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

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ECE, Wroclaw 5.5.2014

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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?

Combined products (oestrogen and progestogen)							
Oral							
N-oral							
Progestogen only products							
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
Combined products							
Middle							
Low							
Nat oe							
N-oral							
Progestogen only products							
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
Combined products							
Middle	**1st**	**2nd gen**		**3rd gen**		**4th gen**	
Low							
Nat oe							
N-oral							
Progestogen only products							
Oral	POP			Cerazette®			
N-oral	Depot	IUS		Implant			

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

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Combined products							
Middle	**1st**	**2nd gen**		**3rd gen**		**4th gen**	
Low							
Nat oe	E2V-DNG			E2 NOMAC			
N-oral			Patch	Vaginal ring			
Progestogen only products							
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

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospire-none	CPA Cyproterone-acetate
Combined products							
Middle	**3**	**3**		**6**		**6**	**6**
Low		**?**		**5**			
Nat oe	E2V-DNG **4.5**			E2 NOMAC			
N-oral			Patch **7**	Vaginal ring **6**			
Progestogen only products							
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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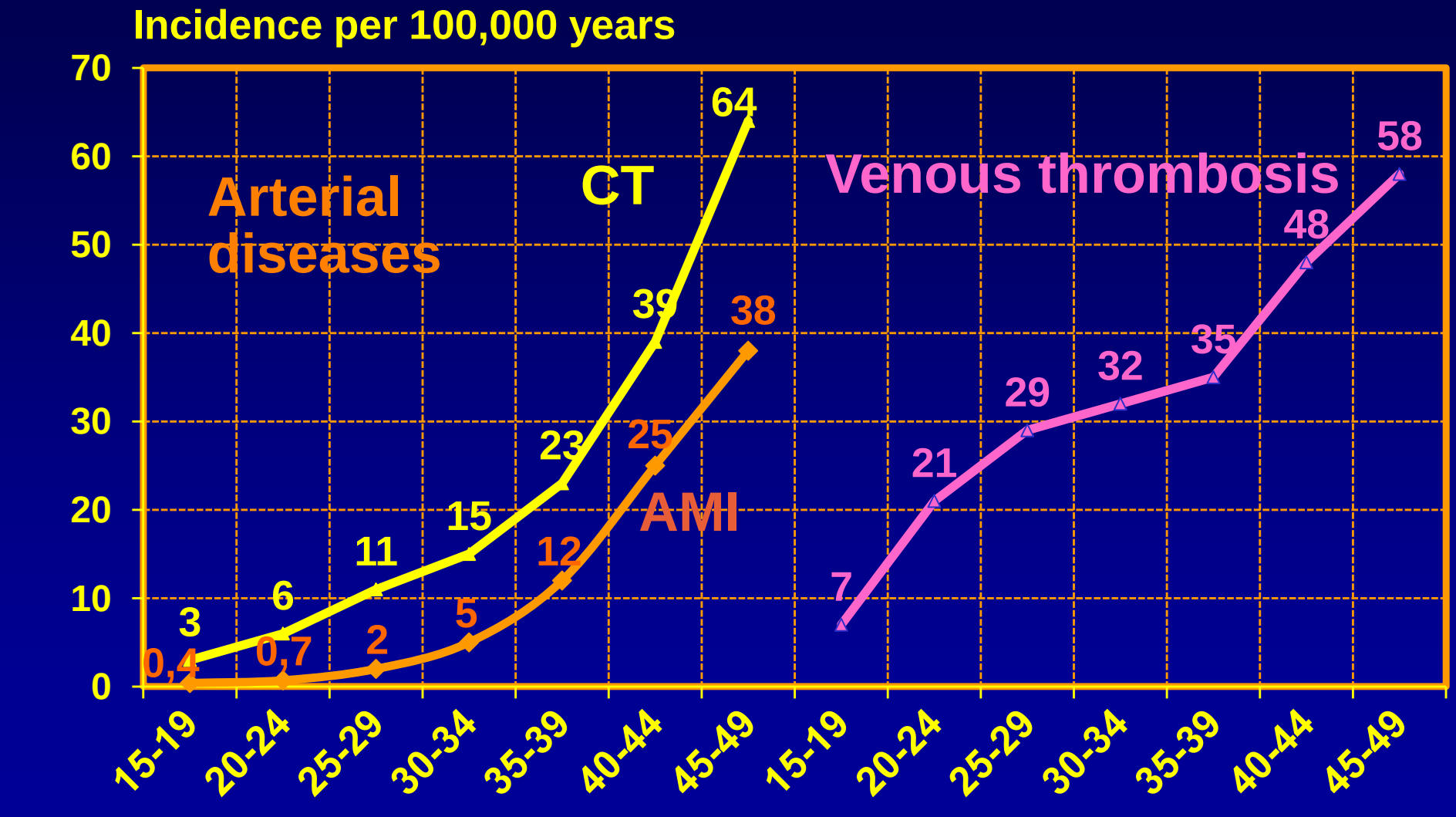
Medical diseases	5%?	2-5

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

Pregnant and puerperal women excluded



Lidegaard et al NEJM 2012 and BMJ 2011

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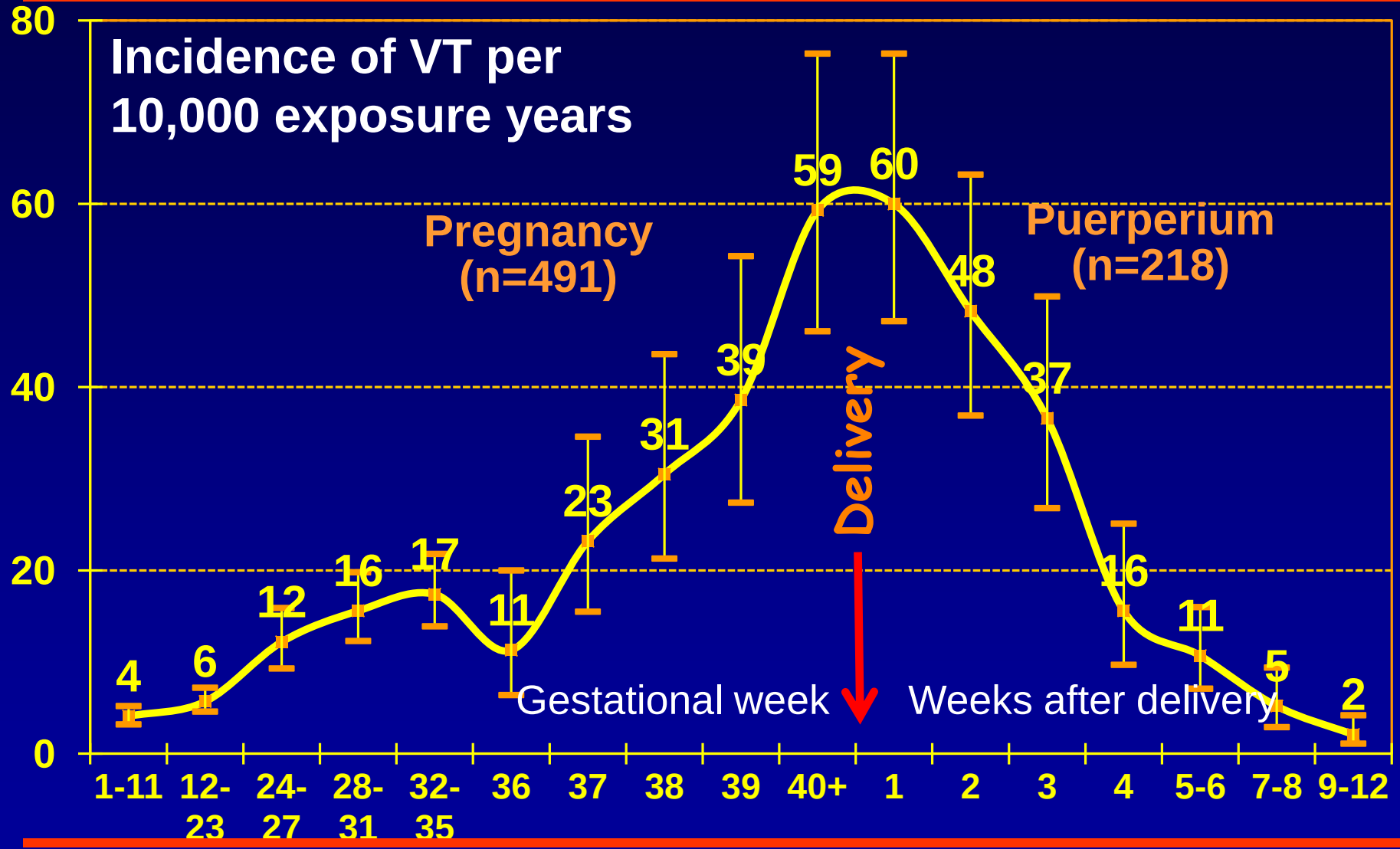
Venous thrombosis in pregnant and puerperal women, DK 1995-2005. N=709



Virkus et al. Thromb Haemost 2011; 106: 304-9

Li/12

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Danish infrastructure

National Health Registry (>1977)

VT diagnoses,

Previous CaVD/canc.

Pregnancies, surgery

Danish infrastructure

National Health Registry (>1977)

VT diagnoses,

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Pregnancies, surgery

National Registry of Medicinal products (>1994): HC use

Medication against

BP↑, DM, Hyperchol.

Danish infrastructure

National Health Registry (>1977)

VT diagnoses,

Previous CaVD/canc.

Pregnancies, surgery

National Registry of Medicinal products (>1994): OC use

Medication against

BP↑, DM, Hyperchol.

1995 → 2005

Cause of Deaths Registry (>1977)

Lethal VT

Statistics of Denmark

PIN-codes, education

vital status, emigration

BMJ

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 manager[4]

[1]Gynaecological 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

BMJ

RESEARCH

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]

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

Critique

REVIEW

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

Medication against

BP↑, DM, Hyperchol.

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Lidegaard et al. BMJ 2009

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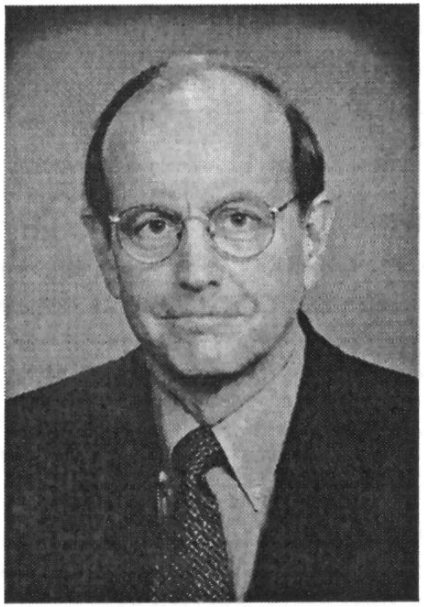
An Editor

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

Grimes, Obstet Gynecol Nov 2010, 116: 1018-19

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 quality[3]. Similarly, epidemiologic research using adminstrative databases, such as the Danish National Patient Registry, must at a minimum validate each reported outcome by chart review[9] or by patient interview.

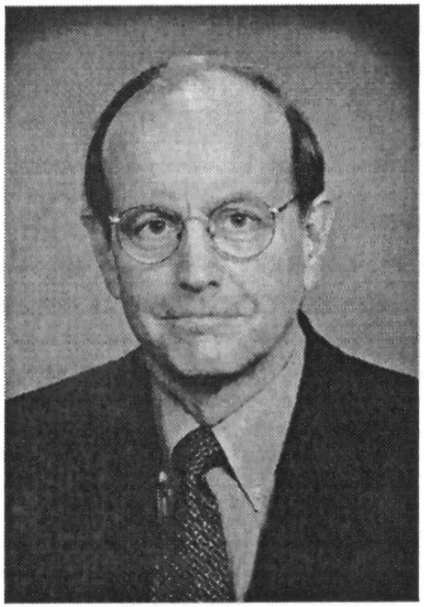
In recent decades, the computer science concept of "GIGO" ("garbage in, garbage out") has somehow come to mean "garbage in, gospel out[10]." When computer software tackles a large database, many accept the "computerized" output as trustworthy, regardless of the quality of the input. Sadly, no fancy statistical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

Grimes. Obstet Gynecol 2010; 116: 1018-19

Editorial

Epidemiologic Research Using Administrative Databases

Garbage In, Garbage Out



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Financial Disclosure

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

Grimes, Obstet Gynecol Nov 2010, 116: 1018-19

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 → 2005 → 2009

1.3 million women

Cause of Deaths Registry (>1977)

Lethal VT

Statistics Denmark

PIN-codes, education

vital status, emigration

Lidegaard et al. BMJ 2011

BMJ

BMJ 2011;343:d6423 doi: 10.1136/bmj.d6423

RESEARCH

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

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]

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

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[1]Director, ZEG - Berlin Center for Epidemiology and Health Research, Berlin, Germany
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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'.

Dinger & Shapiro. J Fam Plan Repr Health Care2011: Nov. 14.

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.

Philip Hannaford. BMJ 2011; 343: d6592

BMJ

BMJ 2012;344:e2990 doi: 10.1136/bmj.e2990

RESEARCH

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

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

[1]Gynaecological Clinic 4232, Blegdamsvej 9, DK-2100 Copehagen Ø, Juliane Marie Centre, Rigshospitalet, University of Copenhagen, Denmark; [2]Department 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

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospi-renone	CPA Cyproterone-acetate
Combined products							
Middle	**2.2***	**3.0***	**3.5***	**6.6***	**6.2***	**6.4***	**6.4***
Low				**4.8***	**5.1***	**6.9***	
Nat oe	E2V-DNG **4.5***			E2 NOMAC			
N-oral			Patch **7.9***	Vaginal ring **6.5***			
Progestogen only products							
Oral	POP **0.7**			Cerazette **0.6**			
N-oral	Depot	IUS **0.6**		Implant **1.4**			

HC according to risk of VTE

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Combined products							
Middle	**3**	**3**		**6**		**6**	**6**
Low		**2.5?**		**5**			
Nat oe	E2V-DNG **4.5**			E2 NOMAC			
N-oral			Patch **7**	Vaginal ring **6**			
Progestogen only products							
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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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

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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.

Shapiro S. J Fam Plan Reproduc Health Care 2013: 39: 89-96

VT and drospirenone

	VT	IR[4]	Rate ratio
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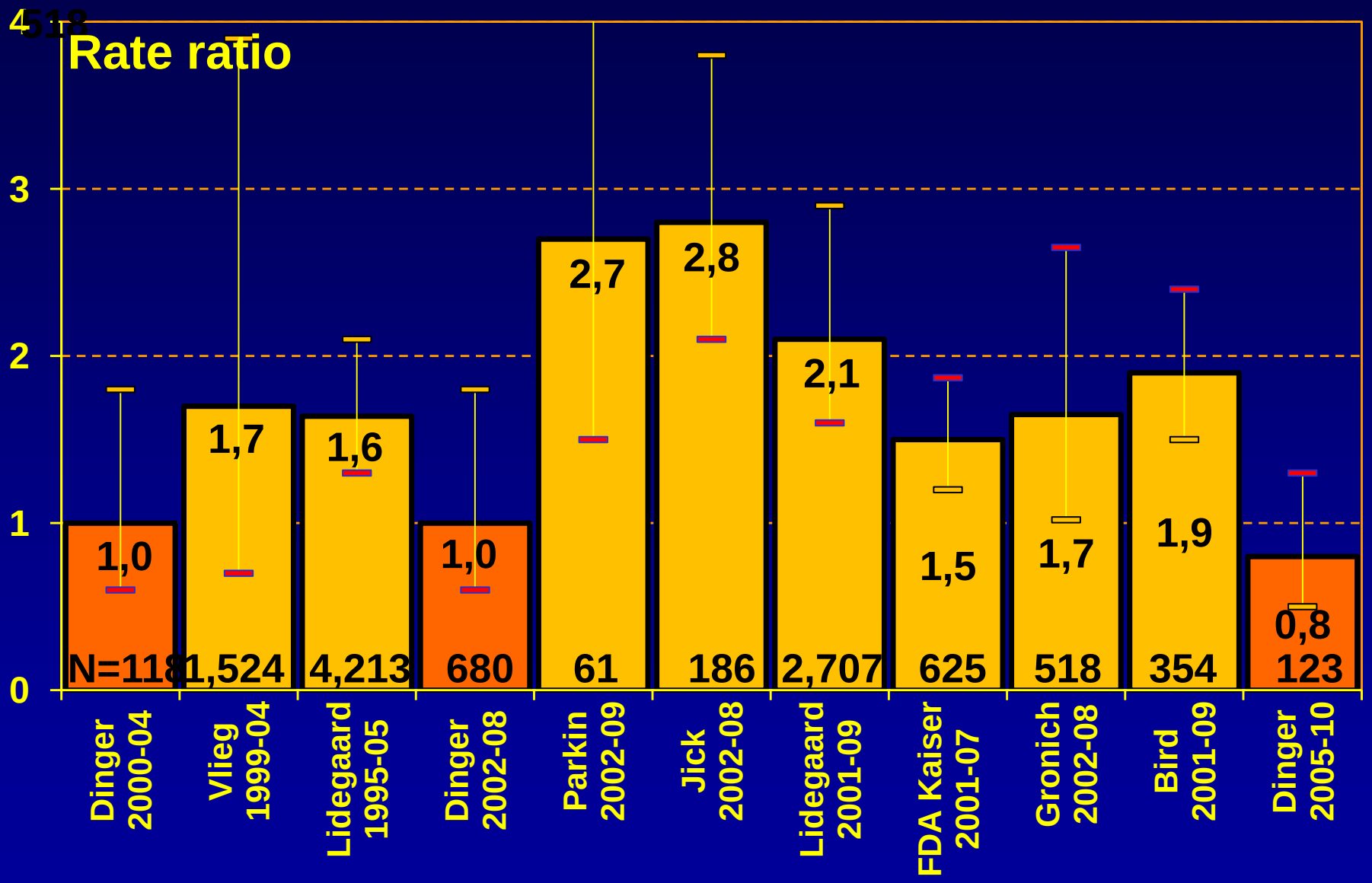
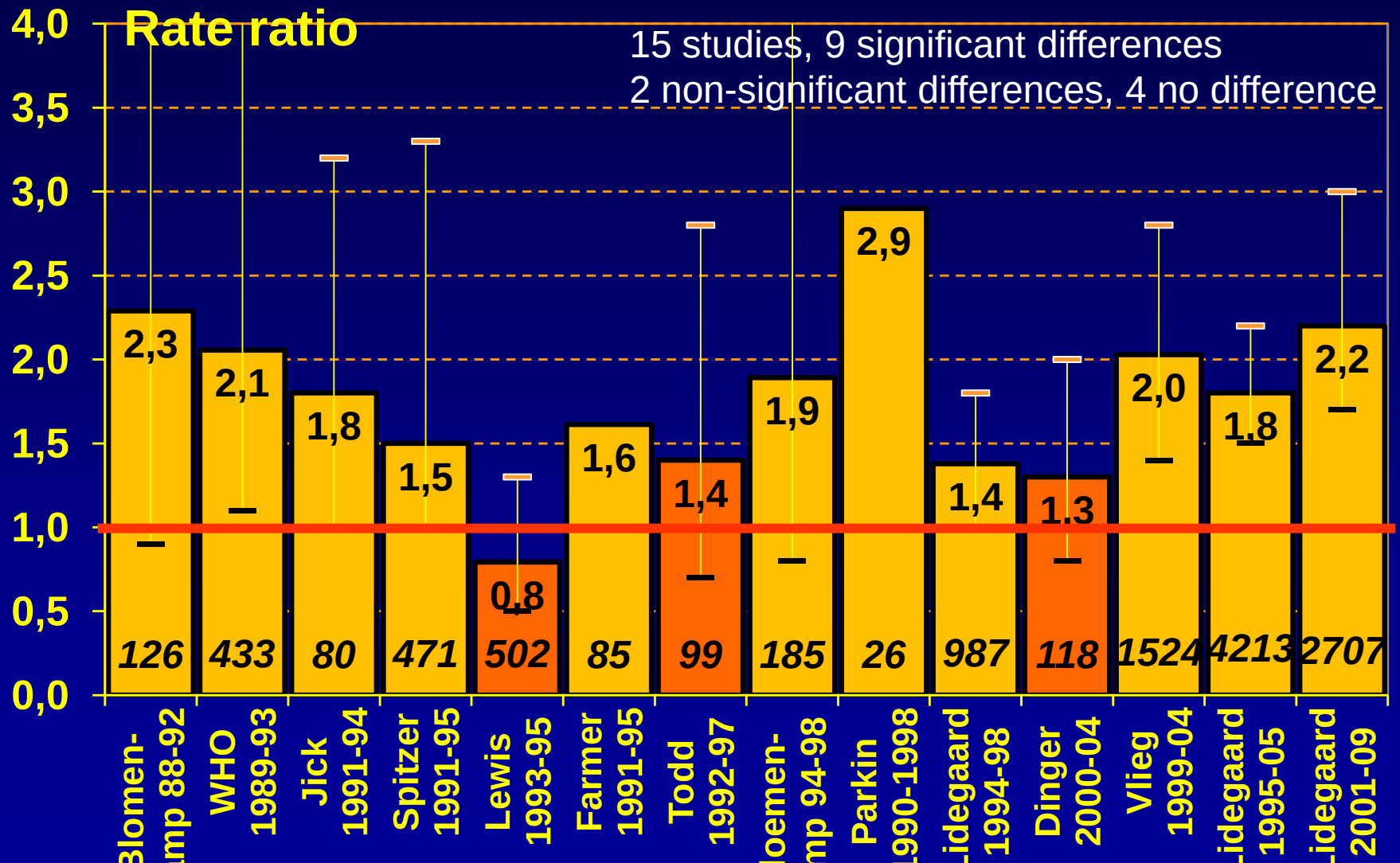
Gronich[11]	518	8.6	1.7 (1.0-2.7) 4th/2nd
Bird[13]	354	18.0	1.9 (1.5-2.4) 4th/2nd

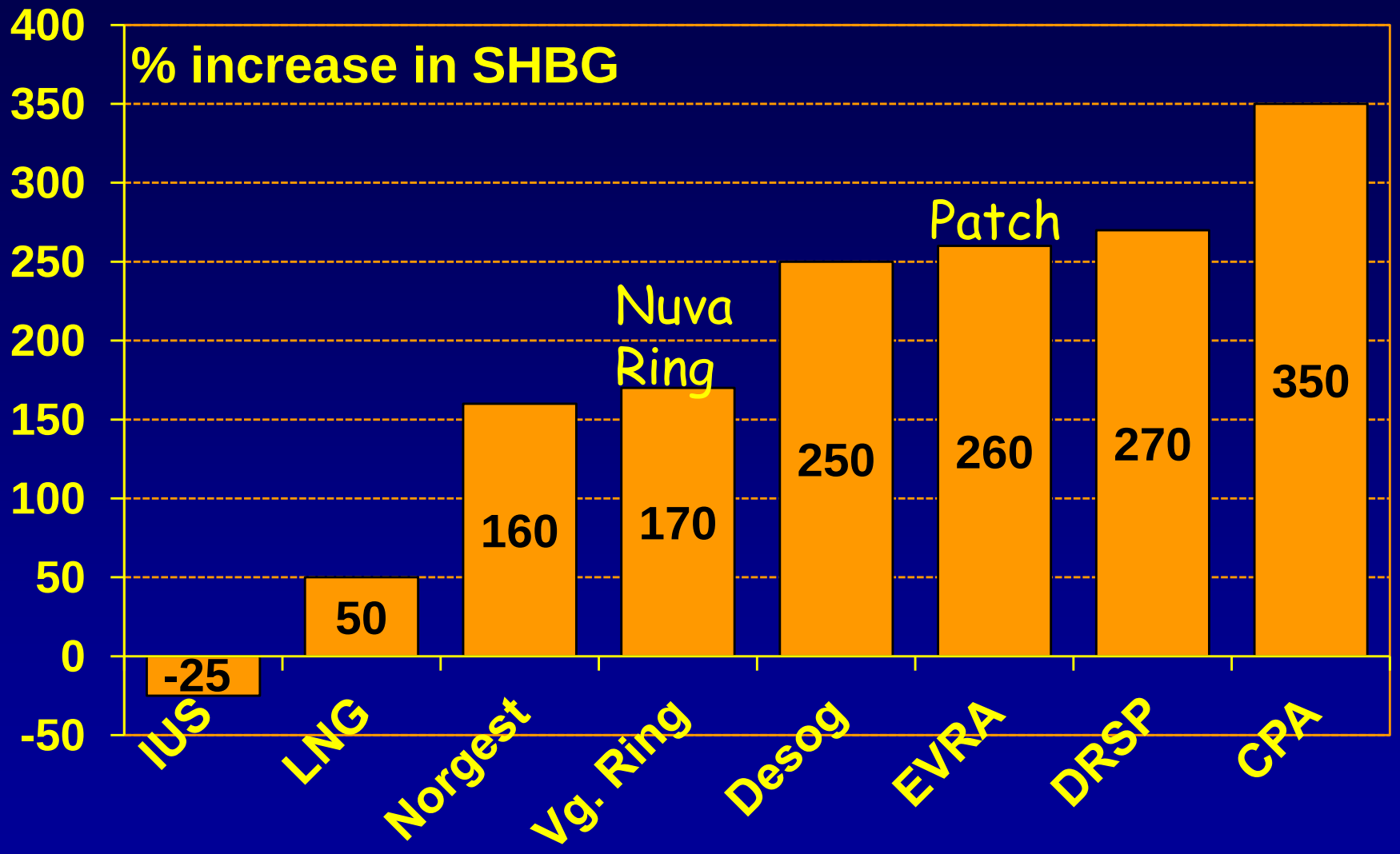
COC with DRSP vs LNG



3rd versus 2nd generation COC

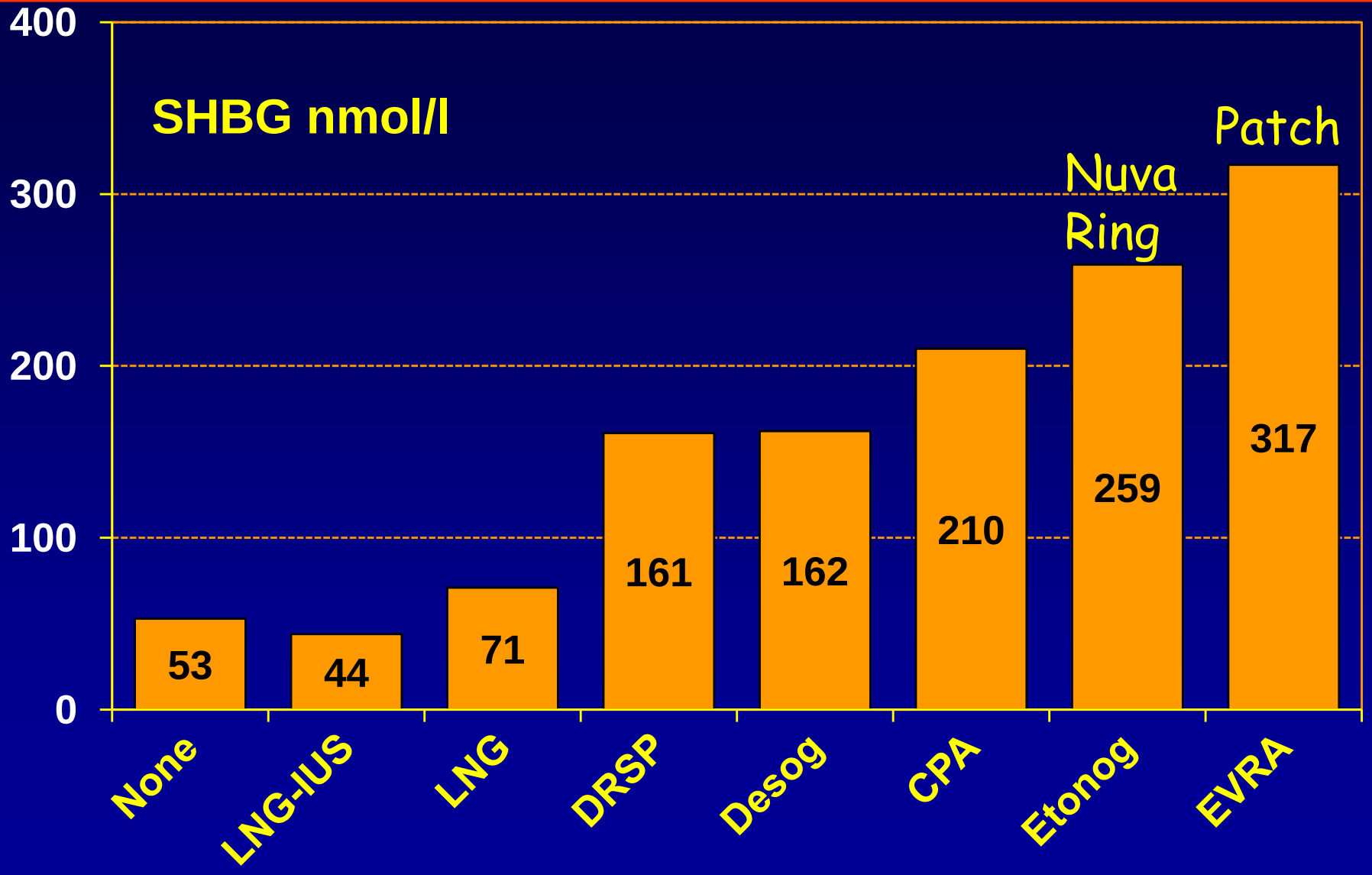


Hormonal contraception and SHBG



Odlin et al. Acta Obstet Gynecol Scand 2002; 81: 482-90

Hormonal contraception & SHBG



Raps et al. Thrombosis Haemostasis 2012; doi: 10.1111

…….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)
- Mary E. Gaffield (16.5.2012)
  "These new data .. may lead to a new (unfounded) scare…."

…….on the road again

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- Anne Szarewski (14.5.2012)
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- Julie M Chandler (17.5.2012)

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

…….on the road again

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- Mary E. Gaffield (16.5.2012)
- Julie M Chandler (17.5.2012)
- Anne L Connolly (18.5.2012)

  "…poor studies such as this one…"

…….on the road again

Publication in BMJ on May 10, 2012

- Anne Szarewski (14.5.2012)
- Samuel Shapiro (16.5.2012)
- Mary E. Gaffield (16.5.2012)
- Julie M Chandler (17.5.2012)
- 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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception

Øjvind Lidegaard, Dr. Med. Sci., Ellen Løkkegaard, Ph.D., Aksel Jensen, M.Sc., Charlotte Wessel Skovlund, M.Sc., and Niels Keiding, M.Sc.

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

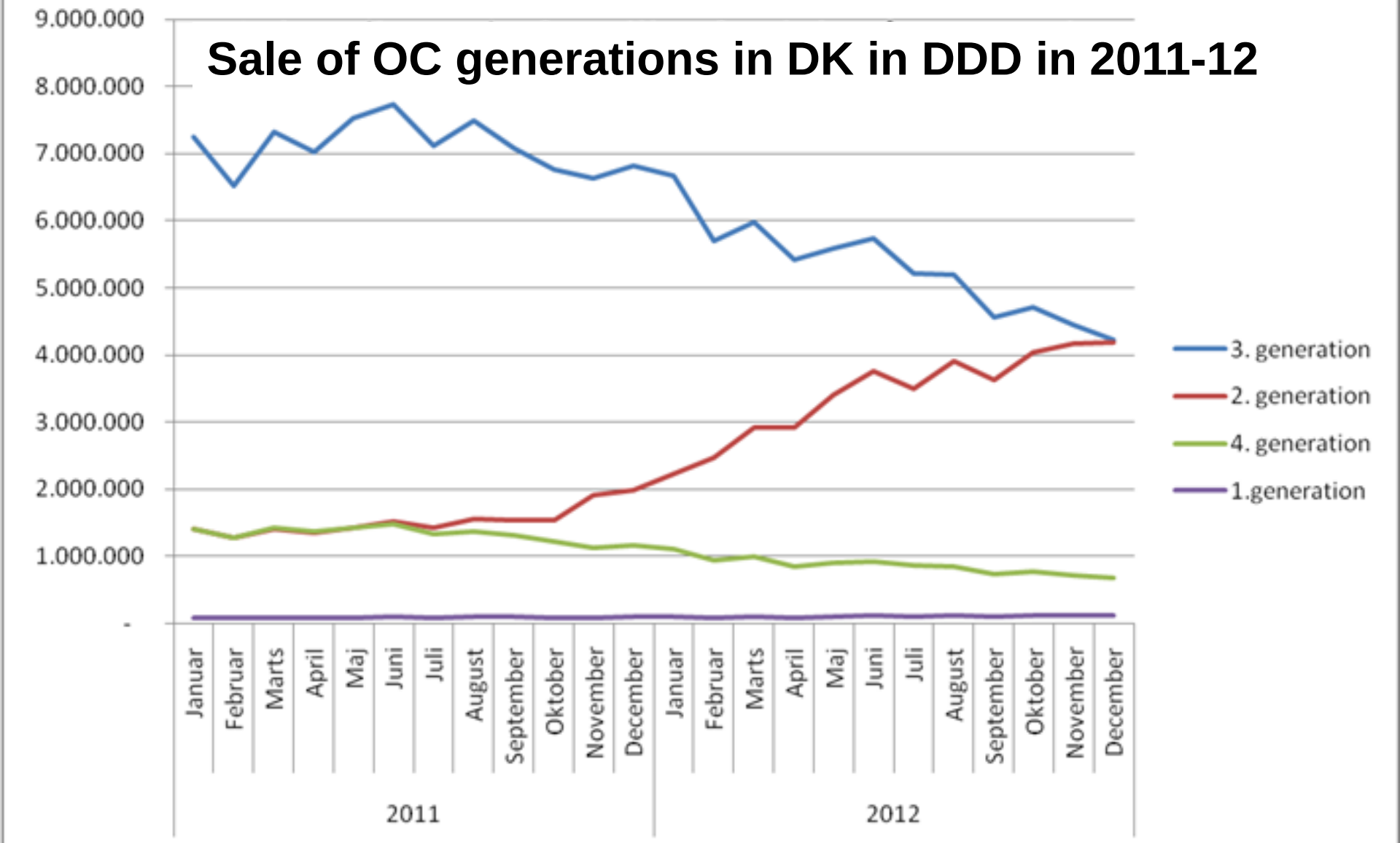
Lidegaard et al. N Engl J Med 2012; 366: 2257-66

HC and thrombotic stroke

No risk <1.5	Low risk 1.5-4	High risk 5-7	Few data	No data

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospi-renone	CPA Cyproterone-acetate
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 oe	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-forsoeg/bivirkninger/nyheder/laeger-foelger-anbefalinger-for-brugen-af-p-piller

Hormonal contraception - age

Young women (<35 years)

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

Women from 35 years or women at risk

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

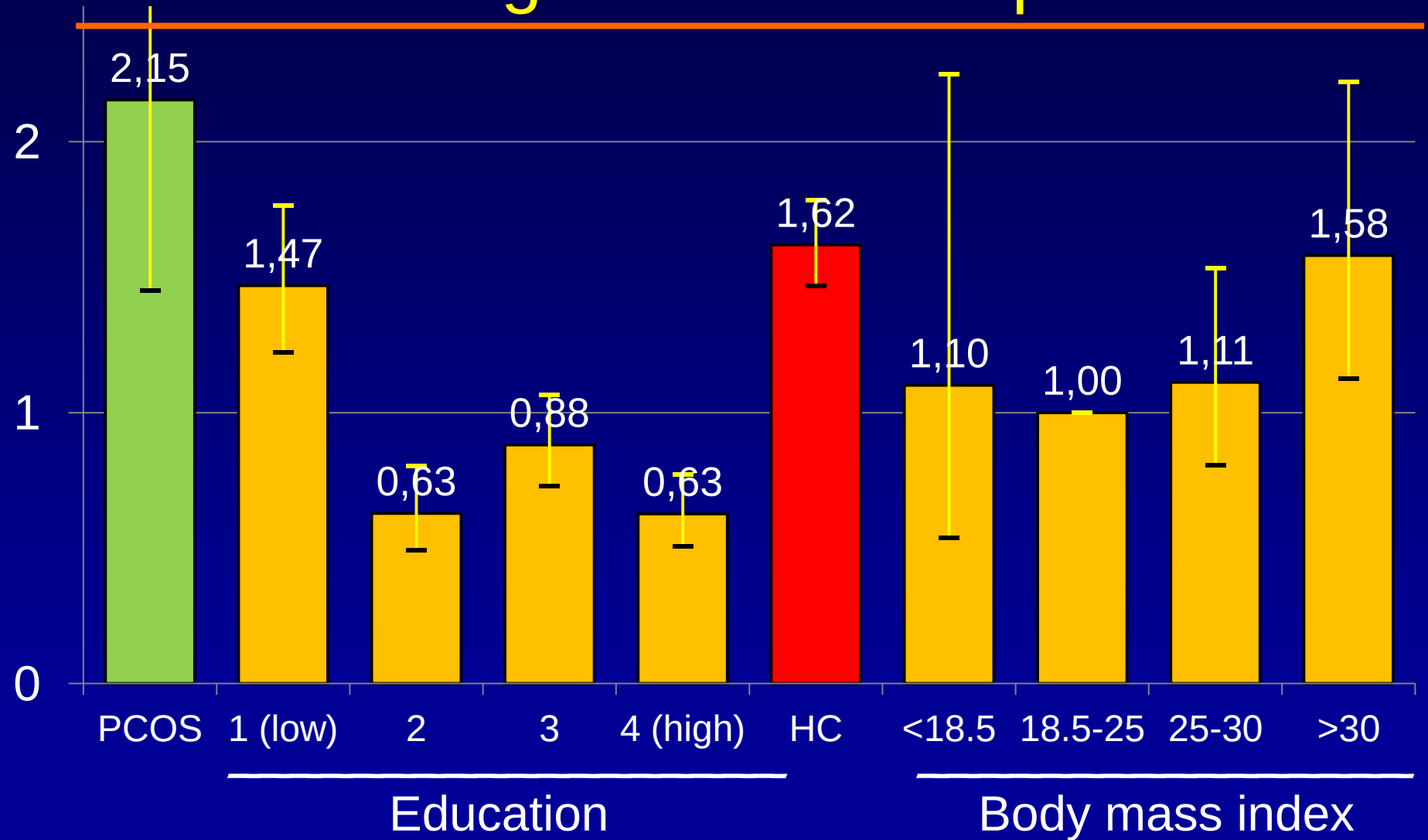
VT: Acquired risk factors

	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

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

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.