

Hormonal contraception and thrombosis. Influence of age, PCOS, and predispositions

Øjvind Lidegaard

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Gynækologisk endokrinologi 6.6.14

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University of Copenhagen**

Hormonal contraception

How to get an overview

<u>Combined products</u> (oestrogen and progestogen)							

<u>Progestogen only products</u>							

Hormonal contraception

How to get an overview?

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<u>Combined products</u> (oestrogen and progestogen)

Oral							
N-oral							

<u>Progestogen only products</u>

Oral							
N-oral							

Hormonal contraception

How to get an overview?

EE dose	NETA Norethis- terone	LNG Levonor- gestrel	NGM Norges- timate	DGS Deso- gestrel	GSD Gesto- dene	DRSP Drospire- none	CPA Cyproterone- acetate
<u>Combined products</u>							
Middle							
Low							
Nat oie							
N-oral							
<u>Progestogen only products</u>							
Oral							
N-Oral							

Hormonal contraception according to oe dose, progestogen type, and route

EE dose	NETA Norethis- terone	LNG Levonor- gestrel	NGM Norges- timate	DGS Deso- gestrel	GSD Gesto- dene	DRSP Drospire- none	CPA Cyproterone- acetate
<u>Combined products</u>							
Middle	1st	2nd gen		3rd gen		4th gen	
Low							
Nat oe							
N-oral							
<u>Progestogen only products</u>							
Oral	POP			Cerazette®			
N-oral	Depot	IUS		Implant			

Hormonal contraception according to oe dose, progestogen type, and route

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<u>Combined products</u>							
Middle	1st	2nd gen		3rd gen		4th gen	
Low							
Nat oe	E2V-DNG			E2 NOMAC			
N-oral			Patch	Vaginal ring			
<u>Progestogen only products</u>							
Oral	POP			Desogestrel		DRSP	
N-oral	Depot	IUS		Implant			

HC according to relative risk of VTE

No risk <1.5	Low risk 1.5-4	High risk 5-7	Few data	No data
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EE dose	NETA Norethis- terone	LNG Levonor- gestrel	NGM Norges- timate	DGS Deso- gestrel	GSD Gesto- dene	DRSP Drospire- none	CPA Cyproterone- acetate
<u>Combined products</u>							
Middle	3	3		6		6	6
Low		?		5			
Nat oie	E2V-DNG 4.5			E2 NOMAC			
N-oral			Patch 7	Vaginal ring 6			
<u>Progestogen only products</u>							
Oral	POP 1			Cerazette 1			
N-oral	Depot 1	IUS 1		Implant 1.4			

Hormonal contraception and thrombosis.

Seven axes of significance

- Combined versus progestogen only
 - Oestrogen dose
 - Oestrogen type (natural vs artificial)
 - Progestogen type
 - Route of administration
 - Duration of use (50% higher the first year)
 - Age and absolute risk
-

VT: Acquired risk factors

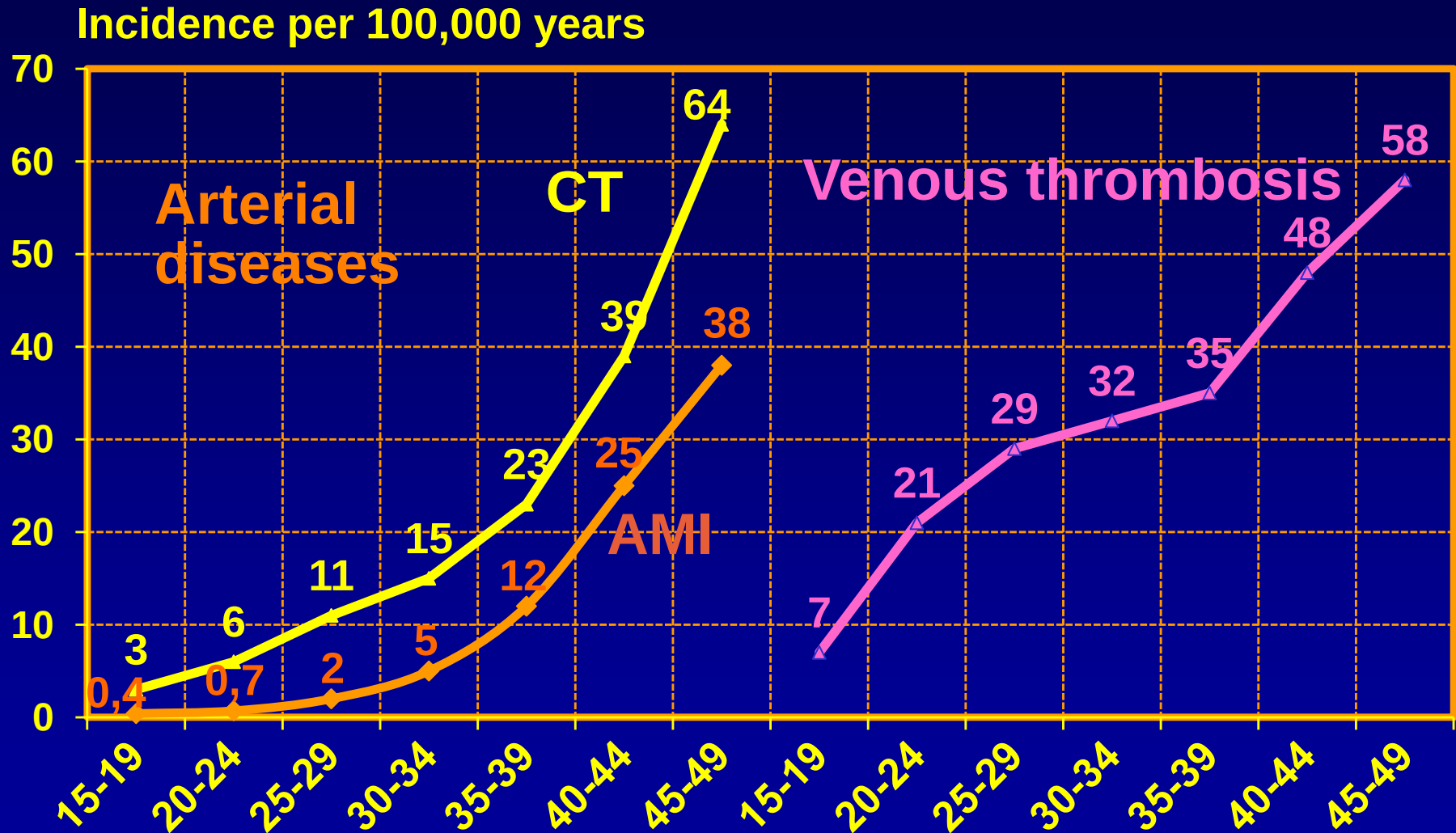
	Prevalence	RR
Age ≥ 30 vs < 30	50%	2.5
Pregnancy	4%	8
Adiposity (BMI > 25)	30%	2
Varicose veins	8%	2
Immobilisation/trauma	?	2-10
Hormonal contraception	35%	3-7
PCOS	5-10%	2
Medical diseases	5%?	2-5

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CT, AMI and VT in DK 2001-2009/10

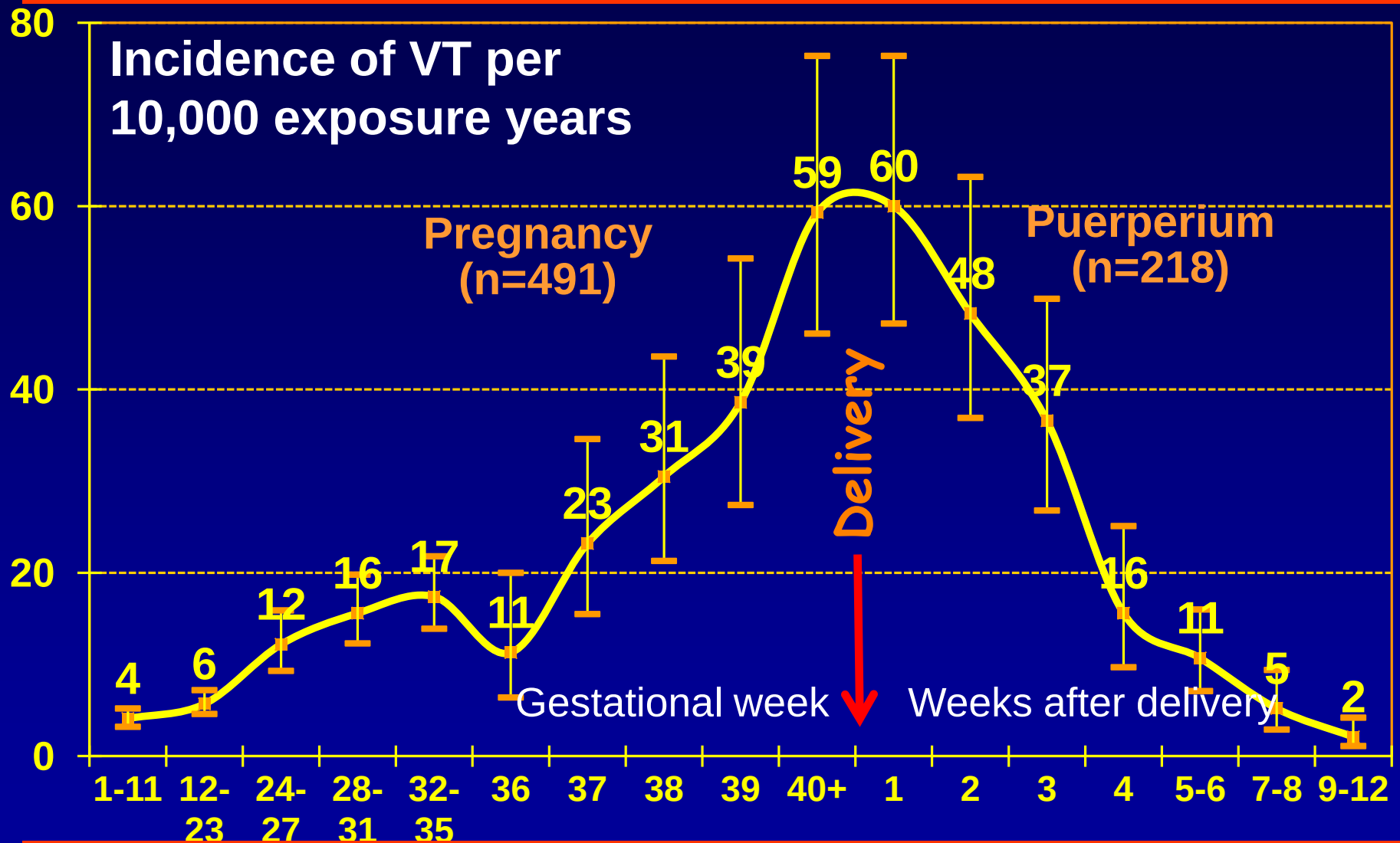
Pregnant and puerperal women excluded



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Venous thrombosis in pregnant and puerperal women, DK 1995-2005. N=709



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Danish infrastructure

National Health Registry (>1977)

VT diagnoses,
Previous CaVD/canc.
Pregnancies, surgery

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National Registry of Medicinal products (>1994):

HC use
Medication against
BP↑, DM, Hyperchol.

Danish infrastructure

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OC use
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BP↑, DM, Hyperchol.

1995

→ 2005

Cause of Deaths Registry (>1977)

Lethal VT

Statistics of Denmark

PIN-codes, education
vital status, emigration

Hormonal contraception and risk of venous thromboembolism: national follow-up study

Øjvind Lidegaard, professor,¹ Ellen Løkkegaard, consultant,² Anne Louise Svendsen, statistician,³ Carsten Agger, data manager⁴

¹Gynaecological Clinic, Rigshospitalet, Copenhagen University, DK-2100 Copenhagen, Denmark

ABSTRACT

Objective To assess the risk of venous thrombosis in current users of different types of hormonal

risk of venous thrombosis than oral contraceptives with levonorgestrel. Progestogen only pills and hormone releasing intrauterine devices were not associated with

The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study

A van Hylckama Vlieg, research fellow,¹  Helmerhorst, professor of clinical epidemiology of fertility,^{1,2} J P Vandenbroucke, professor of clinical epidemiology,¹ C J M Doggen, research fellow,¹ F R Rosendaal, professor of clinical epidemiology, head of department^{1,3,4}

VT and drospirenone

	VT no	Risk /10,000	Rate ratio DRSP/2nd gen
Dinger ⁰⁷	118	9.1	1.0 (0.6-1.8) 4th/2nd
Seeger ⁰⁷	57	13.0*	0.9 (0.5-1.6) 4th/???
Vlieg ⁰⁹	1,524	na	1.7 (0.7-3.9) 4th/2nd
Lidegaard ⁰⁹	4.213	7.8	1.6 (1.3-2.1) 4th/2nd

Risk of venous thromboembolism among users of oral contraceptives: a review of two recently published studies

Samuel Shapiro, Jürgen Dinger

Abstract

Background Two recent studies, a cohort study from Denmark, and a case-control study from The Netherlands, have reported increased risks of venous thromboembolism (VTE) among users of oral contraceptives (OCs) containing desogestrel, gestodene, drospirenone and cyproterone, relative to the use of levonorgestrel.

Critique In the Danish study the comparisons were not valid. (1) VTE risk is highest soon after commencement of OC use, and duration of use was underestimated for levonorgestrel users, but not for drospirenone users; for the remaining compounds duration was only slightly underestimated. The underestimation for levonorgestrel resulted in systematic overestimation of the relative risks for the compared OCs. (2) Duration was also incorrectly estimated: only the duration of current use, *not duration of all episodes of use* was relevant to VTE risk. (3) Confounding was not adequately controlled.

In The Netherlands study the comparisons were not

valid. (1) The relative risk for drospirenone versus levonorgestrel was not statistically significant. (2) Extensive publicity had been given to the risk of VTE among users of desogestrel, gestodene, drospirenone and cyproterone: information bias and detection bias were therefore likely. (3) Inadequate allowance was made for duration of use. (4) The combination of two different control groups, both of them likely to have been biased, into a single category was not valid.

Conclusion The best evidence continues to suggest that the increased risk of VTE in OC users is a class effect, dependent on the estrogen dose and duration of use, and independent of the progestogen used.

Keywords combined oral contraceptives, progestogen, risk assessment, venous thromboembolism

J Fam Plann Reprod Health Care 2010; 36(1): 33–38
(Accepted 25 November 2009)

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OC and VT: Methods

National Registry of Patients (>1977)

VT diagnoses,

Previous CaVD/canc.
Pregnancies, surgery

National Registry of Medicinal products (>1995): OC use

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BP↑, DM, Hyperchol.

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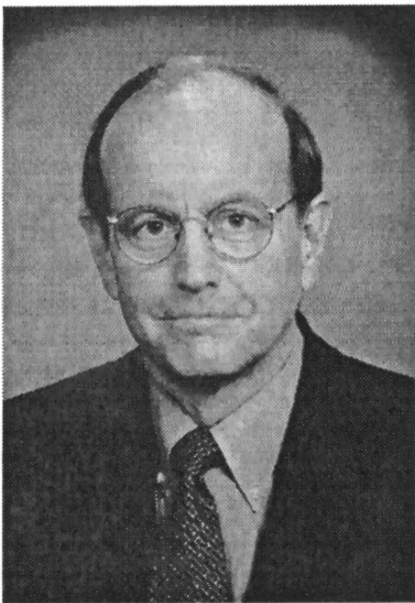
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Dinger ¹⁰	680	na	1.0 (0.5-1.8) 4th/2nd

An Editor

Epidemiologic Research Using Administrative Databases

Garbage In, Garbage Out



David A. Grimes, MD

Administrative databases stem from claims made for services by health care providers and institutions.¹ Simply put, they are billing systems. These databases were created for reasons other than epidemiologic research—a key limitation. Data fields commonly include only basic demographic information, drug dispensing, provider visits, and hospitalization. Examples of administrative databases often used by researchers include Medicare, Medicaid, and those of health maintenance organizations such as Kaiser Permanente.

Vital records, such as birth certificates, represent another administrative database commonly used for epidemiologic research.^{2,3} Again, these data are collected for civil and legal purposes, not for research.

Research using administrative databases has important strengths and weaknesses. Sample sizes are often large, which provide power to find differences. Those enrolled may be representative of the community of interest. Recording of drug prescriptions occurs contemporaneously, which

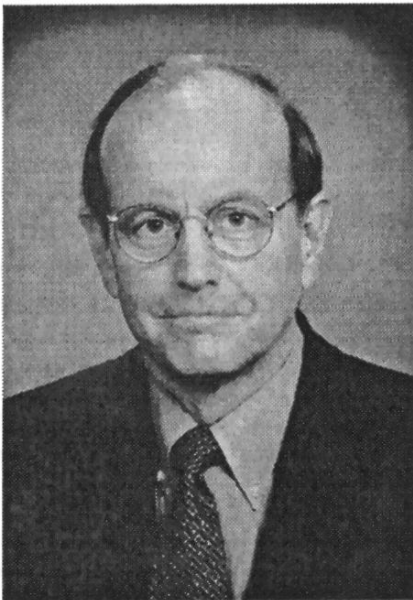
Research using vital records should be limited to simple descriptive reports with caveats about data accuracy. Using birth certificate information for epidemiologic analyses is inappropriate because of well documented deficiencies in information quality³. Similarly, epidemiologic research using administrative databases, such as the Danish National Patient Registry, must at a minimum validate each reported outcome by chart review⁹ or by patient interview.

In recent decades, the computer science concept of "GIGO" ("garbage in, garbage out") has somehow come to mean "garbage in, gospel out"¹⁰. When computer software tackles a large database, many accept the "computerized" output as trustworthy, regardless of the quality of the input. Sadly, no fancy statistical machinations can compensate for poor-quality data. Publications relying on unconfirmed database reports of venous thromboembolism should be ignored.

Editorial

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Financial Disclosure

Dr. Grimes serves as a consultant (DSMB member) for Bayer.

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OC and VT: Methods

National Registry of Patients (>1977)

VT diagnoses,
Previous CaVD/canc.
Pregnancies, surgery

Registry of Medicinal products (>1995):

OC use (>1995)

Anticoagulation therapy

BP↑, DM, Hyperchol.

1995



2001

1.3 million women

2005



2009

Cause of Deaths Registry (>1977)

Lethal VT

Statistics Denmark

PIN-codes, education
vital status, emigration

RESEARCH

Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9



OPEN ACCESS

Øjvind Lidegaard *professor of obstetrics and gynaecology*¹, Lars Hougaard Nielsen *statistician*¹, Charlotte Wessel Skovlund *data manager and scientific assistant*¹, Finn Egil Skjeldestad *professor of clinical medicine*², Ellen Løkkegaard *senior registrar in obstetrics and gynaecology*³

¹Gynaecological Clinic 4232, Rigshospitalet, University of Copenhagen, Denmark; ²Department of Obstetrics and Gynaecology, Institute of Clinical Medicine, University of Tromsø, Norway; ³Department of Obstetrics and Gynaecology, Hillerød Hospital, University of Copenhagen, Denmark

Abstract

Objective To assess the risk of venous thromboembolism from use of

thromboembolism was not increased with use of progestogen only pills or hormone releasing intrauterine devices. If oral contraceptives with

VT and drospirenone

	VT no	Risk /10,000	Rate ratio DRSP/2nd gen
Dinger ⁰⁷	118	9.1	1.0 (0.6-1.8) 4th/2nd
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Lidegaard ⁰⁹	4,213	7.8	1.6 (1.3-2.1) 4th/2nd
Dinger ¹⁰	680	na	1.0 (0.5-1.8) 4th/2nd
Parkin ¹¹	61	2.3	2.7 (1.5-4-7) 4th/2nd
Jick ¹¹	186	3.1	2.8 (2.1-3.8) 4th/2nd
Lidegaard ¹¹	4,246	9.3	2.1 (1.6-2.8) 4th/2nd

IR = incidence per 10,000 women years

Combined oral contraceptives, venous thromboembolism, and the problem of interpreting large but incomplete datasets

Jürgen Dinger,¹ Samuel Shapiro²

¹Director, ZEG - Berlin Center for Epidemiology and Health Research, Berlin, Germany

²Visiting Professor of Epidemiology, Department of Epidemiology, University of Cape Town, Cape Town, South Africa

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Received 11 November 2011

Accepted 14 November 2011

Background

In 2009, Lidegaard *et al.*¹ published findings in the *British Medical Journal*, derived from a Danish retrospective cohort study of the risk of venous thromboembolism (VTE) associated with the use of combined oral contraceptives (COCs). Their analysis was based on data derived from national health registries, and they concluded that “oral contraceptives with desogestrel, gestodene, or drospirenone were associated with a significantly higher risk of VTE than oral contraceptives with levonorgestrel”. That report has previously

in the publication differ from those mentioned in the re-analysis submitted to EMA (one example is given below).

Since the mid-1990s there has been heated debate regarding the risk of VTE associated with the use of different progestogens, and those who have followed the discussion can only note with concern its confrontational and increasingly sharp tone, which, unfortunately, is also reflected in the published responses to the re-analysis,^{5–7} and more particularly in the authors’ replies.^{8,9}

The heat of the debate may have some-

Dinger & Shapiro, on the road again

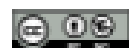
We conclude that the best evidence continues to suggest that the increased risk of VTE among COC users is a class effect. In the Danish data an analysis confined to women who used COCs for the first time from 2001 onward did not support any differential effects of progestogens. Surprisingly, this information was neither presented nor discussed in the published re-analysis.⁴ Any potential differences, if they exist at all, are probably beyond the resolving power of the 'epidemiological microscope'.

BMJ Editorial Nov 2011

This new study has tackled many of the concerns expressed about the earlier investigation. Although unpalatable to some, it is difficult not to conclude that combined oral contraceptives with desogestrel, gestodene, or drospirenone confer a higher risk of venous thromboembolism than those with levonorgestrel.

RESEARCH

Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10



OPEN ACCESS

Øjvind Lidegaard *professor*¹, Lars Hougaard Nielsen *statistician*¹, Charlotte Wessel Skovlund *data manager*¹, Ellen Løkkegaard *senior registrar*²

¹Gynaecological Clinic 4232, Blegdamsvej 9, DK-2100 Copenhagen Ø, Juliane Marie Centre, Rigshospitalet, University of Copenhagen, Denmark;

²Department of Obstetrics and Gynaecology, Hillerød Hospital, University of Copenhagen, Denmark

Abstract

Objective To assess the risk of venous thrombosis in current users of

Conclusion Women who use transdermal patches or vaginal rings for contraception have a 7.9 and 6.5 times increased risk of confirmed

HC according to risk of VTE

No risk <1.5	Low risk 1.5-4	High risk 5-7	Few data	No data
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EE dose	NETA Norethis- terone	LNG Levonor- gestrel	NGM Norges- timate	DGS Deso- gestrel	GSD Gesto- dene	DRSP Drospi- renone	CPA Cyproterone- acetate
<u>Combined products</u>							
Middle	2.2*	3.0*	3.5*	6.6*	6.2*	6.4*	6.4*
Low				4.8*	5.1*	6.9*	
Nat oel	E2V-DNG 4.5*			E2 NOMAC			
N-oral			Patch 7.9*	Vaginal ring 6.5*			
<u>Progestogen only products</u>							
Oral	POP 0.7			Cerazette 0.6			
N-oral	Depot	IUS 0.6		Implant 1.4			

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Middle	3	3		6		6	6
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<u>Progestogen only products</u>							
Oral	POP 1			Cerazette 1			
N-oral	Depot 1	IUS 1		Implant 1.4			

VT and drospirenone

	VT	IR	Rate ratio	
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Jick ¹¹	186	3.1	2.8 (2.1-3.8)	4th/2nd
Lidegaard ¹¹	4,246	9.3	2.1 (1.6-2.8)	4th/2nd
FDA Kaiser ¹¹	625	7.6	1.5 (1.2-1.9)	4th/2nd

IR = incidence per 10,000 women years

Combined hormonal contraceptives and the risk of venous and arterial thromboembolism and cardiovascular death: misuse of automated databases

Samuel Shapiro

Visiting Professor of Epidemiology, Department of Family Medicine and Public Health, University of Cape Town School of Medicine, Cape Town, South Africa

Correspondence to

Professor Samuel Shapiro, Department of Family Medicine and Public Health, University of Cape Town School of Medicine, Anzio Road, Observatory, Cape Town, South Africa; samshap@miweb.co.za

ABSTRACT

Background In December 2011, the US Food and Drug Administration (FDA) convened a public Advisory Committee meeting to review evidence from a study commissioned by the agency. An analysis of findings derived from four databases was published on the FDA website, and presented at the meeting. Among users of combined hormonal contraceptives containing ethinylestradiol (EE) plus drospirenone (DRSP) the risks of venous (VTE) and arterial thromboembolism (ATE) were higher than

[myocardial infarction (MI) and stroke combined], in users of recently introduced combined estrogen/progestogen hormonal contraceptives (CHCs).¹ At the time of the meeting the findings had only been published on the FDA website, but not in a peer-reviewed journal.

The investigators concluded that their data “[provided] another positive finding to the increasing body of evidence linking [drospirenone (DRSP)] to increased risk of VTE relative to standard low-dose

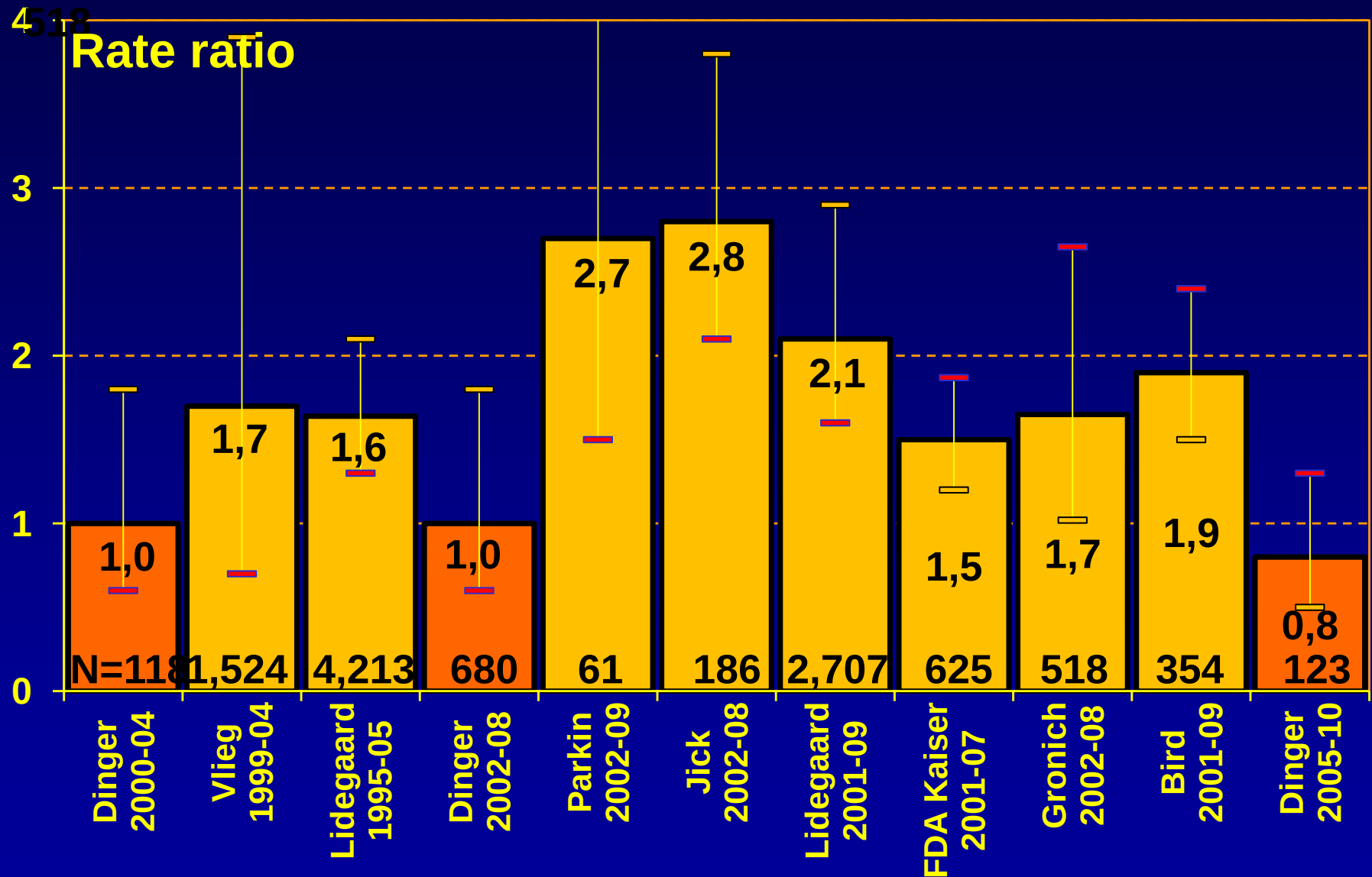
Shapiro, critique of FDA

Conclusions The best evidence continues to suggest that the increased risk of VTE in combined hormonal contraceptive users is dependent on the dose of estrogen, and independent of the progestogen used. The best evidence also suggests that DRSP does not increase the risk of ATE, and may reduce it.

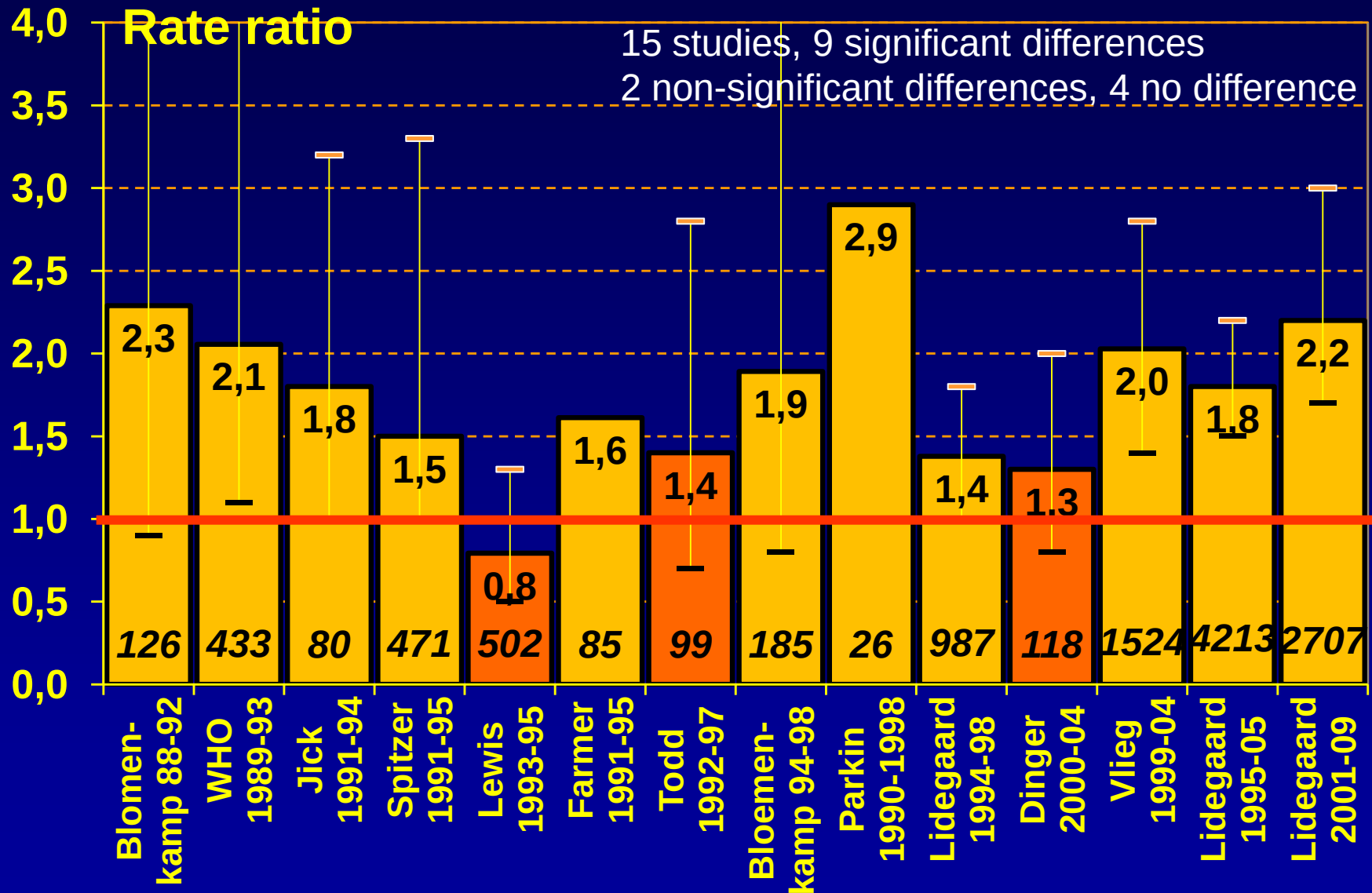
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Gronich ¹¹	518	8.6	1.7 (1.0-2.7)	4th/2nd
Bird ¹³	354	18.0	1.9 (1.5-2.4)	4th/2nd

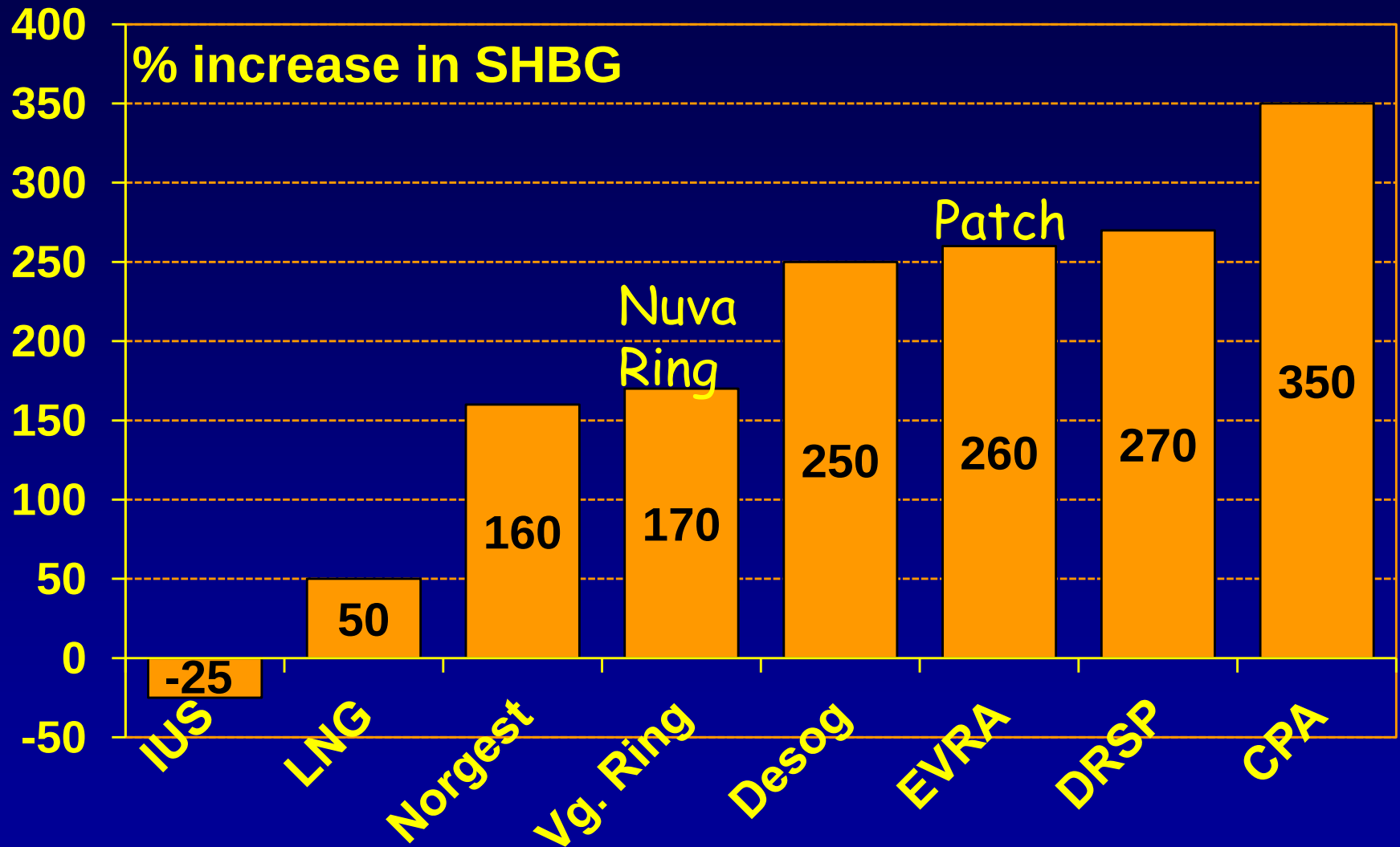
COC with DRSP vs LNG



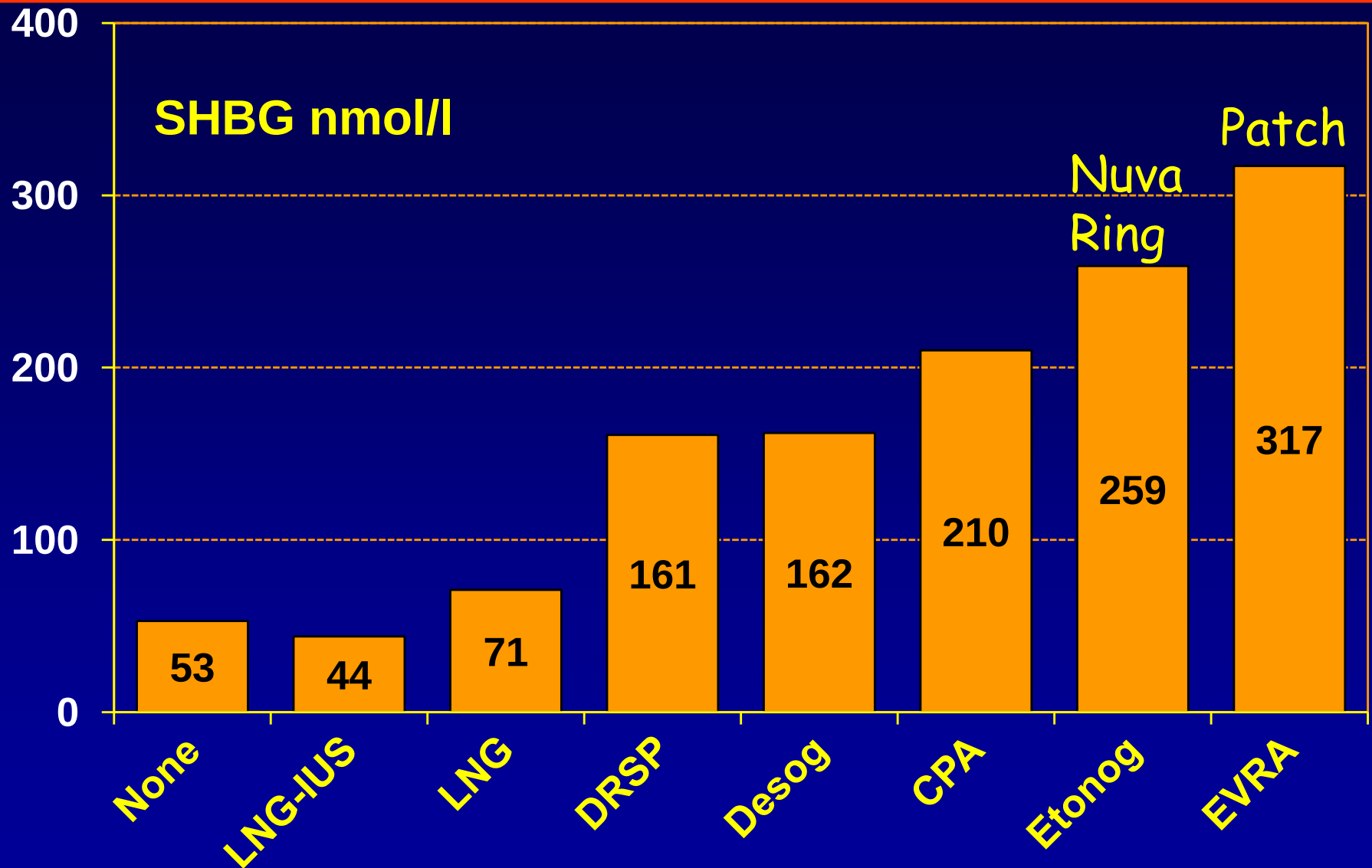
3rd versus 2nd generation COC



Hormonal contraception and SHBG



Hormonal contraception & SHBG



.....on the road again

Publication in BMJ on May 10, 2012

- Anne Szarewski (14.5.2012)
“...*biologically nonsensical results*”



.....on the road again

Publication in BMJ on May 10, 2012

- Anne Szarewski (14.5.2012)
- Samuel Shapiro (16.5.2012)

“..the Danish registry is an unsuitable resource for the evaluation of VTE risk”

.....on the road again

Publication in BMJ on May 10, 2012

- Anne Szarewski (14.5.2012)
- Samuel Shapiro (16.5.2012)
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“These new data .. may lead to a new (unfounded) scare....”

.....on the road again

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*“Higher abortion rate in areas where
....prescribing restrictions are in place”*

.....on the road again

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“...poor studies such as this one...”

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- Anne L Connolly (18.5.2012)
- Sven Skouby (19.5.2012)

“We find no reason to repeat the clear and concise arguments by Anne Szarewski”

George Monbiot

One of the most widespread human weaknesses is our readiness to accept claims that fit our beliefs and reject those that clash with them. We demand impossible standards of proof when confronted with something we don't want to hear, but will believe any old cobblers if it confirms our prejudices:

Guardian, November 22, 2011

ORIGINAL ARTICLE

Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception

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ABSTRACT

BACKGROUND

Although several studies have assessed the risk of venous thromboembolism with newer hormonal contraception, few have examined thrombotic stroke and myocardial infarction, and results have been conflicting.

HC and thrombotic stroke

Reference: Non-users

- All women in Denmark 15-49 years old during the period January 1995 through December 2009 (15 years)
 - Data from four National registries
 - Included: 1,626,158 women
14,251,063 women years
4,914,401 current use
3,311 thrombotic strokes
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Lidegaard et al. N Engl J Med 2012; 366: 2257-66

HC and thrombotic stroke

No risk <1.5	Low risk 1.5-4	High risk 5-7	Few data	No data
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EE dose	NETA Norethis- terone	LNG Levonor- gestrel	NGM Norges- timate	DGS Deso- gestrel	GSD Gesto- dene	DRSP Drospi- renone	CPA Cyproterone- acetate
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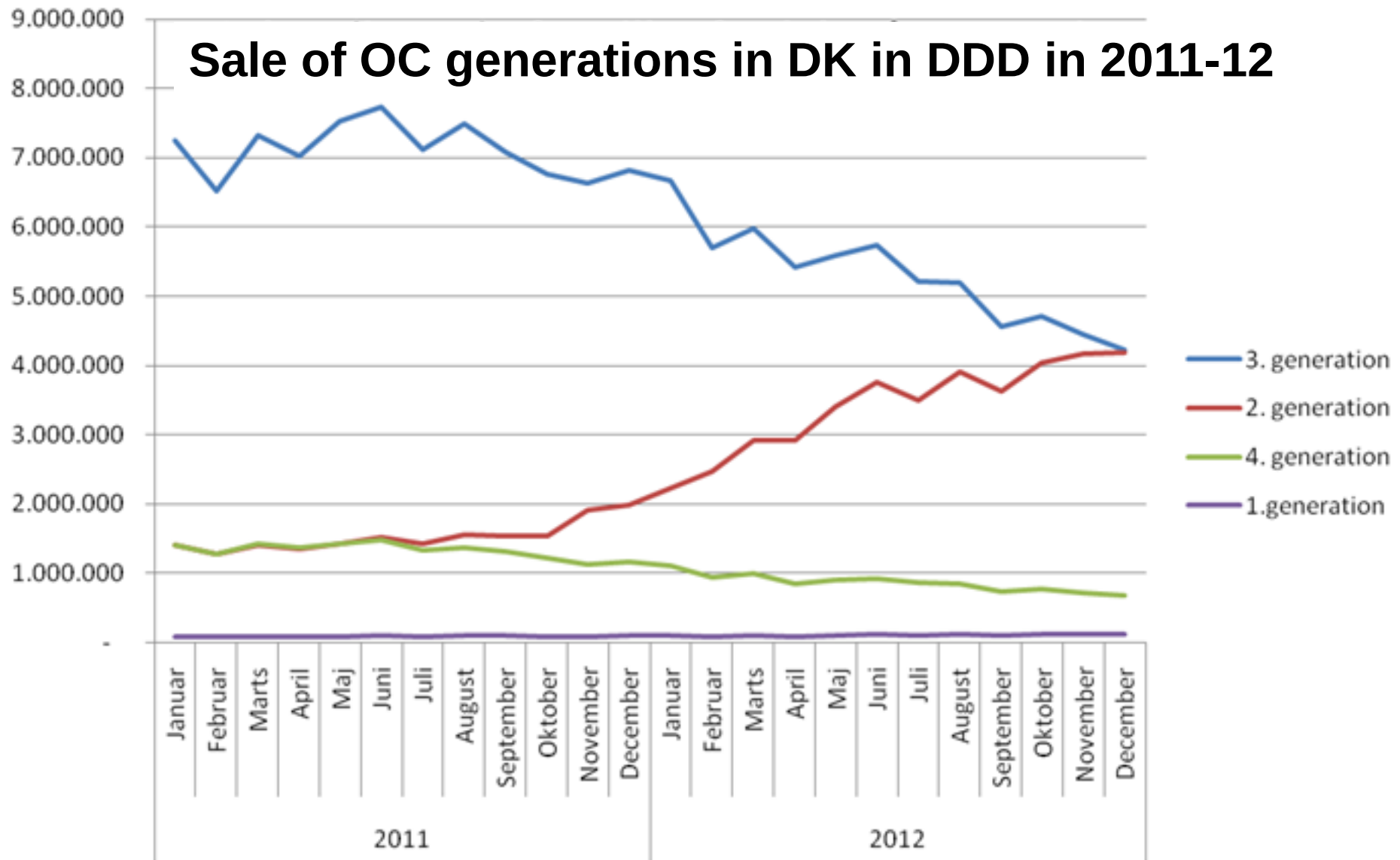
Combined products

Middle	2.2*	1.7*	1.5*	2.2*	1.8*	1.6*	1.4
Low				1.5*	1.7*	0.9	
Nat o/e	E2V-DNG			E2 NOMAC			
N-oral			Patch 3.2	Vaginal ring 2.5*			

Progestogen only products

Oral	POP 1.4			Cerazette 1.4			
N-oral	Depot	IUS 0.7		Implant 0.9			

Sale of OC generations in DK in DDD in 2011-12



<http://laegemiddelstyrelsen.dk/da/topics/bivirkninger-og-forsog/bivirkninger/nyheder/laeger-foelger-anbefalinger-for-brugen-af-p-piller>

Hormonal contraception - age

Young women (<35 years)

1 st choice	Low risk (2 nd gen) COC
2 nd choice	No risk LNG-IUS (e.g Jaydess)
3 rd choice	High risk 3 rd or 4 th gen COC

Women from 35 years or women at risk

1 st choice	No risk LNG-IUS
2 nd choice	Low risk 2 nd gen. COC
3 rd choice	Non hormonal contraception

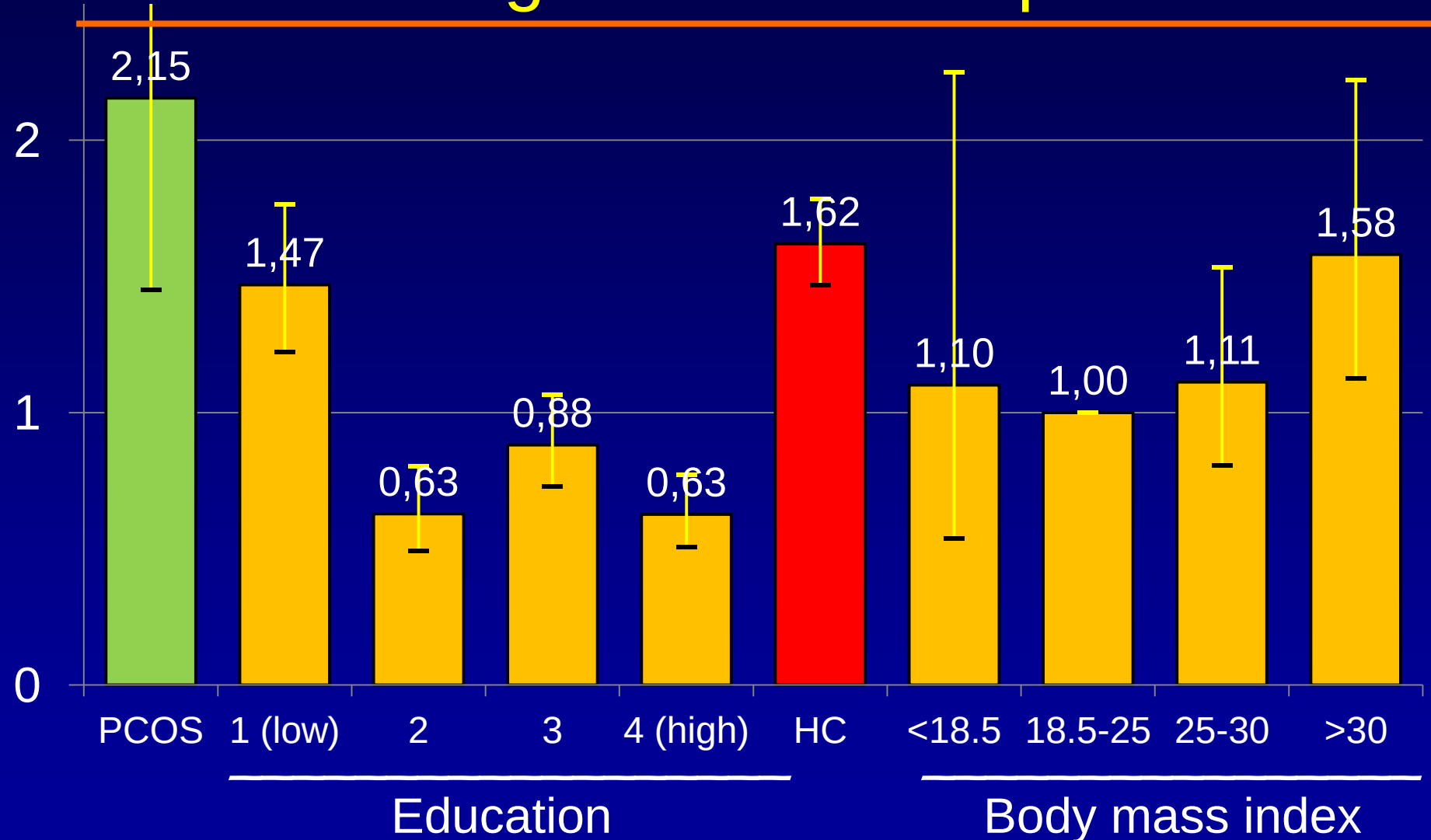
VT: Acquired risk factors

	Prevalence	RR
Age ≥ 30 vs < 30	50%	2.5
Pregnancy	4%	8
Adiposity (BMI > 25)	30%	2
Varicose veins	8%	2
Immobilisation/trauma	?	2-10
Hormonal contraception	35%	3-6
PCOS	5-10%	2
Medical diseases	5%?	2-5

PCOS and thrombotic stroke

- 9,640 women with PCOS were included (0.7% of all included women)
 - 3,994 (41%) of these had a recorded BMI
 - 2,029 women experienced a thrombotic stroke, of these 25 in women with PCOS
 - The Incidence rate of thrombotic stroke increased more than 100% through the study period, and 20 times with increasing age
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Adj. relative risk of cerebral infarction according to different exposures



*) Adjusted for year, education, hormonal contraception, and BMI

Conclusion

- Fertile women with PCOS have a doubled risk of thrombotic stroke which is not explained by a higher BMI or use of hormonal contraception.
 - Other studies have demonstrated also a doubled risk of venous thrombosis in women with PCOS.
 - Therefore, also women with PCOS should have low risk 2nd generation hormonal contraception as first choice
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Hormonal contraception and thrombosis

Thanks for your attention

www.lidegaard.dk/slide

Conflicts of interest: The primary investigator has been an expert witness in a legal process in USA in 2011 and 2012.
