Hormonal contraception and thrombosis. An update

Øjvind Lidegaard
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Department of Gynaecology, Rigshospitalet
Faculty of Health Science
University of Copenhagen

Hormonal contraception
How to get an overview?

<u>Combined products</u> (estrogen and progestogen)							
<u>Progestogen only products</u>							

Hormonal contraception
Combined - route

<u>Combined products</u> (estrogen and progestogen)							
Oral							
Non oral							
<u>Progestogen only products</u>							
Oral							
Non oral							

Hormonal contraception
Combined – route – e-dose – e-type

Combined products (estrogen and progestogen)							
Middle							
Low							
Nat e							
N-oral							
Progestogen only products							
Oral							
N-oral							

Hormonal contraception
Combined – route – e-dose – e/p-type

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 e							
N-oral							
Progestogen only products							
Oral							
N-Oral							

Hormonal contraception - generations
Combined – route – e-dose – e/p type

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							
N-oral							

Hormonal contraception
Combined – route – e-dose – e/p type

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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			

Hormonal contraception and venous thrombosis. Seven axes of significance

- Combined versus progestogen only
- Route of administration
- Progestogen type
- Estrogen dose
- Estrogen type (natural vs artificial)
- Duration of use (found for 2nd generation)
- 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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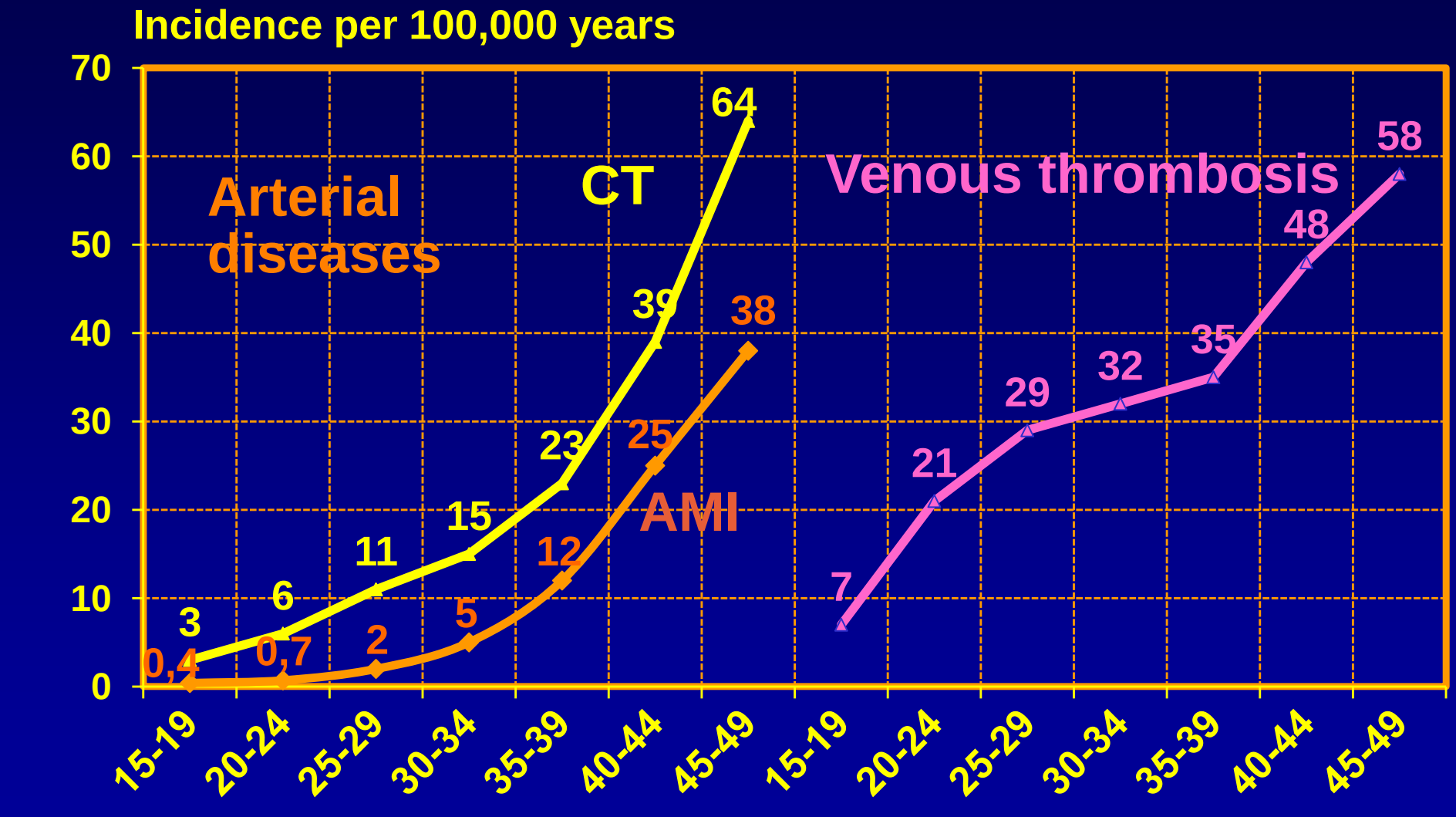
Medical diseases	5%?	2-5

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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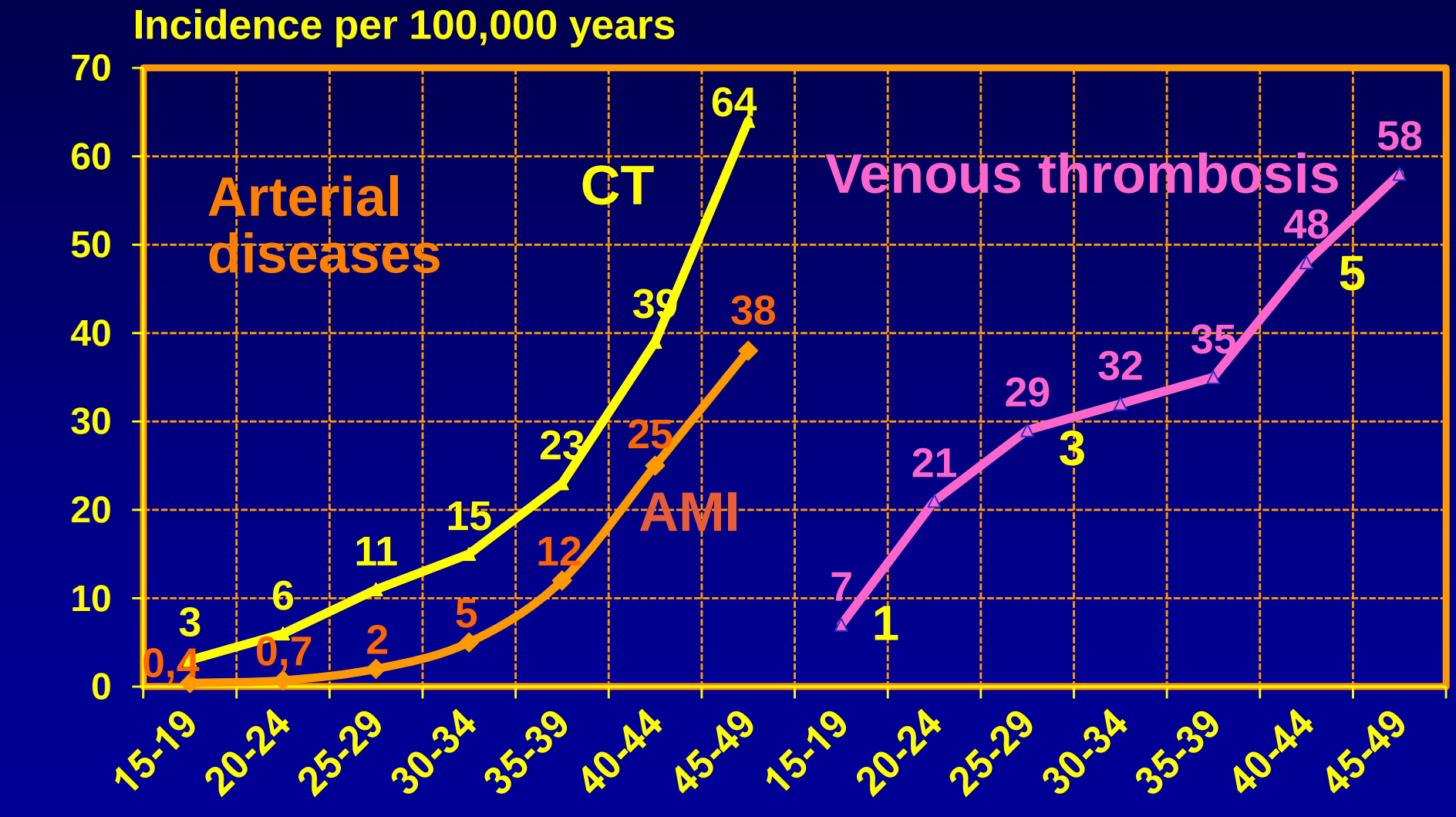

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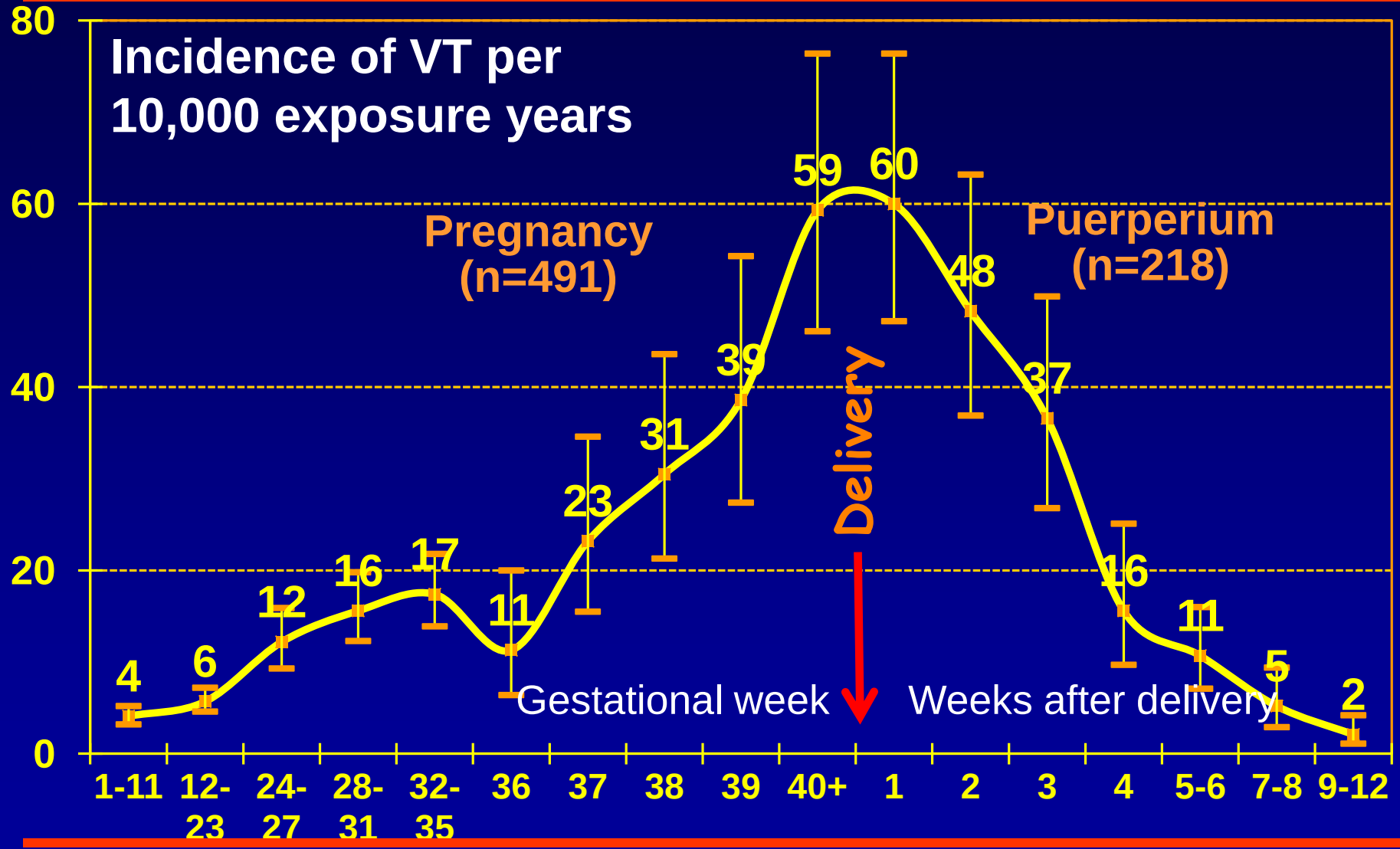
Medical diseases	5%?	2-5

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



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

Li/12

1st myth: HC vs pregnancy

Age	Exposure	VTE/10,000 years
30	pregnancy, 1st trim	3
30	pregnancy, 2nd trim	4
30	pregn, birth, puerp:	8
20	low risk pill (2nd gen)	3
20	high risk pill (3rd, 4th)	6
30	low risk pill	9
30	high risk pill	18

Conclusion: The risk of VTE is *higher* with HC than with pregnancy.

VT: Acquired risk factors

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Danish infrastructure

National Health Registry (>1977)

VT diagnoses, BMI

CaVD/canc. smoking

Pregnancies, surgery

Danish infrastructure

National Health Registry (>1977)

VT diagnoses, BMI

CaVD/canc. smoking

Pregnancies, surgery

Prescription Registry (>1994): HC use

Medication against hypertension↑, DM, hyperlipidaemia

Danish infrastructure

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1995 → 2014

Cause of Deaths Registry (>1977)

Lethal VT

Statistics of Denmark

PIN-codes, education

vital status, emigration

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/???

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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
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Lidegaard[09]	4.213	7.8	1.6 (1.3-2.1)	4th/2nd

Expert Meeting on the
Benefits and Risks of Oral Contraceptives

Saturday, 12 December 2009, 11am to 4 pm

Maritim Pro Arte Hotel, Friedrichstrasse 151, Berlin

Faculty:

Prof. Corinne de Vries Dept Pharmacy & Pharmacology, Bath Univ, UK

Dr. Jürgen Dinger

Dr. Diana Mansour Gynaecologist, Contraception and sexual health Newcastle,

Prof. Samuel Shapiro

Dr. Anne Szarewski Clinical Officer family planning, Margaret Pyke, UK

Dr. Carolyn L. Westhoff Director, division of Family Planning and Preventiv

Invitation sent out by Bayer in November 2009

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)

OC and VT: Methods

National Registry of Patients (>1977)

VT diagnoses, BMI

CaVD/canc. Smoking

Pregnancies, surgery

Prescription Registry (>1994): HC use

Medication against hypertension, DM, hyperlipidaemia

1995 → 2005

Cause of Deaths Registry (>1977)

Lethal VT

Statistics Denmark

PIN-codes, education

vital status, emigration

Lidegaard et al. BMJ 2009

VT and drospirenone

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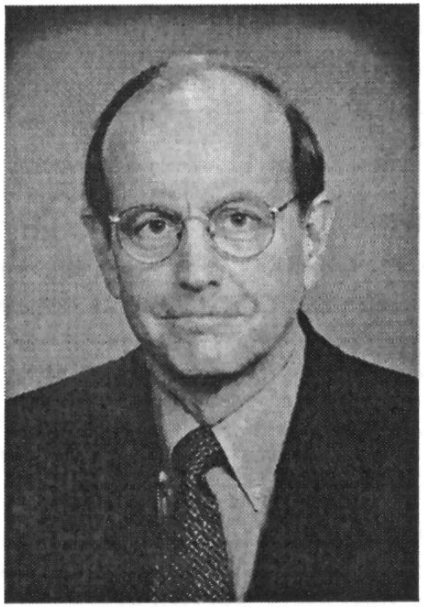
An Editor

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.

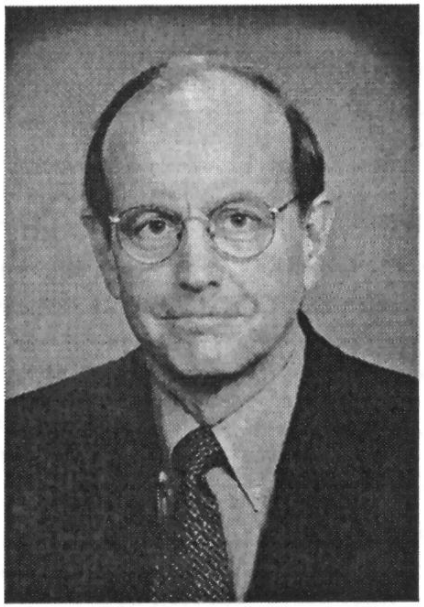
In recent decades, the computer science concept of "GIGO" ("garbage in, garbage out") has somehow come to mean "garbage in, gospel out[10]." When computer software tackles a large database, many accept the "computerized" output as trustworthy, regardless of the quality of the input. Sadly, no fancy statistical 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

An editor

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.

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

OC and VT: Methods

National Registry of Patients (>1977)

VT diagnoses,

Previous CaVD/canc.

Pregnancies, surgery

Prescription Registry (>1995): HC use

Anticoagulation therapy

hypertension, DM,

Hyperlipidaemia

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
Lidegaard[11]	4,246	9.3	2.1 (1.6-2.8) 4th/2nd

IR = incidence per 10,000 women years

VT and drospirenone

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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 Shapiro[2]

[1]Director, ZEG - Berlin Center for Epidemiology and Health Research, Berlin, Germany
[2]Visting Professor of Epidemiology, Department of Epidemiology, University of Cape Town, Cape Town, South Africa

Correspondence to
Dr Jürgen Dinger, ZEG - Berlin Center for Epidemiology and Health Research, Invalidenstrasse 115, 10115 Berlin, Germany; dinger@zeg-berlin.de

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'.

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 relative risk of VTE

No risk <1.5	Low risk 1.5-4	High risk >4	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**			

…….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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  “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…"

…….on the road again

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- 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"

VT and drospirenone/LNG

	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

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@mweb.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.

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

VT and drospirenone/LNG

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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
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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
Dinger[14]	123	7.2	0.8 (0.5-1.6) 4th/2nd

May 2015: New English study

Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases

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Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmj.h2135)

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doi: 10.1136/bmj.h2135

Accepted: 19 March 2015

ABSTRACT

OBJECTIVE

To investigate the association between use of combined oral contraceptives and risk of venous thromboembolism, taking the type of progestogen into account.

DESIGN

Two nested case-control studies.

SETTING

General practices in the United Kingdom contributing to the Clinical Practice Research Datalink (CPRD; 618 practices) and QResearch primary care database (722 practices).

PARTICIPANTS

Women aged 15-49 years with a first diagnosis of venous thromboembolism in 2001-13, each matched with up to five controls by age, practice, and calendar year.

MAIN OUTCOME MEASURES

Odds ratios for incident venous thromboembolism and

confidence interval 2.78 to 3.17) compared with no exposure in the previous year. Corresponding risks associated with current exposure to desogestrel (4.28, 3.66 to 5.01), gestodene (3.64, 3.00 to 4.43), drospirenone (4.12, 3.43 to 4.96), and cyproterone (4.27, 3.57 to 5.11) were significantly higher than those for second generation contraceptives levonorgestrel (2.38, 2.18 to 2.59) and norethisterone (2.56, 2.15 to 3.06), and for norgestimate (2.53, 2.17 to 2.96). The number of extra cases of venous thromboembolism per year per 10 000 treated women was lowest for levonorgestrel (6, 95% confidence interval 5 to 7) and norgestimate (6, 5 to 8), and highest for desogestrel (14, 11 to 17) and cyproterone (14, 11 to 17).

CONCLUSIONS

In these population based, case-control studies using two large primary care databases, risks of venous thromboembolism associated with combined oral contraceptives were, with the exception of norgestimate, higher for newer drug preparations than for second generation drugs.

Vinogradova 2015

VTE confirmed	Vinogradova
Non use	1 reference
COC levonorgestrel	3.0 (2.6-3.3)
COC norgestimate	3.5 (2.9-4.4)
COC desogestrel	6.2 (5.0-7.7)
COC gestodene	6.5 (5.0-8.4)
COC drospirenone	6.1 (4.7-7.8)
COC cyproterone	6.0 (4.7-7.7)

Vinogradova et al. BMJ 2015; 350: h2135

Vinogradova vs Lidegaard

VTE confirmed	Vinogradova	Lidegaard
Non use	1 reference	1 reference
COC levonorgestrel	3.0 (2.6-3.3)	3.0 (2.2-4.0)
COC norgestimate	3.5 (2.9-4.4)	3.5 (2.9-4.3)
COC desogestrel	6.2 (5.0-7.7)	6.6 (5.6-7.8)
COC gestodene	6.5 (5.0-8.4)	6.2 (5.6-7.0)
COC drospirenone	6.1 (4.7-7.8)	6.4 (5.4-7.5)
COC cyproterone	6.0 (4.7-7.7)	6.4 (5.1-7.9)

Vinogradova et al. BMJ 2015; 350: h2135
Lidegaard et al. BMJ 2011; 343: d6423

VT and drospirenone/LNG

	VT	IR[4]	Rate ratio	
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
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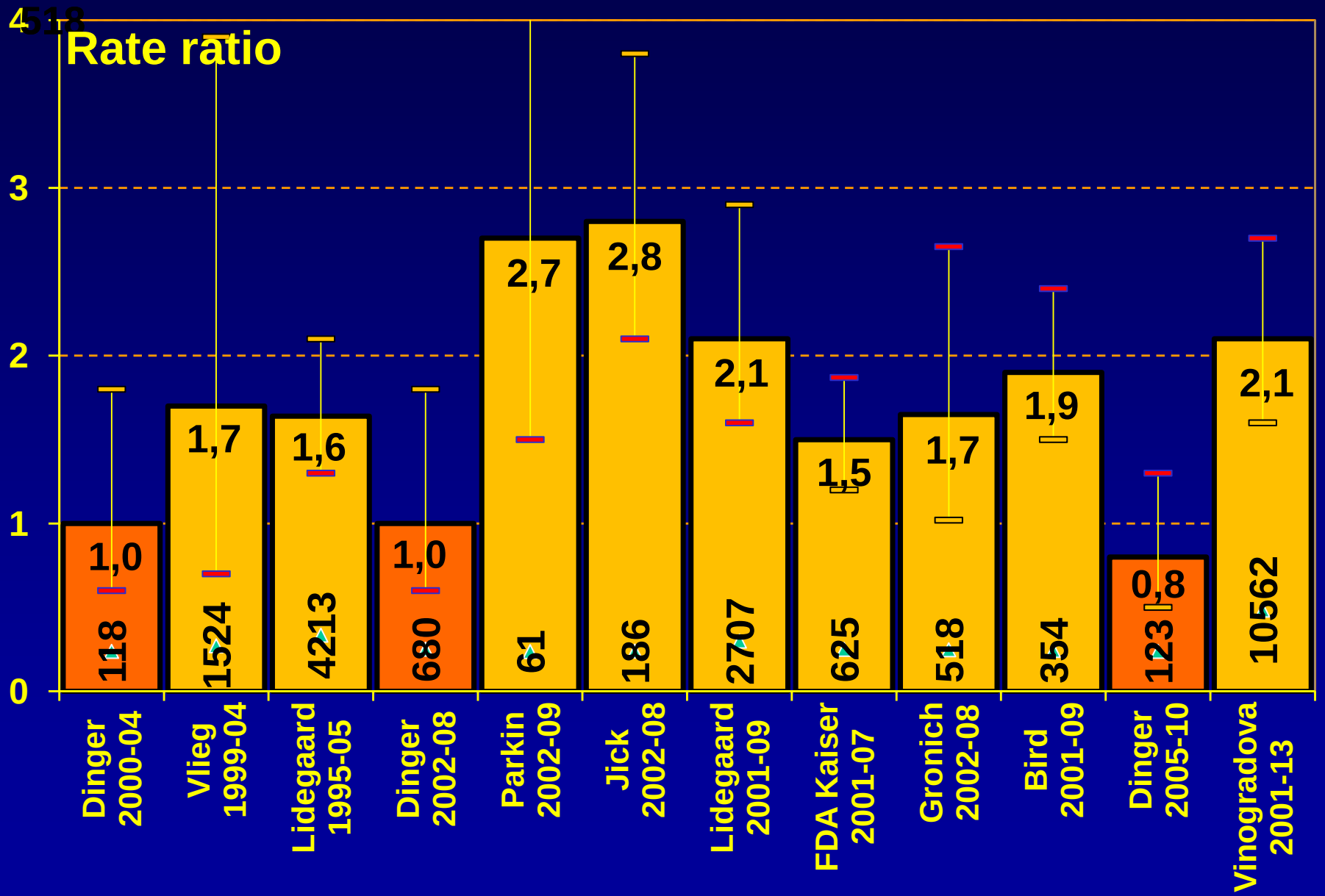
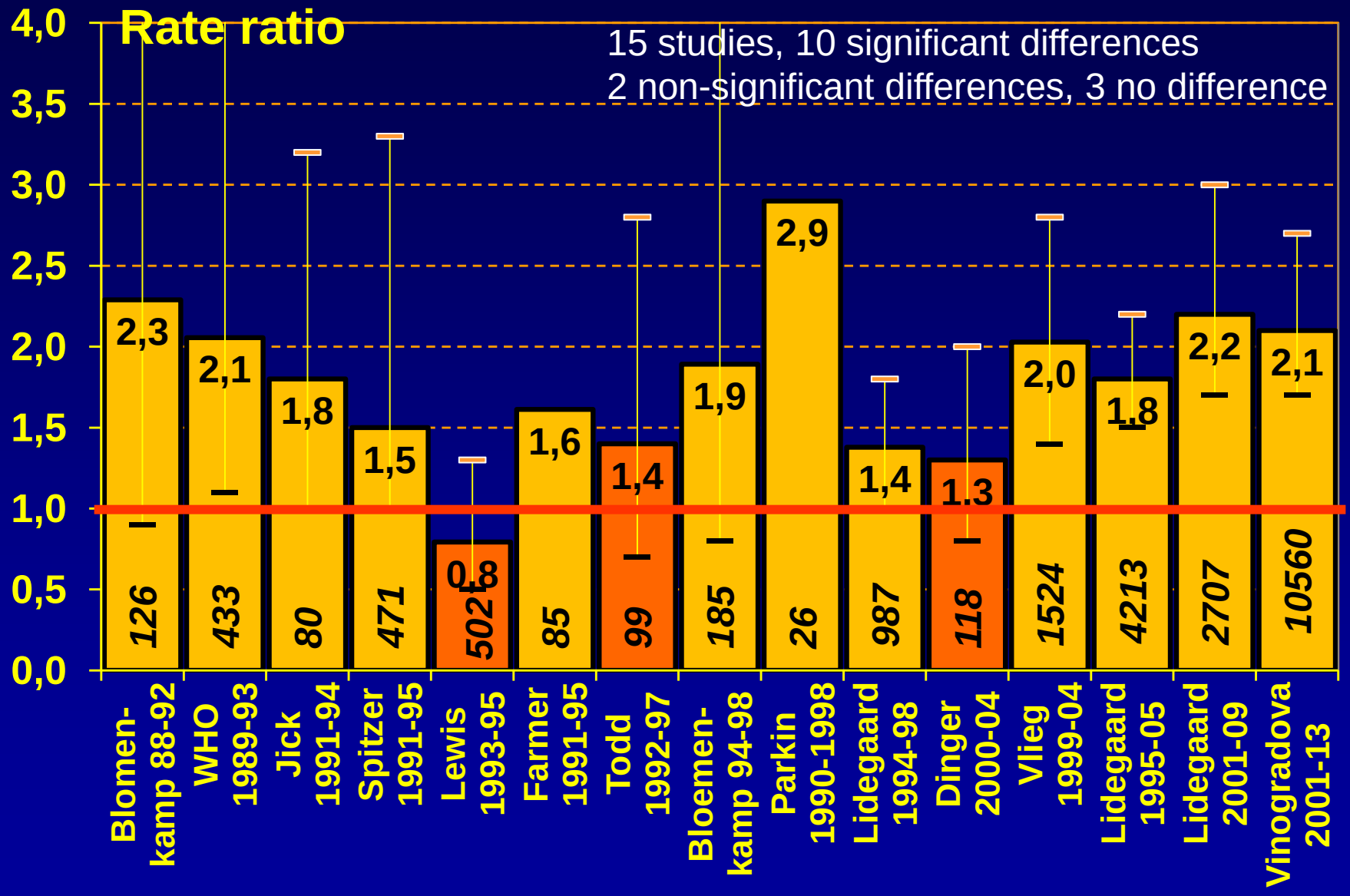
Bird[13]	354	18.0	1.9 (1.5-2.4)	4th/2nd
Dinger[14]	123	7.2	0.8 (0.5-1.6)	4th/2nd
Vinogradova[15]	10,562	na	2.1 (1.6-2.7)	4th/2nd

COC with DRSP vs LNG



3rd versus 2nd generation COC

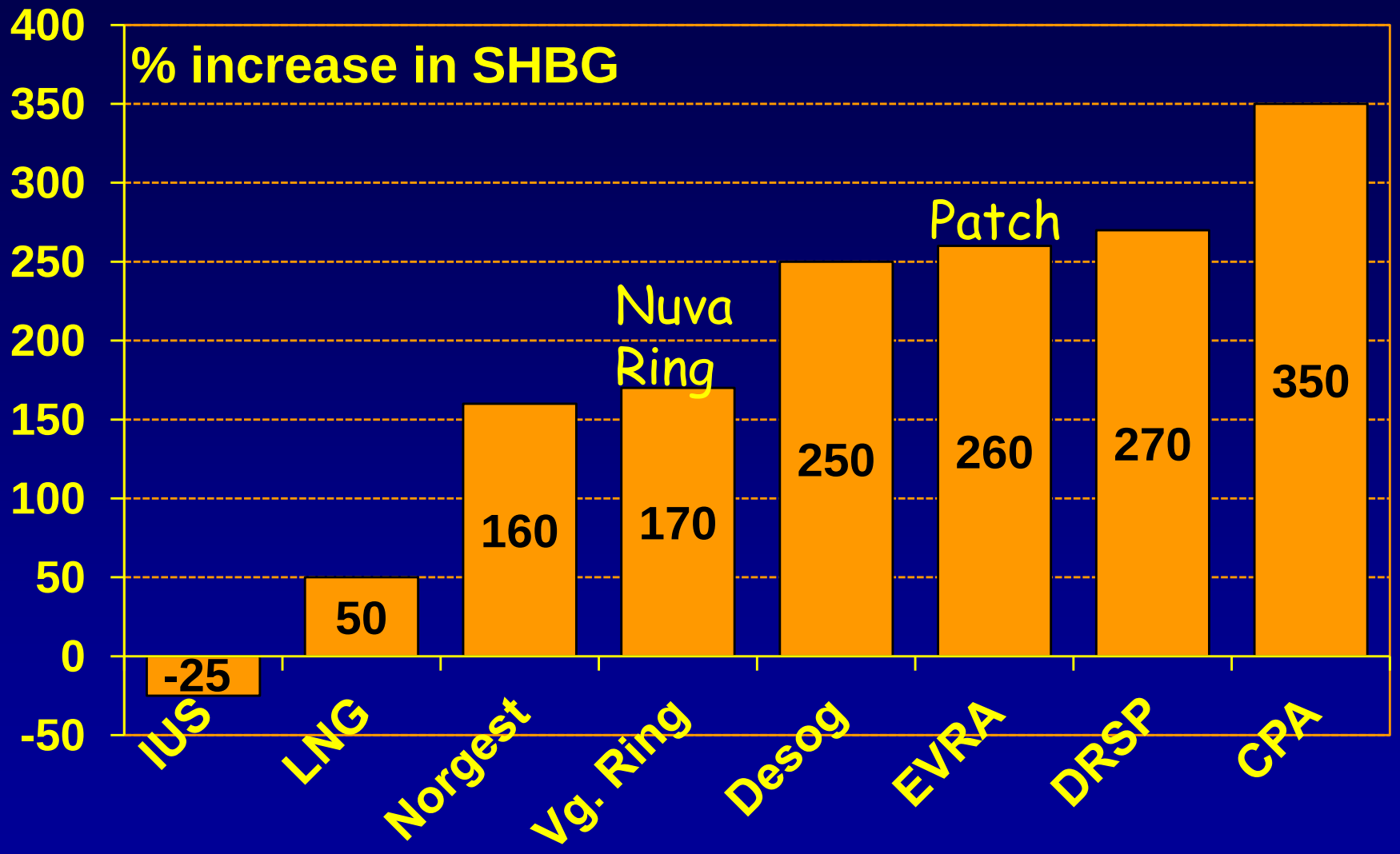


HC and RR of VTE: Conclusion

No risk <1.5	Low risk 1.5-4	High risk >4	Few data	No data

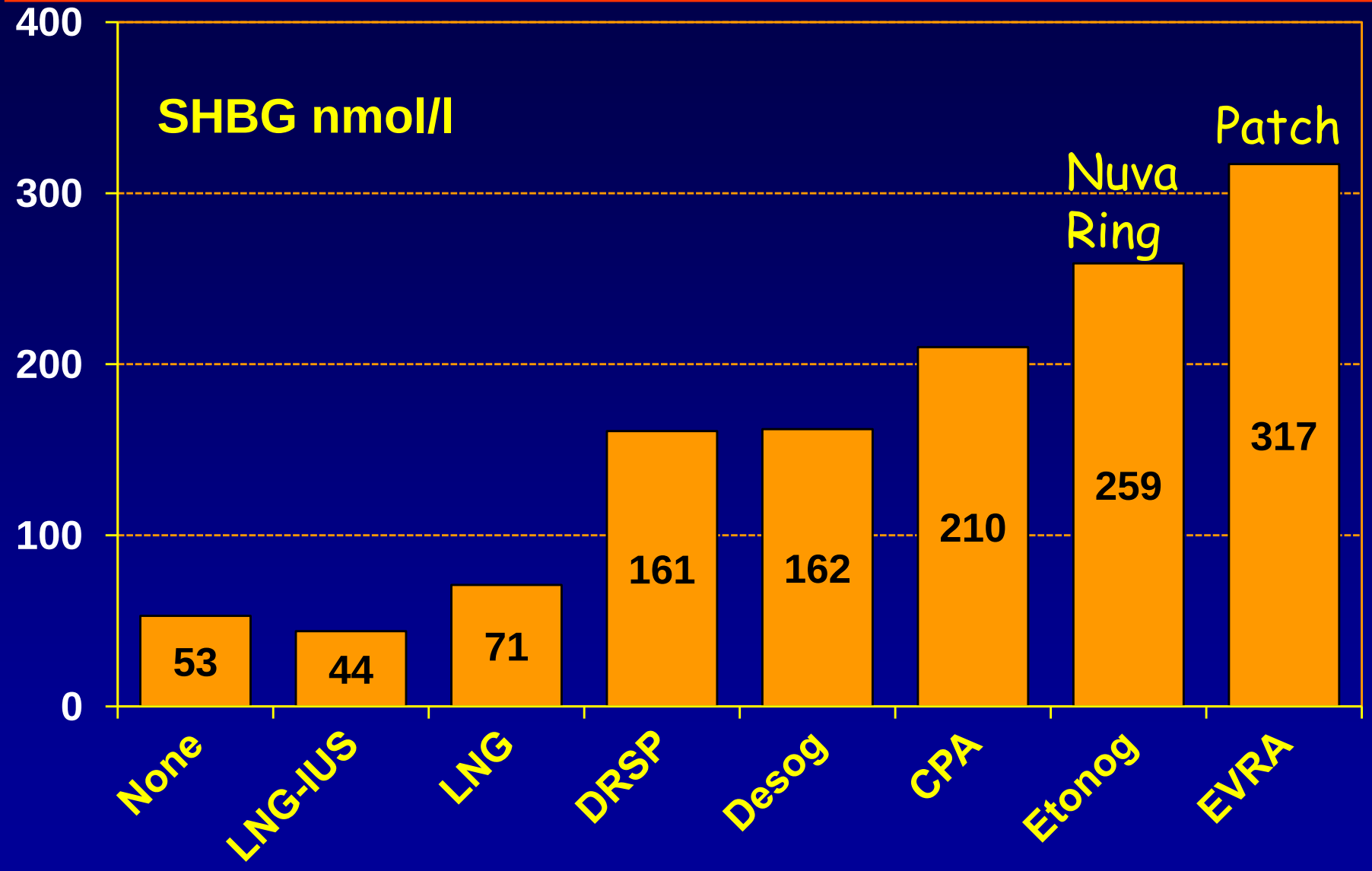
EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospire-none	CPA Cyproterone-acetate
Combined products							
Middle	3	3		6		6	6
Low		2.5?		5			
Nat oe		E2V-DNG **4.5**			E2 NOMAC		
N-oral			Patch **7**	Vaginal ring **6**			
Progestogen only products							
Oral	POP **1**			Cerazette **1**			
N-oral	Depot **1**	IUS **1**		Implant **1.4**			

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

Statement on combined hormonal contraceptives containing third- or fourth-generation progestogens or cyproterone acetate, and the associated risk of thromboembolism

Johannes Bitzer

Cosignatories

Jean-Jacques Amy,[1] Rob Beerthuizen,[2] Martin Birkhäuser,[3] Teresa Bombas,[4] Mitchell Creinin,[5] Philip D Darney,[6] Lisa Ferreira Vicente,[7] Kristina Gemzell-Danielsson,[8] Bruno Imthurn,[9] Jeffrey T Jensen,[10] Andrew M Kaunitz,[11] Ali Kubba,[12] Medlard M Lech,[13] Diana Mansour,[14] Gabriele Merki,[15] Thomas Rabe,[16] Katarina Sedlecki,[17] David Serfaty,[18] Jacques Seydoux,[19] Lee P Shulman,[20] Regine Sitruk-Ware,[21] Sven O Skouby,[22] Anne Szarewski,[23] James Trussell,[24] Carolyn Westhoff[25]

Bitzer et al. Contraception 2013; J Fam Plann Reprod Health 2013

SUMMARY OF THE CURRENT EVIDENCE CONCERNING THE RISK OF VTE

The inherent inability of database studies to adequately control for baseline confounders render this design less suitable for providing further clarification.

Some epidemiologists question whether the RR increase of around 2 described in the aforementioned case-control studies reflects a clinically relevant difference.

Several studies have shown that the risk of VTE during pregnancy and the postpartum period is considerably higher (29–300 per 10 000 users) than during use of a CHC.[21]

Bitzer et al. Contraception 2013; J Fam Plann Reprod Health 2013

Dinger versus Lidegaard

Inclusion of potential confounders	Dinger	Lidegaard
Age	Yes	Yes
Education	No	Yes
Length of use	Yes	Yes
Oestrogen dose	No	Yes
Ovarian stimulation	No	Yes
Major surgery	No	Yes
BMI	Yes	No
Family disposition	No	No

2nd myth: Confounders

- The Danish registry studies are not only the studies with the most detailed and most valid exposure data.
- The studies also include and control for more potential confounders than any other study conducted on HC and venous thrombosis.

SUMMARY OF THE CURRENT EVIDENCE CONCERNING THE RISK OF VTE

The inherent inability of database studies to adequately control for baseline confounders render this design less suitable for providing further clarification.

Some epidemiologists question whether the RR increase of around 2 described in the aforementioned case-control studies reflects a clinically relevant difference.

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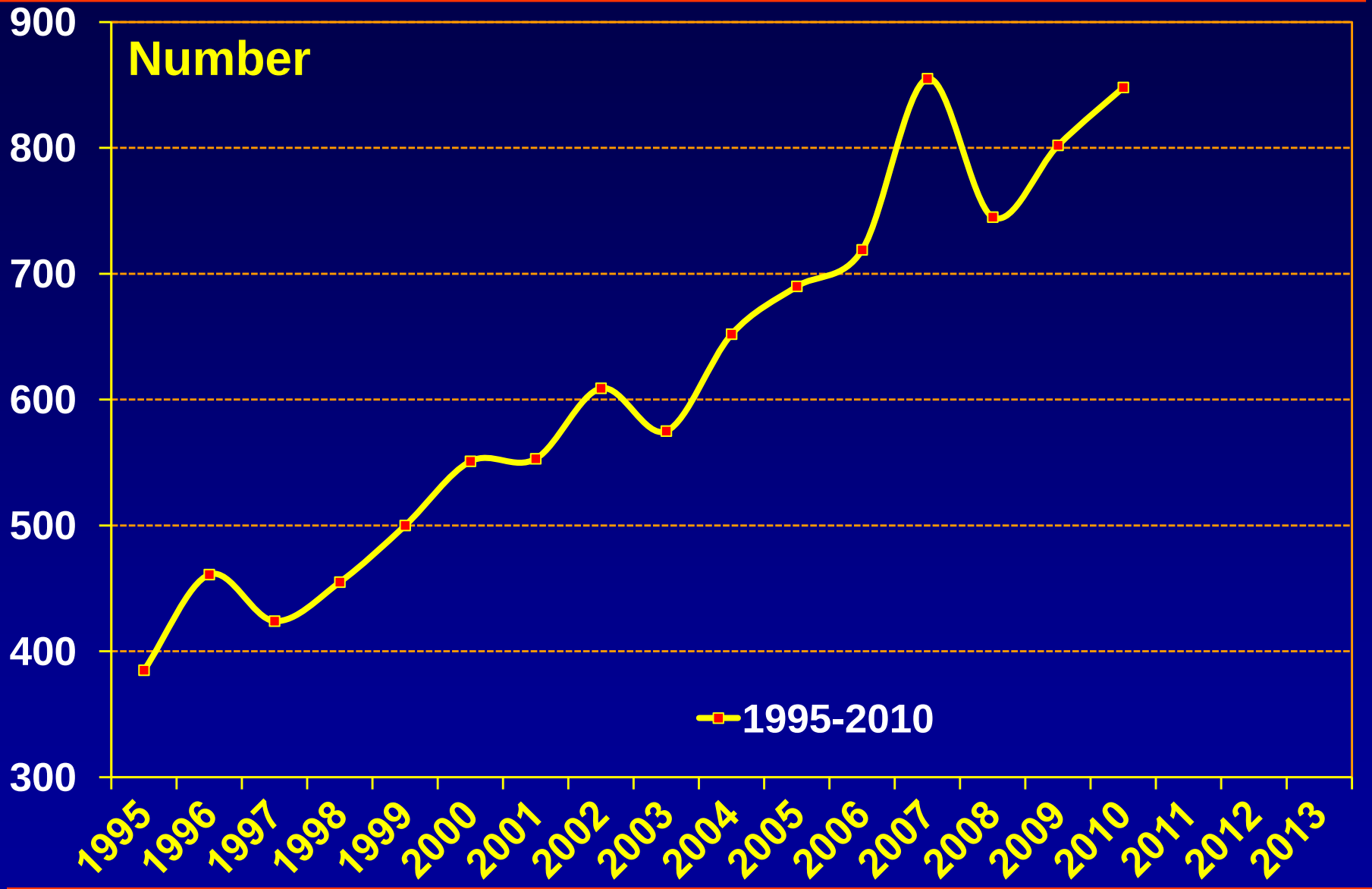
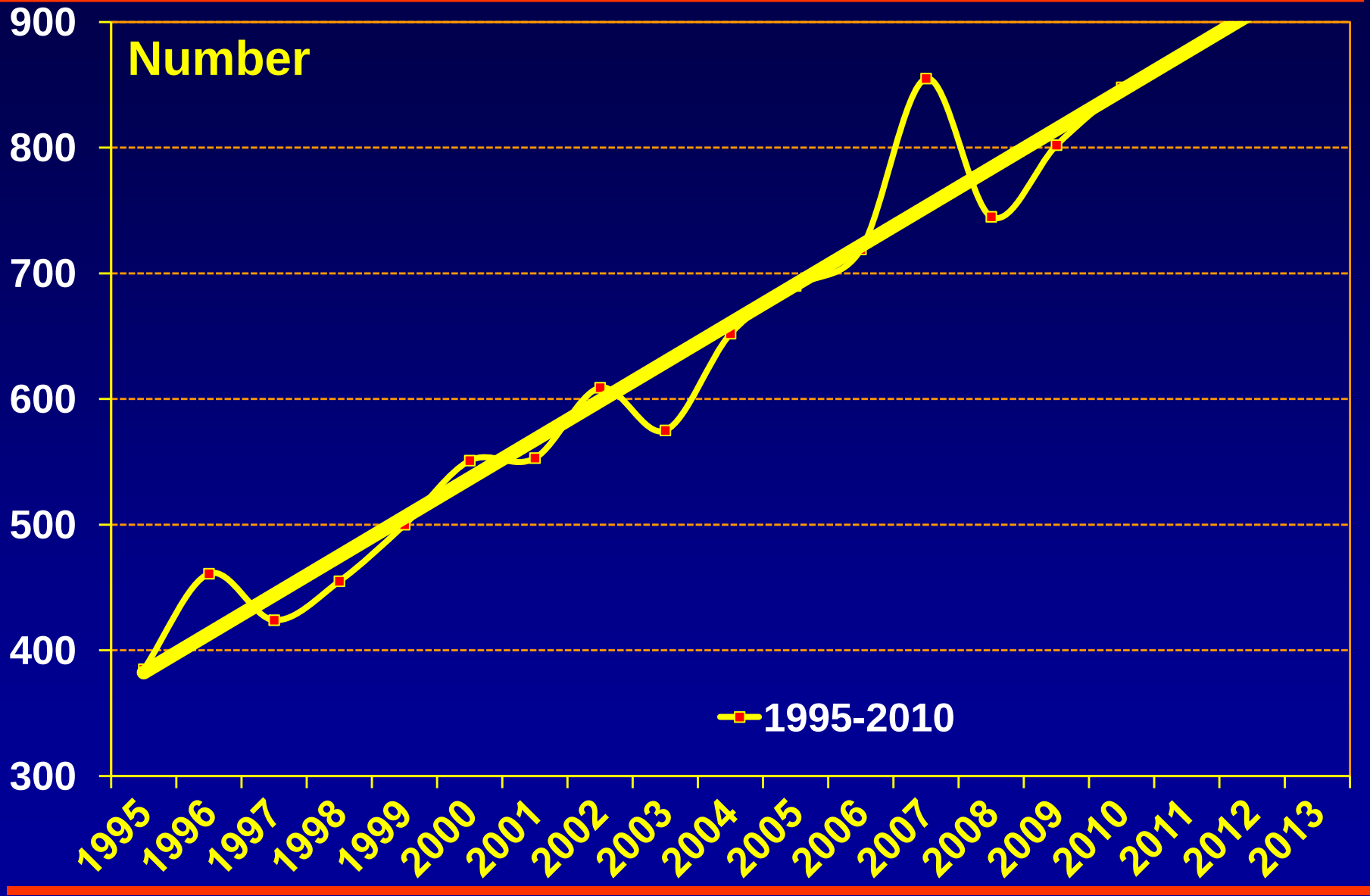
Bitzer et al. Contraception 2013; J Fam Plann Reprod Health 2013

First ever VTE, women 15-49



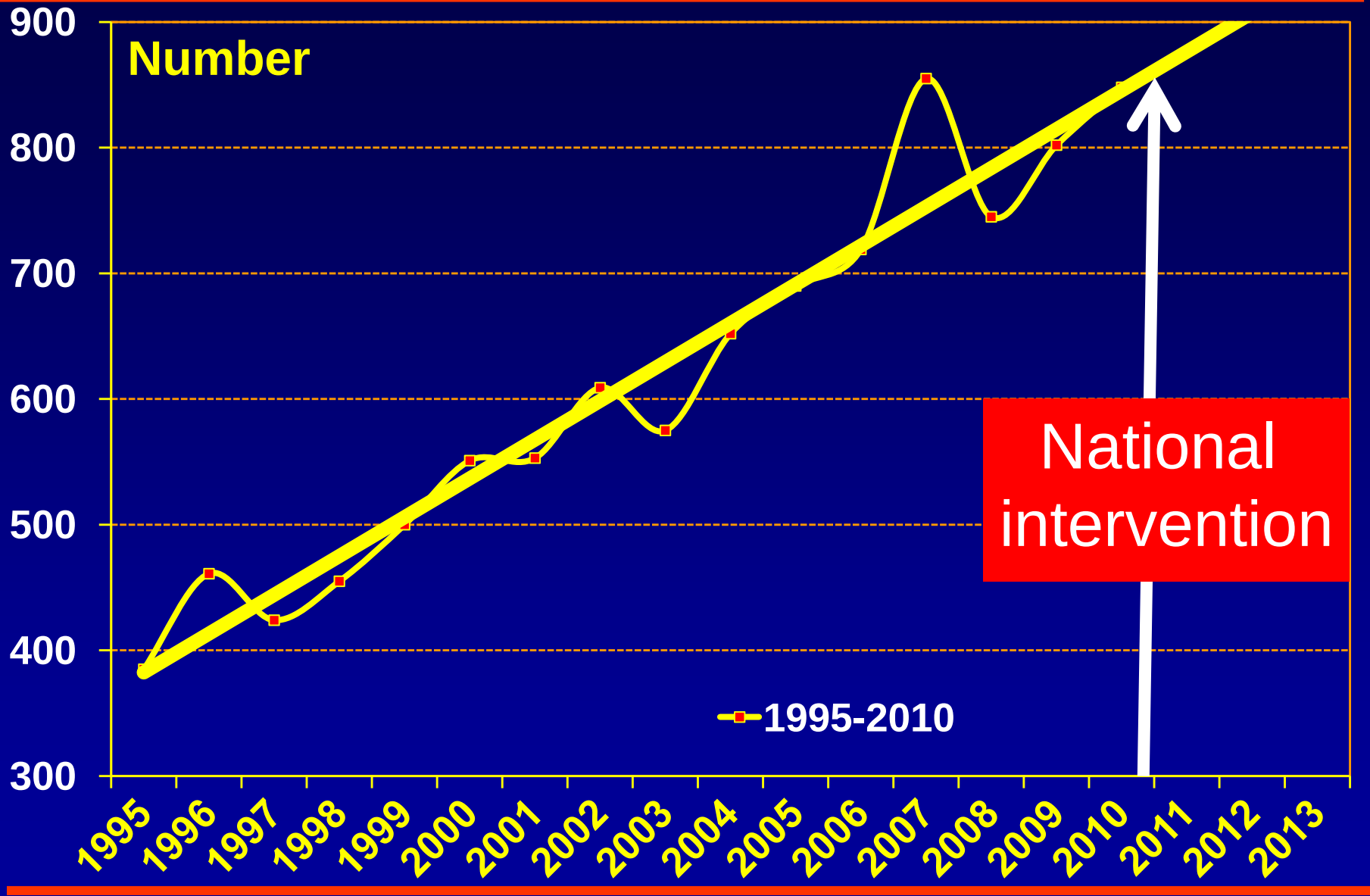
National Health Registry, Denmark

First ever VTE, women 15-49



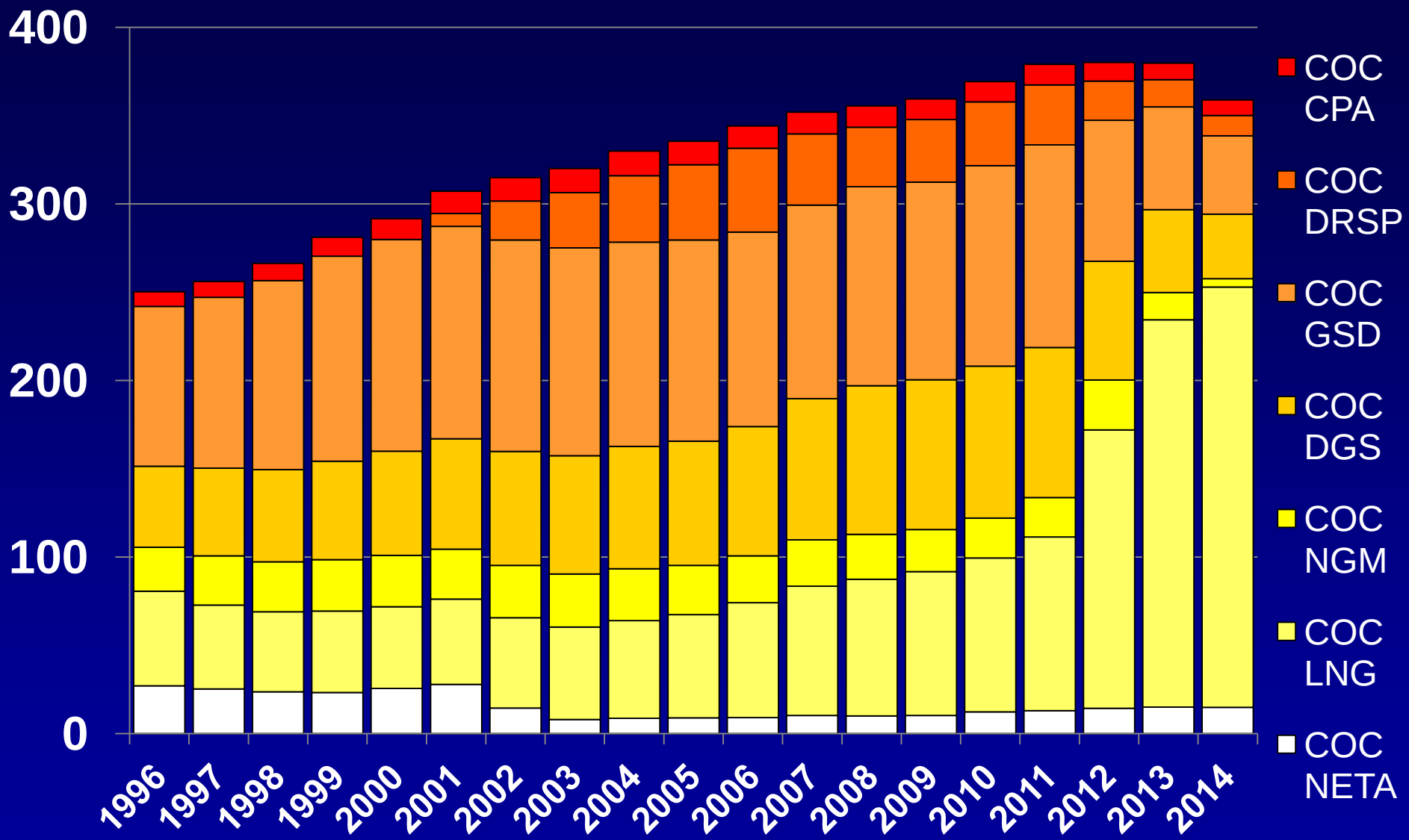
National Health Registry, Denmark

First ever VTE, women 15-49



National Health Registry, Denmark

Sale of COC in DK acc to progestogen 1996-2014

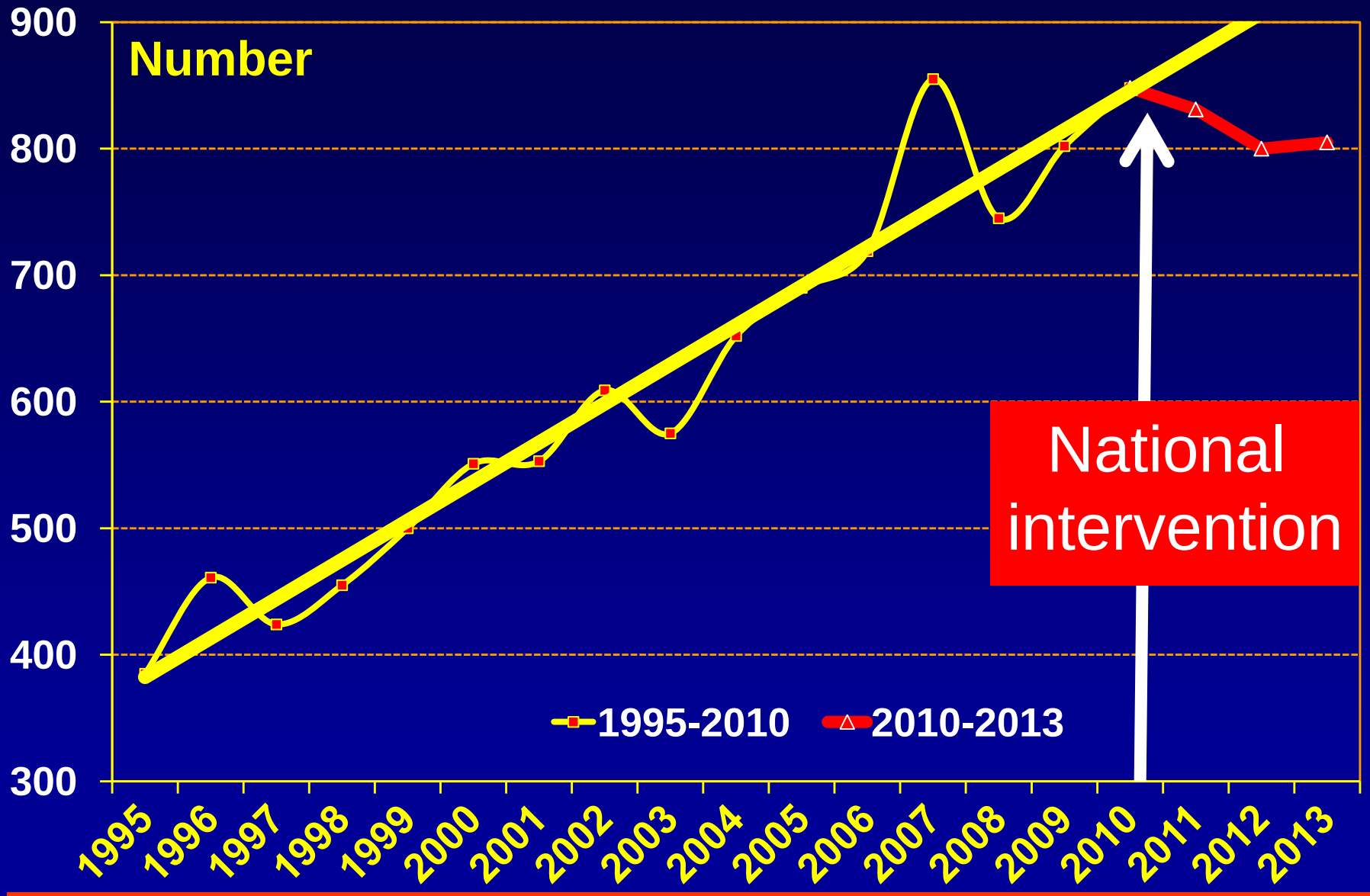


National Prescription Registry, Denmark 1996-2014

3rd myth: Pill scares

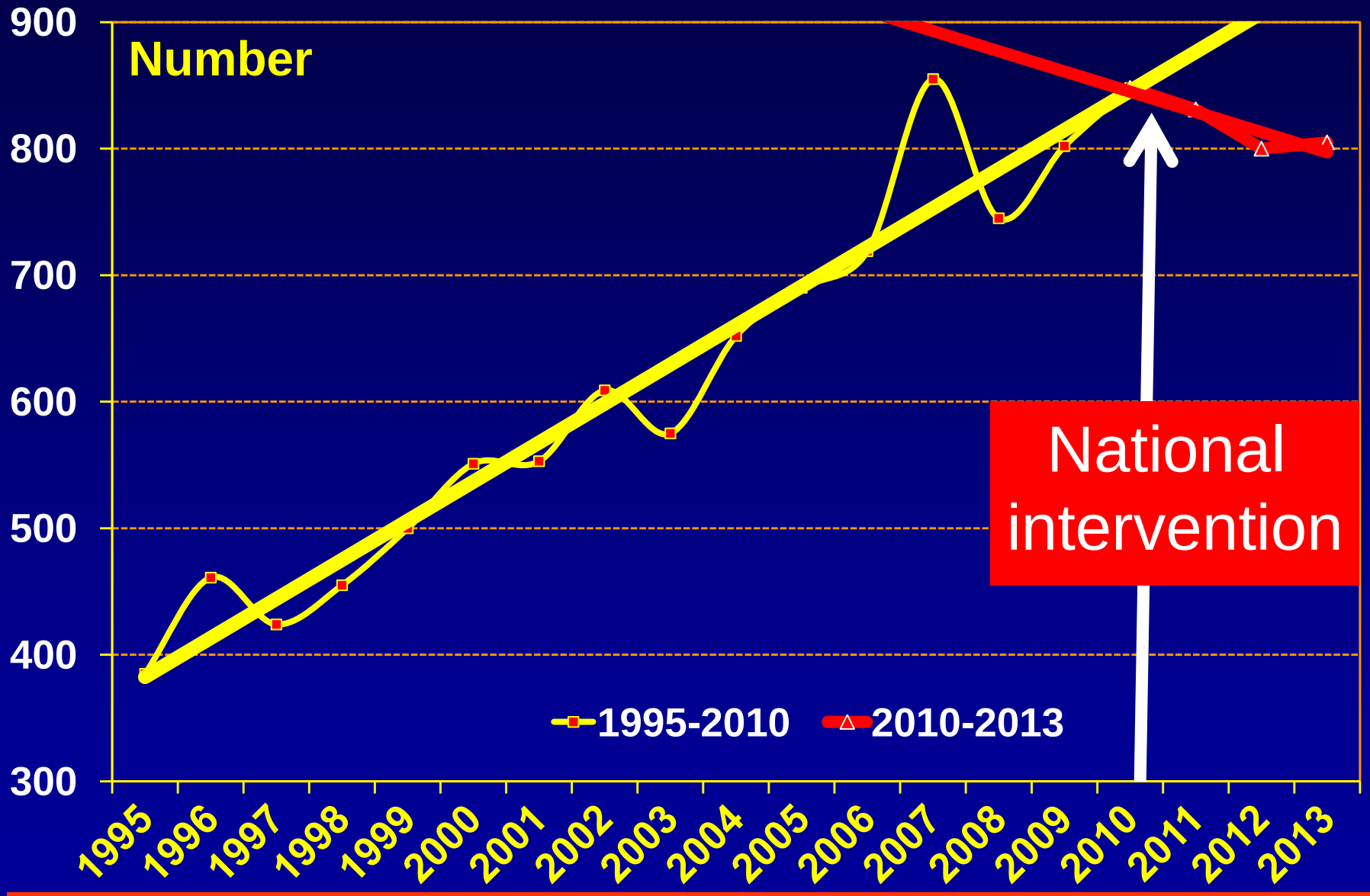
- An appropriate information about thrombotic risks with different product types is mandatory in order to
- Ensure the lowest possible risk of VTE
- Ensure immediate action in case of an event
- Such sober information does not cause a new pill scar, but contrary keeps people's confidence in advices from experts
- Hiding or manipulating scientific evidence has been responsible for all serious pill scares in the past.

First ever VTE, women 15-49



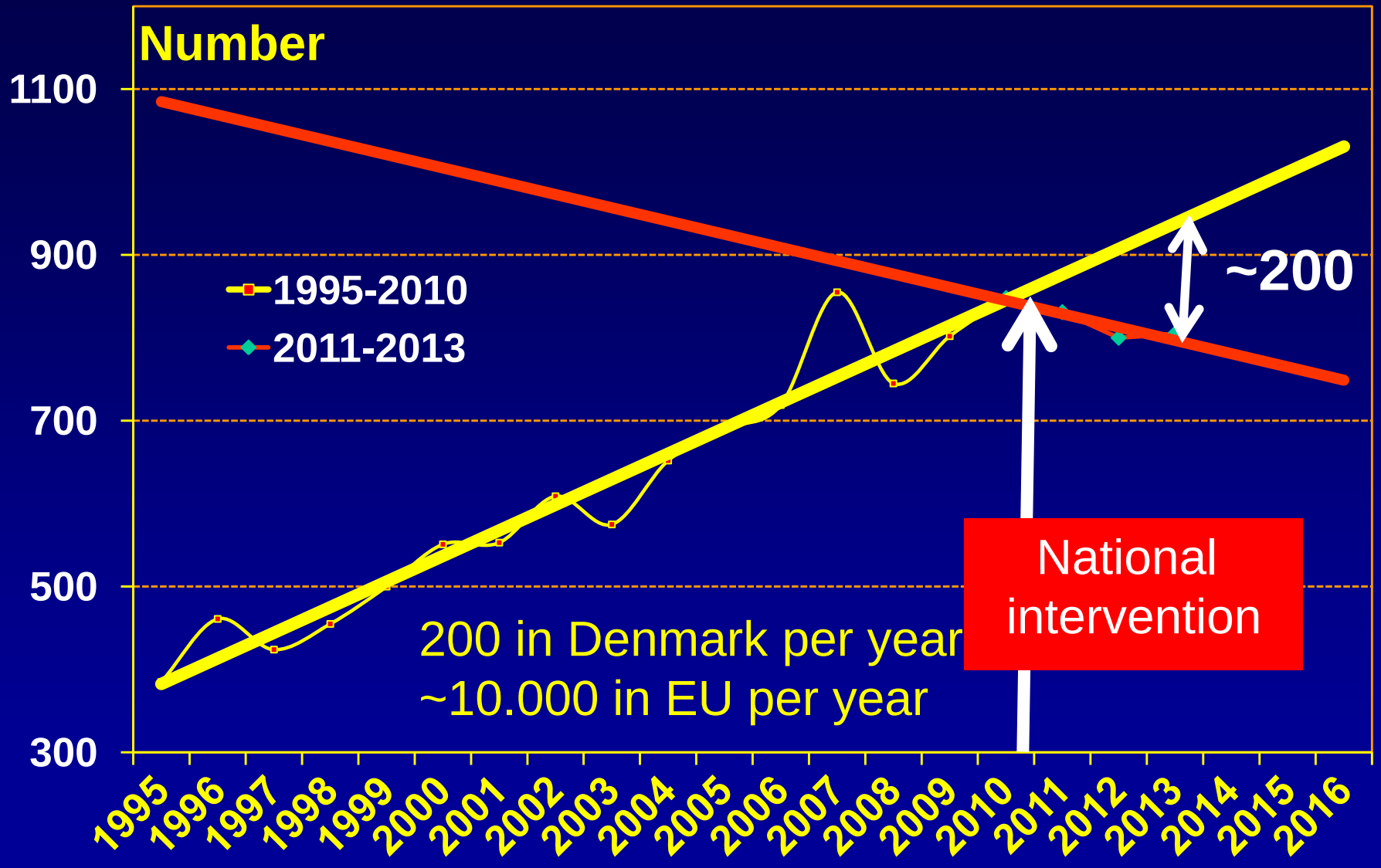
National Health Registry, Denmark

First ever VTE, women 15-49



National Health Registry, Denmark

First ever VTE, women 15-49



National Health Registry, Denmark

An appropriate practice

- Scientists have to reach consensus
- Health authorities should update their recommendations
- The press should inform the public without overdramatizing the scientific evidence
- The general practitioners should follow the updated recommendations.
- Women should be informed about the symptoms of VT to ensure immediate action

Lidegaard, Expert Opinion Drug Safety 2014: 13: 1353-60

IPPF

From choice, a world of possibilities

February 2013

IMAP= International Medical Advisory Panel

IPPF Medical Bulletin

IMAP Short Statement on the Safety of Third and Fourth Generation Oral Contraceptives

Based on the analysis conducted by the United States Food and Drugs Administration (FDA) (2013) and the recommendations contained on the publications "Family Planning: a Global Handbook for Providers" by WHO (2011) and Medical Eligibility Criteria (WHO, 2010),[i] IMAP Members provide guidance to IPPF's Member Associations on the safety of third and fourth generation oral contraceptives. This statement is developed in response to recent public alarm in European countries, where women sued manufacturers for potential fatal blood clots (Venous Thromboembolism) as a result of using Meliane (Gestodene-containing oral contraceptive pill). The conclusions presented below do not apply to implants, IUS or other products containing the active components in third and fourth generation oral contraceptives.

What are third and fourth generation

What is Venous Thromboembolism

The term venous thromboembolism (VTE) refers to both deep vein thrombosis (DVT) – a blood clot in one of the deep veins of the body; and pulmonary embolism – a blood clot that travels through the bloodstream and lodges in one of the lungs.

Evidence on third and fourth generation pills

- Recent epidemiological studies reviewed by the FDA have not shown the magnitude of increased risk of Venous Thromboembolism (VTE) reported in earlier studies as a result of using third and fourth generation oral contraceptives[ii].
- Earlier studies reporting increased risk of VTE produced conflicting results and had methodological limitations that call into question the validity of their findings and conclusions about the magnitude of the additional risk associated with using these products.
- Changes in the results of coagulations tests as a result of using third and fourth generation oral contraceptives suggested in earlier studies have not been shown to be directly responsible

Evidence on third and fourth generation pills

- Recent epidemiological studies reviewed by the FDA have not shown the magnitude of increased risk of Venous Thromboembolism (VTE) reported in earlier studies as a result of using third and fourth generation oral contraceptives[ii].
- Earlier studies reporting increased risk of VTE produced conflicting results and had methodological limitations that call into question the validity of their findings and conclusions about the magnitude of the additional risk associated with using these products.

Grimes on the road again

Human Reproduction, Vol.0, No.0 pp. 1–4, 2015
doi:10.1093/humrep/dev151

human reproduction

INVITED COMMENTARY

Epidemiologic research with administrative databases: red herrings, false alarms and pseudo-epidemics

David A. Grimes*

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*Correspondence address. Tel: +1-919-656-7227; E-mail: david_grimes@med.unc.edu

Submitted on May 13, 2015; resubmitted on May 13, 2015; accepted on June 1, 2015

Grimes. Editorial. Hum Reprod 2015: doi:10.1093/humrep/dev151

In Denmark, studies of venous thromboembolism using the National Registry of Patients have produced red herrings as well (Grimes, 2010). For example, reports in high-profile general medical journals claimed that the levonorgestrel intrauterine system was associated with statistically significant protection against venous thrombosis (Lidegaard *et al.*, 2012b) and thrombotic stroke (Lidegaard *et al.*, 2012a). While this intra-uterine device (IUD) has several established non-contraceptive health benefits (Fraser, 2013), prevention of clots and prevention of stroke are not among them. Without validation of outcomes (Severinsen *et al.*, 2010; U.S. Food and Drug Administration) and adequate control

Facts: Three studies have demonstrated ***decreasing*** levels of SHBG among users of LNG-IUS. SHBG is a surrogate marker for the risk of venous thromboembolism.
Therefore, the decreased risk of venous thromboembolism among users of LNG-IUS is expected and in agreement with bio-medical findings.

are not among them. Without validation of outcomes (Severinsen *et al.*, 2010; U.S. Food and Drug Administration) and adequate control for potential confounding (Dinger and Shapiro, 2012), these database studies (Lidegaard *et al.*, 2012a,b) are not credible.

Facts:

In contrast to the study by Dinger et al. all events of venous thromboembolism were in our study cross checked with succeeding anticoagulation therapy. Thus all our end points were objectively confirmed. In the study of Dinger et al. just an increased D-dimer was taken as evidence of a true venous thrombosis.

Facts:

Our study was controlled for more confounders than any other study done so far.

Dr. Grimes knows that fact but continuous nevertheless with these groundless claims. Why?

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: 1.5-2	High risk: >2	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**			

Hormonal contraception – age Clinical recommendations

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

Lidegaard, Expert Opinion Drug Safety 2014: 13: 1353-60

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

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

Hormonal contraception
That's where we are now.

Thanks for your attention

www.lidegaard.dk/slide

Conflicts of interest: Lidegaard has been an expert witness in legal processes in USA in 2011 and 2012.