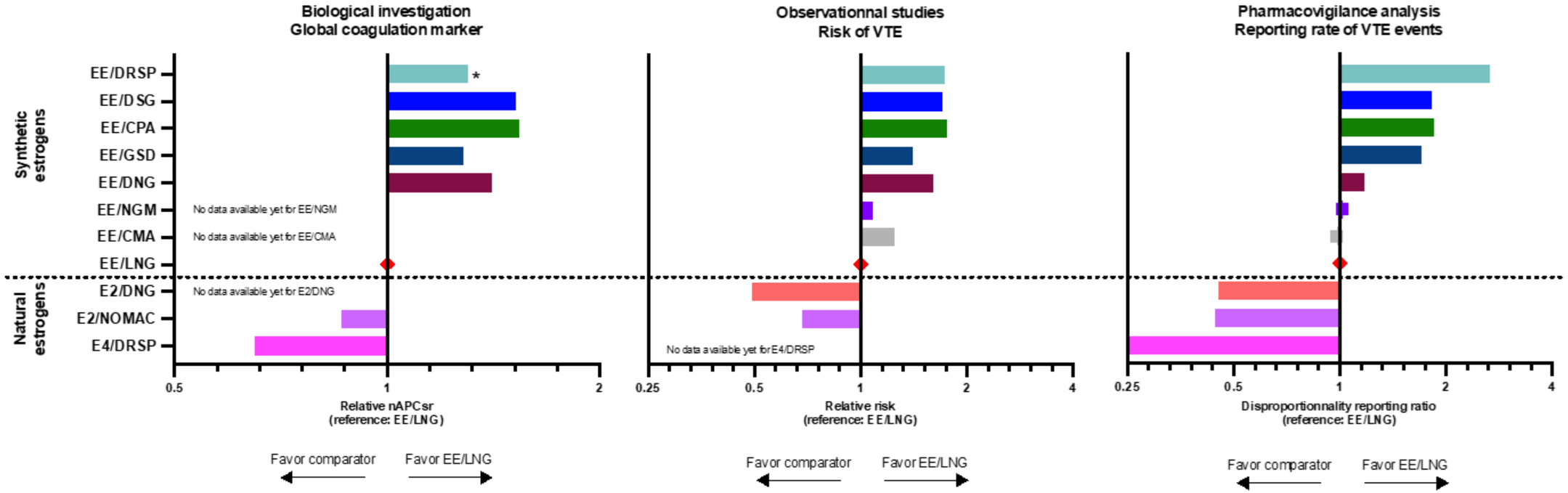


Significant 33% reduction in VTE risk among users of E2-based COCs compared to those using EE-based COCs.

Natural estrogens: towards a safer alternative

Clinical practice Guidelines

These results advocate a shift in first-line contraceptive recommendation toward a safer alternative emphasizing COC containing natural estrogens.



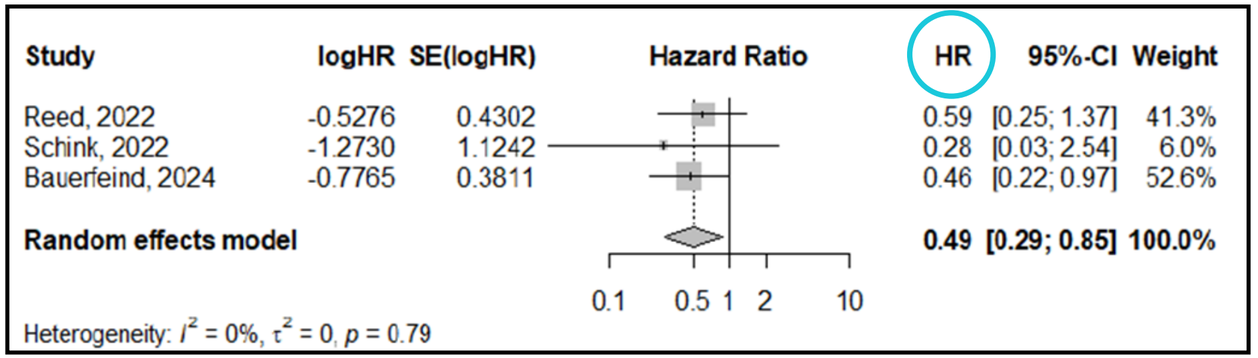
Natural estrogens: towards a safer alternative

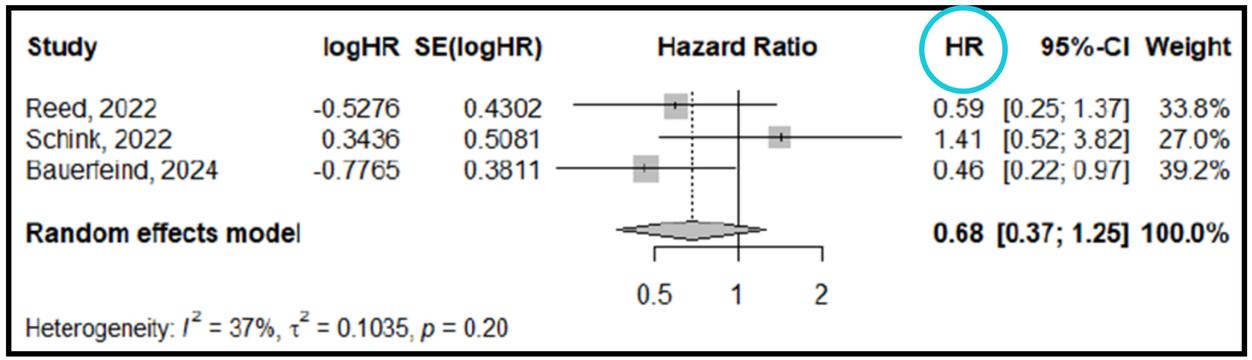
Meta-analysis: stratification analyses

Meta-Analysis
Natural VS Synthetic estrogen

E2-based VS EE-LNG

Adjusted HR were available for 3 studies <u>comparing E2-based COC with EE-LNG</u>. One study, reported two groups with E2-based COC (i.e. E2/NOMAC and E2/DNG) and therefore analyses where run separately to avoid inclusion of the EE-LNG arm twice in the analysis.





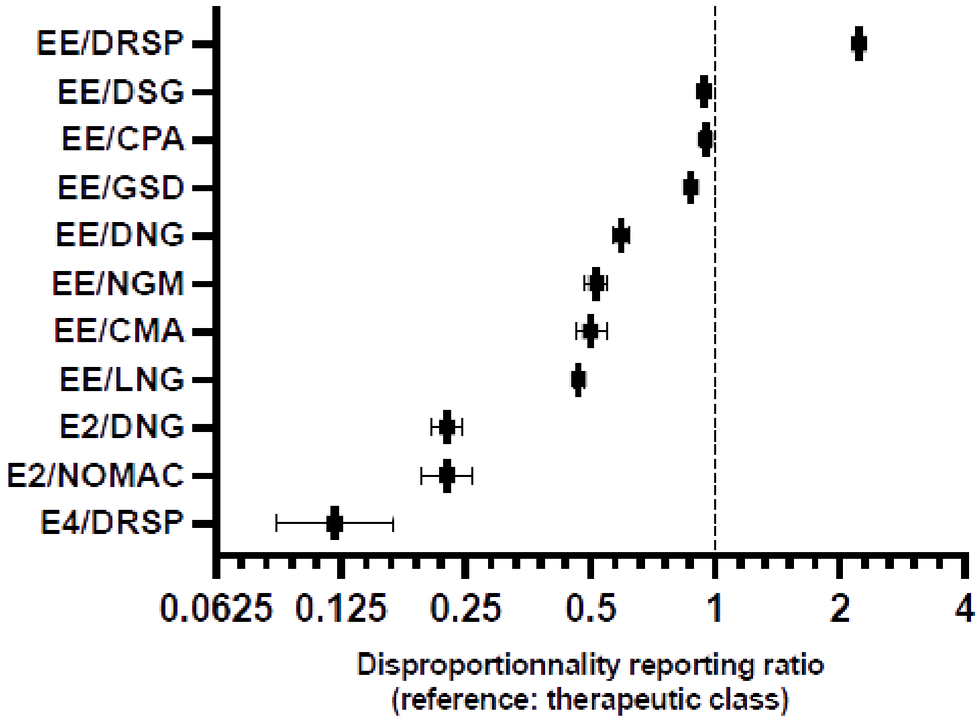
Adjusted HR, adjustment for confounding factors

Stratification analyses: E2/NOMAC or E2/DNG **<u>compared to EE/LNG</u>** yield a statistical lower thrombotic profile after adjustment

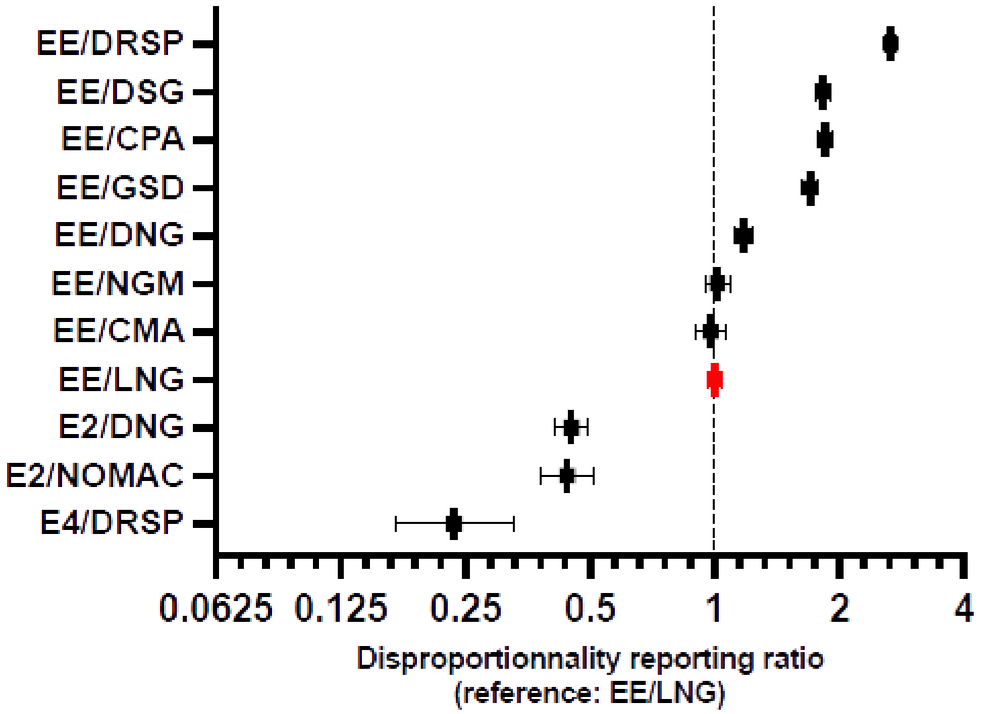
Natural estrogens: pharmacovigilance data

EudraVigilance

LOWEST VTE RISK COMPARED TO CLASS



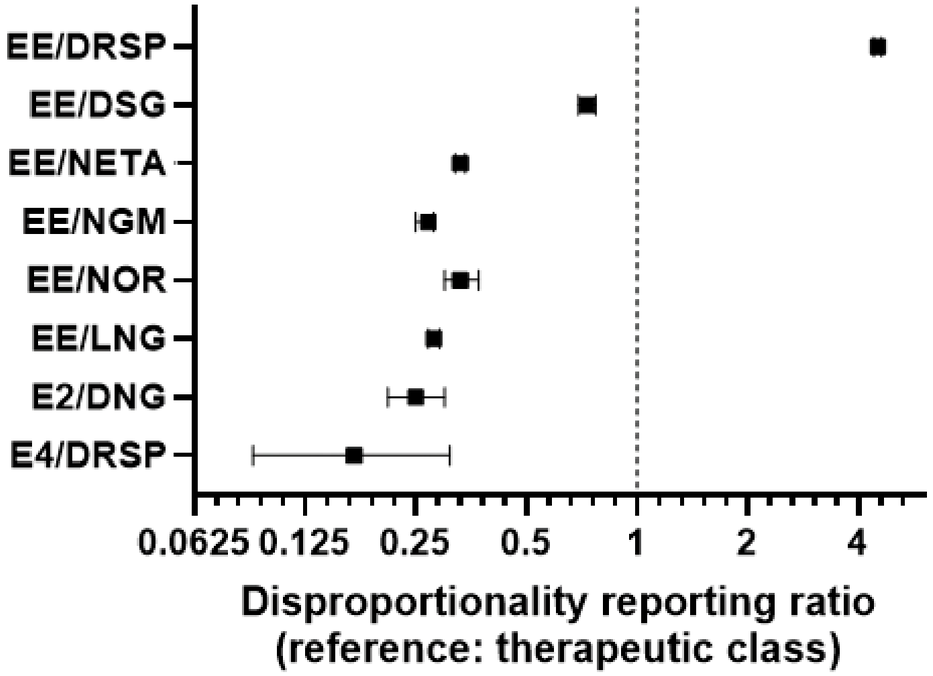
LOWER VTE RISK COMPARED TO EE/LNG



Natural estrogens: pharmacovigilance data

FAERS

LOWEST VTE RISK COMPARED TO CLASS



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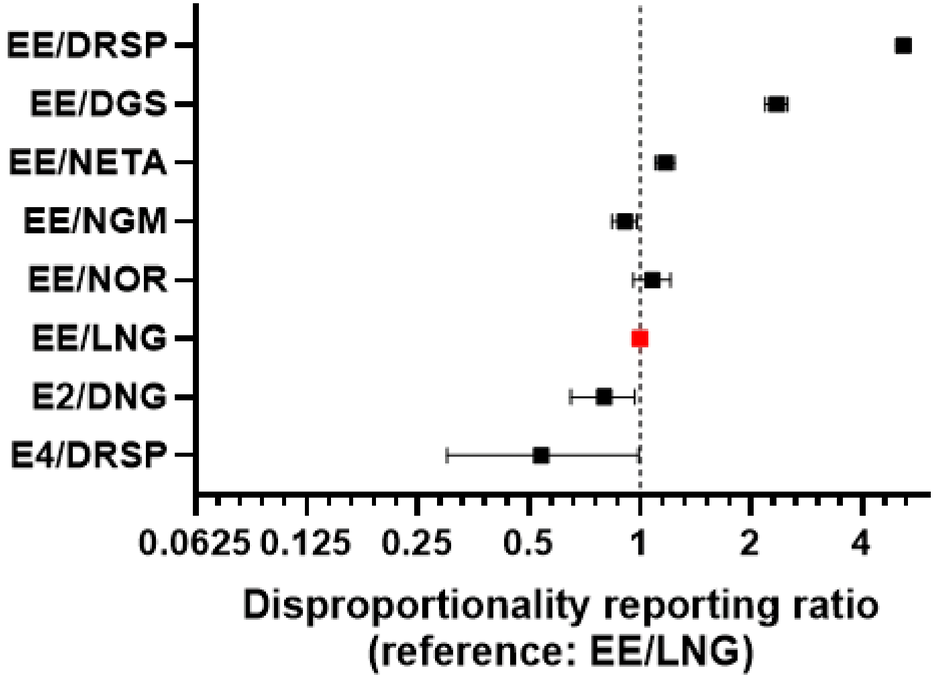

EudraVigilance : RR

Estroprogestative association	Number of "thrombotic" events reported**	Number of adverse events reported	Reporting ratio
E2/DNG	428	3,330	*0.13*
E2/NOMAC	158	1,256	*0.13*
E4/DRSP	34	507	*0.07*
EE/CMA	396	1,419	*0.28*
EE/CPA	2,391	4,552	*0.52(5)*
EE/DNG	1,286	3,852	*0.33*
EE/DRSP	30,022	39,578	*0.76*
EE/DSG	2,275	4,374	*0.52*
EE/GSD	1,616	3,335	*0.48(5)*
EE/LNG (gold standard)	3,869	13,583	*0.28(5)*
EE/NGM	722	2,489	*0.29*
All COC	**43,197**	**78,275**	*0.55*
DSRP*	92	1,361	*0.07*

Abbreviations: CMA, chlormadinone acetate; CPA, cyproterone acetate; DNG, dienogest; DRSP, drospirenone; DSG, desogestrel; GSD, gestodene; LNG, levonorgestrel; NGM, norgestimate; NOMAC, nomegestrol acetate

EudraVigilance : PRR

Estrogen/Progestin combination	Proportionality reporting rate [95% CI] vs the therapeutic class	p-value	Proportionality reporting rate [95% CI] vs the gold standard EE-LNG	p-value
E2/DNG	0.23 [0.21-0.25]	***<0.001***	0.45 [0.41- 0.49]	***<0.001***
E2/NOMAC	0.23 [0.19-0.26]	***<0.001***	0.44 [0.38- 0.51]	***<0.001***
E4/DRSP	0.12 [0.09-0.17]	***<0.001***	0.24 [0.17- 0.33]	***<0.001***
EE/CMA	0.50 [0.46-0.54]	***<0.001***	0.98 [0.90- 1.07]	***0.65***
EE/CPA	0.95 [0.92-0.98]	***<0.001***	1.84 [1.77- 1.92]	***<0.001***
EE/DNG	0.59 [0.57-0.62]	***<0.001***	1.17 [1.11- 1.23]	***<0.001***
EE/DRSP	2.23 [2.19-2.26]	***<0.001***	2.66 [2.59- 2.74]	***<0.001***
EE/DSG	0.94 [0.91-0.97]	***<0.001***	1.83 [1.76- 1.90]	***<0.001***
EE/GSD	0.87 [0.84-0.90]	***<0.001***	1.70 [1.63- 1.78]	***<0.001***
EE/LNG (gold standard)	0.47 [0.46-0.48]	***<0.001***	1.00 [0.96- 1.04]	***1.00***
EE/NGM	0.52 [0.49-0.55]	***<0.001***	1.02 [0.95- 1.09]	***0.59***
DSRP*	*0.12 [0.10-0.15]*	***<0.001***	*0.24 [0.19-0.29]*	***<0.001***

Abbreviations: COC, combined oral contraceptive; CI, confidence interval; CMA, chlormadinone acetate; CPA, cyproterone acetate; DNG, dienogest; DRSP, drospirenone; DSG, desogestrel; GSD, gestodene; LNG, levonorgestrel; NGM, norgestimate; NOMAC, nomegestrol acetate

FAERS: RR

Estroprogestative Association	Number of "thrombotic" events reported*	Number of ICSRs**	Reporting ratio (RR)
E2/DNG	97	1029	0.094
E4/DRSP	10	156	0.064
EE/DRSP	26892	43810	0.614
EE/DSG	996	3581	0.278
EE/NOR	305	2381	0.128
EE/NGM	860	7993	0.108
EE/NETA	1928	13915	0.139
EE/LNG	1693	14278	0.119
All COCs	32855	88751	0.370
DRSP	168	2216	0.076

FAERS: PRR

Control group	EE + LNG								
PRR (EE/LNG)	DSPR + E4	DSPR + EE	Dienogest + E2	DSPR	EE + NETA/NET	EE + DSG	EE + Norgestrel	EE + Ethynodiol	EE + Norgestimate
PRR	0,5406	5,1768	0,795	0,6394	1,1685	2,3457	1,0803		0,9074
95% CI	0,2963 - 0,9863	4,9473 - 5,4169	0,6544 - 0,9658	0,5492 - 0,7444	1.0994 to 1.2420	2,1889 - 2,5137	0,9640 - 1,2107		0,8398 - 0,9804
Significance level	P = 0,0450	P < 0,0001	P = 0,0209	P < 0,0001	P < 0.0001	P < 0,0001	P = 0,1839		P = 0,0138

Control group	All COC									
PRR (All COC)	E4/DRSP	EE/DRSP	E2/DNG	DSPR	EE/NET(A)	EE/DSG	EE/Norgestrel	EE/Ethynodiol	EE/NGM	EE/LNG
PRR	0,1702	4,5168	0,2484	0,1974	0,3289	0,7312	0,3343		0,2668	0,27779
95% CI	0.0934 to 0.3099	4.4058 to 4.6305	0.2055 to 0.3002	0.1707 to 0.2284	0.3152 to 0.3431	0.6931 to 0.7714	0.3010 to 0.3714		0.2503 to 0.2843	0.2656 to 0.2909
Significance	P < 0.0001	< 0,0001	< 0,0001	< 0,0001	<0,0001	< 0,0001	< 0,0001		< 0,0001	< 0,0001