Oral contraception and venous thrombosis An up-date

Øjvind Lidegaard

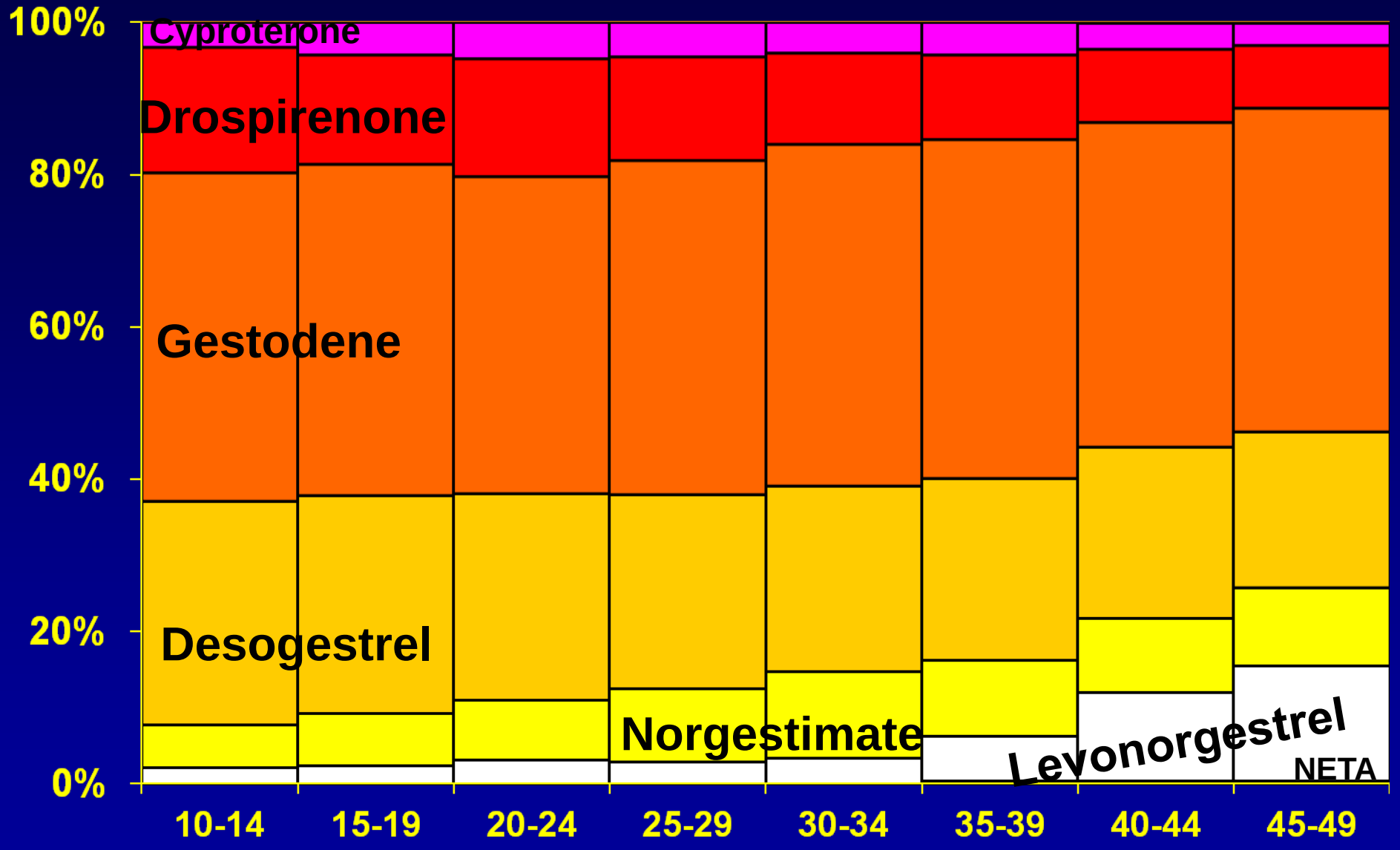
Gynaecological Clinic, Rigshospitalet
University of Copenhagen

OC generations according to oestrogen dose and progestogen type

Progestogen generation

	1 Estrans NETA	2 Levonor-gestrel	"2" Norges-timate	3 Deso-gestrel	3 Gesto-dene	4 Dros-pirenone
50^{high}	High dose		EVRA NuvaRing		-	-
30-40^{mid}	1st	+	2nd +	+	+	+ 4th
20^{low}	-	-	-	3rd	+	+
E2/DNG	+	-	-	-	-	
POP	+	+		+		

COC DK 2009: Progestogen types



Sale statistics. www.laegemiddelstyrelsen.dk

Research story

- 1960s: OC were introduced with success
- 2001: Yasmin came on the market
- 2007: Yasmin most selling OC
- 2007, June: Case report in Danish media
- 2007: First publication on VTE (Dinger)
- 2009 June: BMJ HC-VTE, 1995-2005

BMJ

RESEARCH

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

[2]Department of Obstetrics and Gynaecology, Hillerød Hospital, Copenhagen University

[3]Department of Biostatistics, University of Copenhagen

[4]Research Centre for Prevention and Health, Glostrup Hospital, University of Copenhagen

Correspondence to: Ø Lidegaard Lidegaard@rh.regionh.dk

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doi:10.1136/bmj.b2890

ABSTRACT

Objective To assess the risk of venous thrombosis in current users of different types of hormonal contraception, focusing on regimen, oestrogen dose, type of progestogen, and route of administration.

Design National cohort study.

Setting Denmark, 1995-2005.

Participants Danish women aged 15-49 with no history of cardiovascular or malignant disease.

Main outcome measures Adjusted rate ratios for all first time deep venous thrombosis, portal thrombosis, thrombosis of caval vein, thrombosis of renal vein, unspecified deep vein thrombosis, and pulmonary embolism during the study period.

Results 10.4 million woman years were recorded, 3.3 million woman years in receipt of oral contraceptives. In total, 4213 venous thrombotic events were observed, 2045 in current users of oral contraceptives. The overall absolute risk of venous thrombosis per 10 000 woman

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

INTRODUCTION

Studies have shown an increased risk of venous thrombosis with use of combined oral contraceptives.[1-14] These studies have generally found a higher risk during the first year of use and with oral contraceptives containing desogestrel or gestodene rather than levonorgestrel.[1 4 6 8 9 12]

With the shift from combined pills containing 50 μg ethinylestradiol (oestrogen) to low dose pills containing 30-40 μg, a decrease in the risk of venous thrombosis would be expected. Results have, however, been conflicting,[12 15] and evidence of a further decrease in risk associated with a reduction to 20 μg oestrogen is lacking.[12] In addition, evidence is sparse on the risk of

OC and VTE: Progestagen type adjusted for duration of use

ug EE	Neta	Lng	Norg	Deso	Gest	Drsp	CPA
50	1.4 1.0-2.1	1.2 0.9-1.7	na	na	na	na	na
30-40	1.0 0.7-1.4	1 Ref	1.2 1.0-1.5	1.8 1.5-2.2	1.9 1.6-2.2	**1.64** 1.3-2.1	1.9 1.5-2.4
20	na	na	na	1.5 1.3-1.8	1.5 1.2-1.9	na	na
POP	na	0.3 0.2-0.5		0.5 0.2-1.7			
Mirena	na	0.4 0.3-0.6					

Lidegaard et al. BMJ 2009; 339; b2890

Li/09

BMJ

RESEARCH

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

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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] F M 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]

[1]Department of Clinical Epidemiology, Leiden University

ABSTRACT

Objective To assess the thrombotic risk associated with

INTRODUCTION

The first report of an increased risk of venous throm-

OC and VTE; MEGA study

Design: Case-control study 1999-2004

Cases: 1,524

- Women with VTE 15-49 years old
- Excluded: Previous VTE, pregnancy

Controls: 1,760

- Partner controls: 712
- Matched controls: 1,048
- Excluded: Previous VTE, pregnant

Vlieg et al. BMJ 2009; 339; b2921

VTE and drospirenone

	VTE no	Risk /10,000	Rate ratio DRSP/2nd gen	
EURAS[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
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- 2009 June: BMJ HC-VTE, 1995-2005
- 2009: FDA requires label changes in USA
- 2009: Legal recruitment for lawsuits
- 2009 Dec: Bayer invites for expert meeting

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

Preliminary Agenda

- Welcome/Objectives
- The role of pharmacoepidemiology in assessing the benefit-risk profile of oral contraceptives

The epidemiological evidence on oral contraceptives containing drospirenone

Post-authorization safety studies

- EURAS - design, results and critique
- Ingenix - design, results and critique
- LASS study - design, results and critique
- Discussion, Question & Answers
- Current guidelines and initiatives on Good Pharmacoepidemiological Practice

The epidemiological evidence on oral contraceptives containing drospirenone (part II)

- MEGA study - design, results and critique
- Danish Cohort study - design, results and critique
- Dienogest Case Control study - design, results and critique
- PEM study - design, results and critique
- Discussion, Questions & Answers

Responsible Prescribing of oral contraceptives

General Panel discussion, Question &Answers session

Summary

Research story

- 2010, Jan: Shapiro-Dinger critique*

*) Shapairo & Dinger: J Fam Plann Reprod Health Care 2010; 36: 33-8

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)

Introduction

Since the 1960s it has been known that the use of combined estrogen/progestogen oral contraceptives (COCs) increases the risk of venous thromboembolism (VTE). An increased risk has not generally been identified for progestogen-only preparations, but has been associated with the estrogen dose. In 1995, based on evidence from three studies published in

consider the validity of those claims, and we focus particularly on drospirenone, as results on that progestogen have received the greatest public attention and OCs containing that progestogen are now generally the most commonly used.[14] Most of the following arguments, however, apply also to the other progestogens.

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)*
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Research story

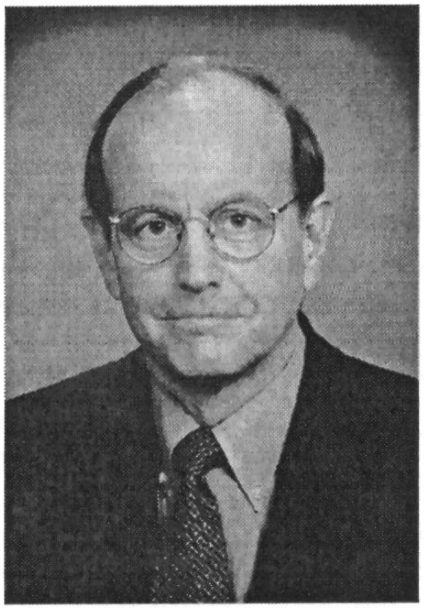
- 2010, Jan: Shapiro-Dinger critique*
- 2010, Jan: EMA request
- 2010, March: Agreement PI, EMA, Bayer
- 2010, June: Steering Committee established (Rothman USA, Skjeldestad N, Shapiro SA)
- 2010, Oct: Protocol agreement
- 2010, Nov: Critique by David Grimes

***) Shapairo & Dinger: J Fam Plann Reprod Health Care 2010; 36: 33-8**

Editorial

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

The Danish National Patient Registry has been used extensively for epidemiologic research, including obstetric and gynecologic studies. In Denmark, all persons get a unique identifier at birth and health care is provided by the government; hence, linkage studies are easy. A highly publicized study of venous thromboembolism concluded that "third-generation" oral contraceptives were more dangerous than "second-generation" pills[6]. The report acknowledged "inclusion of about 10% uncertain diagnoses."

In contrast, an independent validation of 1,100 venous thrombo-embolism diagnoses in this registry found gross misclassification. Only 59% of diagnoses could be confirmed by chart review[7]. Often, physicians entered a code for confirmed venous thromboembolism instead of "observation for venous thromboembolism." This misclassification likely was related to the exposure of interest ("generation" of oral contraceptive), which would bias the results. Other conditions, including rupture of the uterus, hyperten-sion, and rheumatoid arthritis, are coded poorly in this database as well[8].

Grimes. Obstet Gynecol 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

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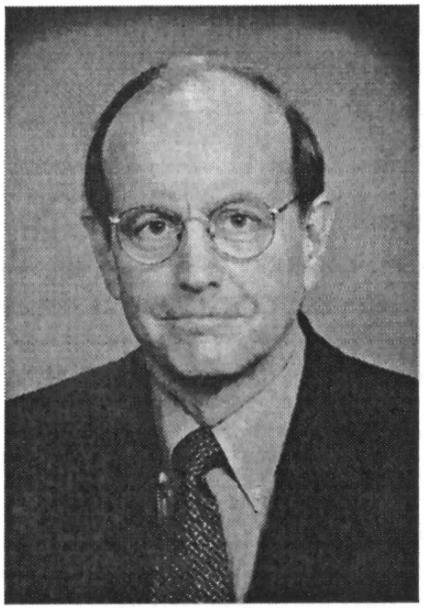

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Financial Disclosure

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

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

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- 2010, Oct: Protocol agreement
- 2010, Nov: Critique by David Grimes
- 2010, New case-control study by Dinger
- 2011, Jan: EMA report first draft.
- 2011, March: Final EMA report delivered

Research story

- 2011, March: Submission to BMJ

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 combined oral contraceptives according to progestogen type and

thromboembolism was not increased with use of progestogen only pills or hormone releasing intrauterine devices. If oral contraceptives with desogestrel, gestodene, or drospirenone are anticipated to increase the

Oral contraception and VTE
A National controlled cohort study
2001-2009

Øjvind Lidegaard, Rigshospitalet

Lars Hougaard Nielsen, Rigshospitalet

Charlotte Wessel Skovlund, Rigshospitalet

Ellen Løkkegaard, Hillerød Hospital

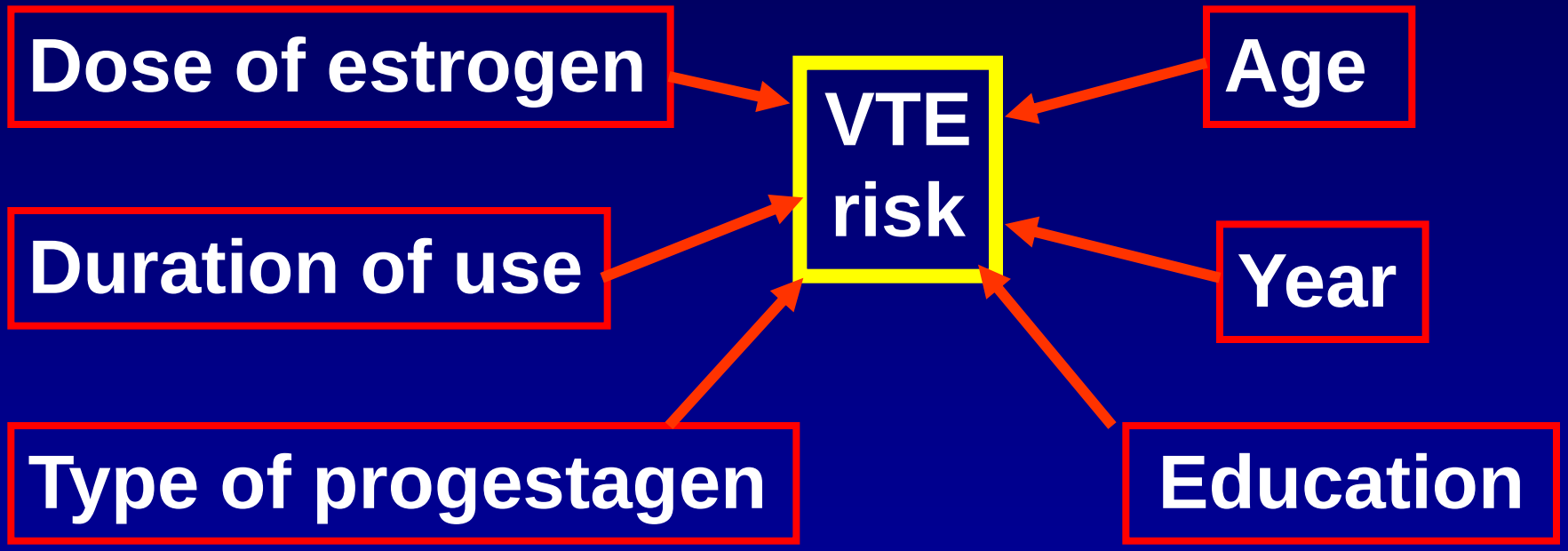
All University of Copenhagen

Finn Egil Skjeldestad, Tromsø University

Objectives

OC axes

Confounders



Lidegaard et al. BMJ 2011; 343: d6423

Material

Inclusion

- All women in Denmark 15-49 years old during the period January 1995 through December 2009 (15 years)
- Study focus: 2001-2009; after launch of OC with drospirenone.
- Data from four National registries:

Lidegaard et al. BMJ 2011; 343: d6423

OC and VTE: Methods

National Registry of Patients (NRP)

VTE diagnoses,

Previous CaVD/canc.

Pregnancies, surgery

National Registry of Medicinal products (NRM): OC use

Anticoagulation therapy

BP↑, DM, Hyperchol.

1995 → 2001 → 2009

Cause of Deaths Registry

Lethal VTE

Statistics of Denmark

PIN-codes, education

vital status, emigration

Lidegaard et al. 2011

Material

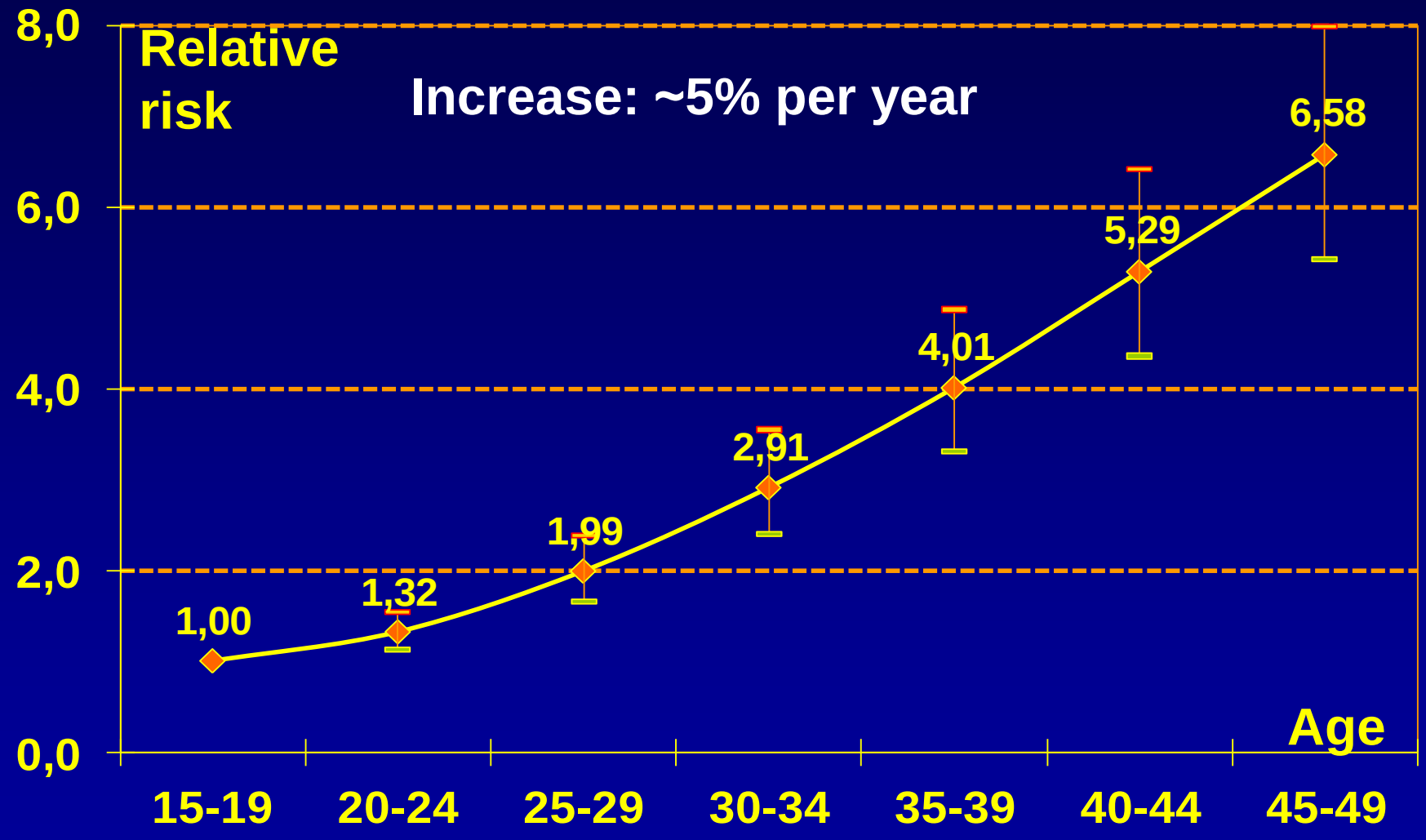
Exclusions (<2001) **& censoring** (≥2001)

- Previous CaVD incl. VTE
- Previous cancer (gyn, abd, breast, lung)
- Hysterectomy, bilat oophorect, sterilisation
- Fertility treatment (analysed separately)
- Diagnosis of thrombophilia
- Pregnant (during pregnancy & puerperium)

Lidegaard et al. BMJ 2011; 343: d6423

Risk of VTE according to age

Adjusted for year, OC-use and education



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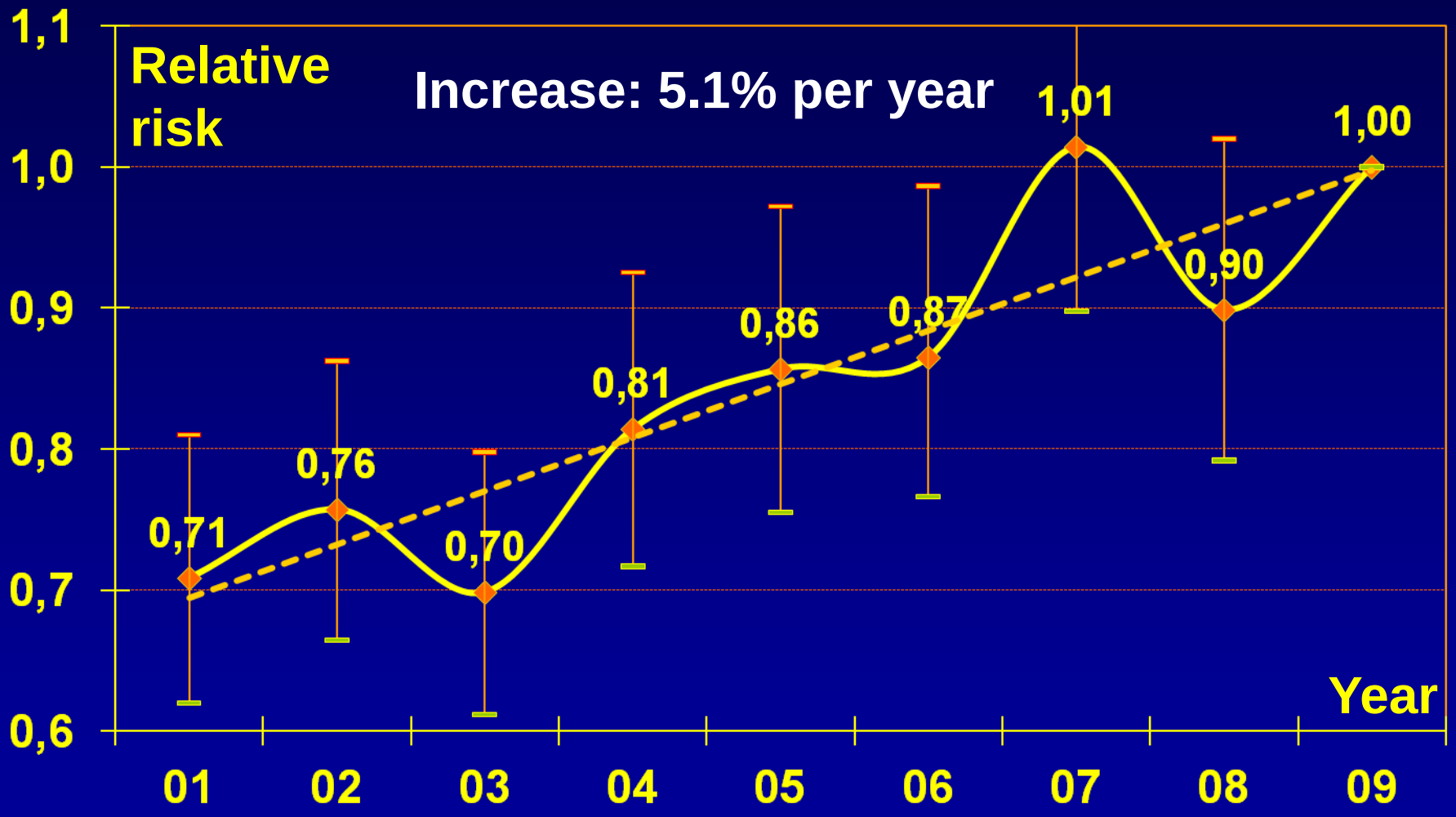
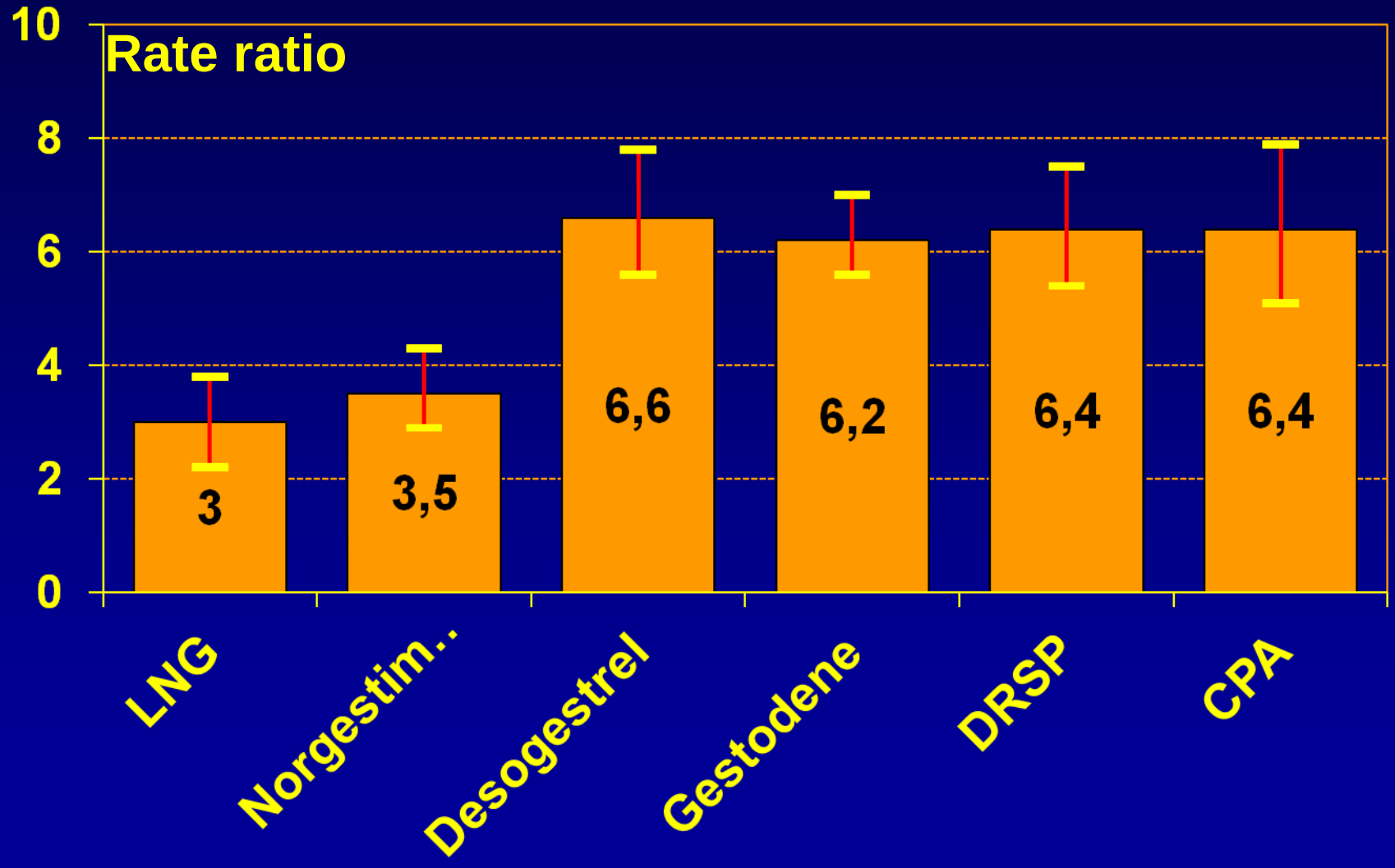


OC and VTE: Progestagen type Confirmed and all vs non-use

ug EE	Neta	Lng	Norg	Deso	Gest	Drsp	Cypr
50	6.2 5.7	4.5 3.5	na	na	na	na	na
30-40	2.2 1.6	3.0 2.2	3.5 2.6	6.6 4.2	6.2 4.2	**6.4** **4.5**	6.4 4.1
20	na	na	na	4.8 3.3	5.1 3.5	6.9 4.8	na
POP	0.7 0.6			0.6 0.6			
Mirena		0.7 0.8					

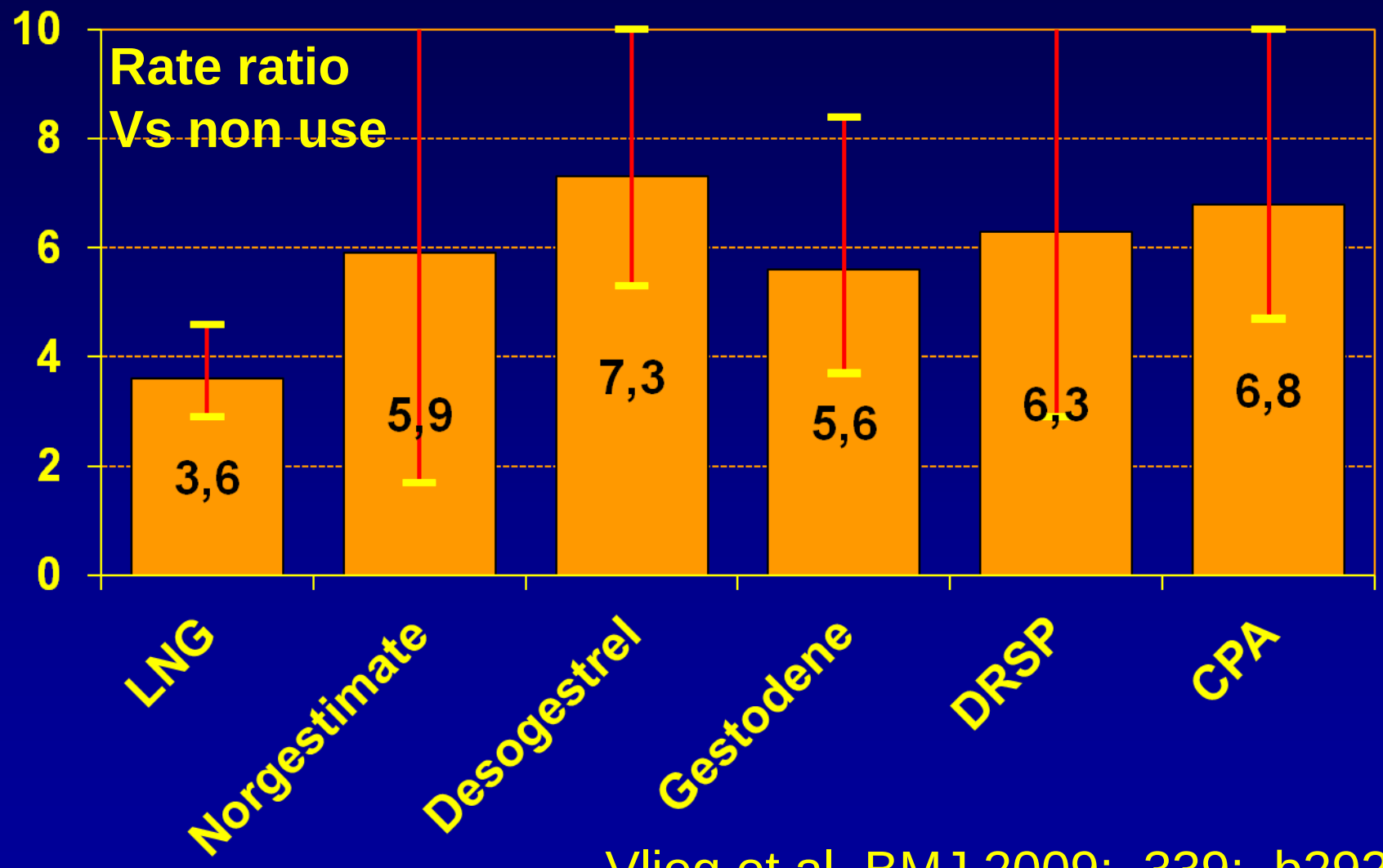
Lidegaard et al. BMJ 2011; 343: d6423

Relative risk versus non-use
Confirmed events only



Lidegaard et al. BMJ 2011; 343: d6423

Relative risk versus non-use



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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

Research story

- 2011, March: Submission to BMJ
- 2011, April: Inconsistency report to EMA
- 2011, April: Revised EMA report delivered
- 2011, May: Two new studies:

VTE and drospirenone

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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

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- 2011, April: Revised EMA report delivered
- 2011, May: Two new studies
- 2011, Oct. 26: BMJ paper published
- 2011, Oct. 27: FDA Kaiser report published

VTE and drospirenone

	VTE	IR	Rate ratio
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FDA Kaiser[11]	625	7.6	1.5 (1.2-1.9) 4th/2nd

HC and VTE according to oestrogen dose and progestogen type

ug EE	Neta	Lng	Ngm	Deso	Gest	Drsp	Cypr
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30-40	na	1 Ref	(ref)	na	na	**1.5** 1.2-1.9	na
20	(ref)	(ref)	na	na	na	na	na

POP	na	na	*) EVRA
Mirena	na		‘) Vaginal ring

FDA Kaiser, 2011. www.fda.gov

HC and VTE according to oestrogen dose and progestogen type

ug EE	Neta	Lng	Ngm	Deso	Gest	Drsp	Cypr
50	6.2 3.0-13.2	4.5 2.9-6.9	7.9* 3.5-17.7	6.5' 4.7-8.9	na	na	na
30-40	2.2 1.1-4.5	3.0 2.4-3.8	3.5 2.9-4.3	6.6 5.6-7.8	6.2 5.6-7.0	**6.4** **5.4-7.5**	6.4 5.1-7.9
20	na	na	na	4.8 4.1-5.6	5.1 4.4-5.9	6.9 4.2-11.5	na
POP	0.7 0.3-1.5			0.6 0.2-1.9			
Mirena		0.7 0.5-1.1					

*EVRA 'Vg ring

Lidegaard et al. BMJ 2011; 343: d6423

Research story

- 2011, March: Submission to BMJ
- 2011, April: Inconsistency report to EMA
- 2011, April: Revised EMA report delivered
- 2011, May: Two new studies
- 2011: Aug: 6,350 law suits in US/Canada
- 2011: Sept: Dinger-Lidegaard at ESG
- 2011, Oct. 26: BMJ paper published
- 2011, Oct. 27: FDA Kaiser report published
- 2011, Nov: Gronich study

VTE and drospirenone

	VTE	IR	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
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
Gronich[11]	518	8.6	1.7 (1.0-2.7)	4th/2nd

IR = incidence per 10,000 women years

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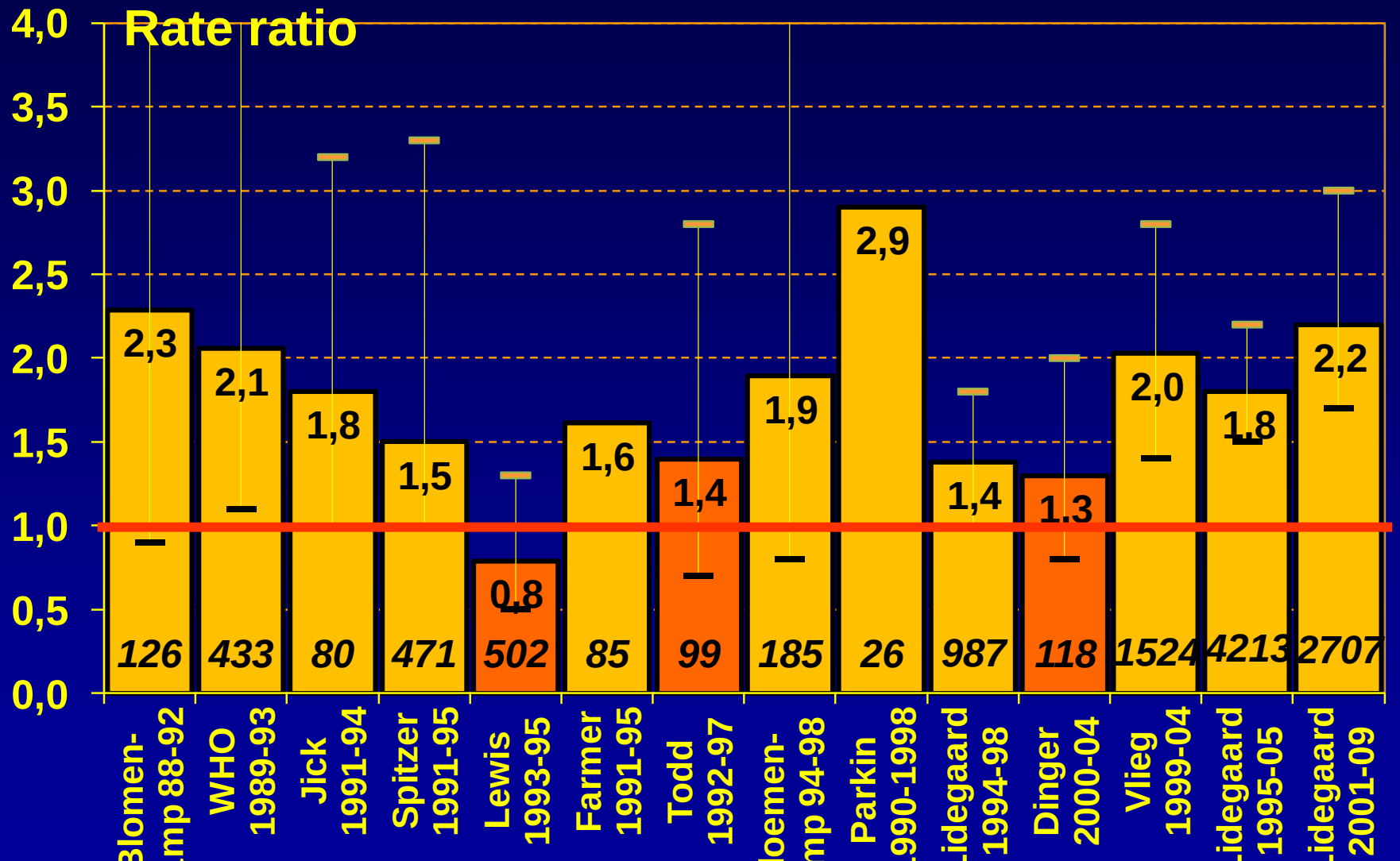
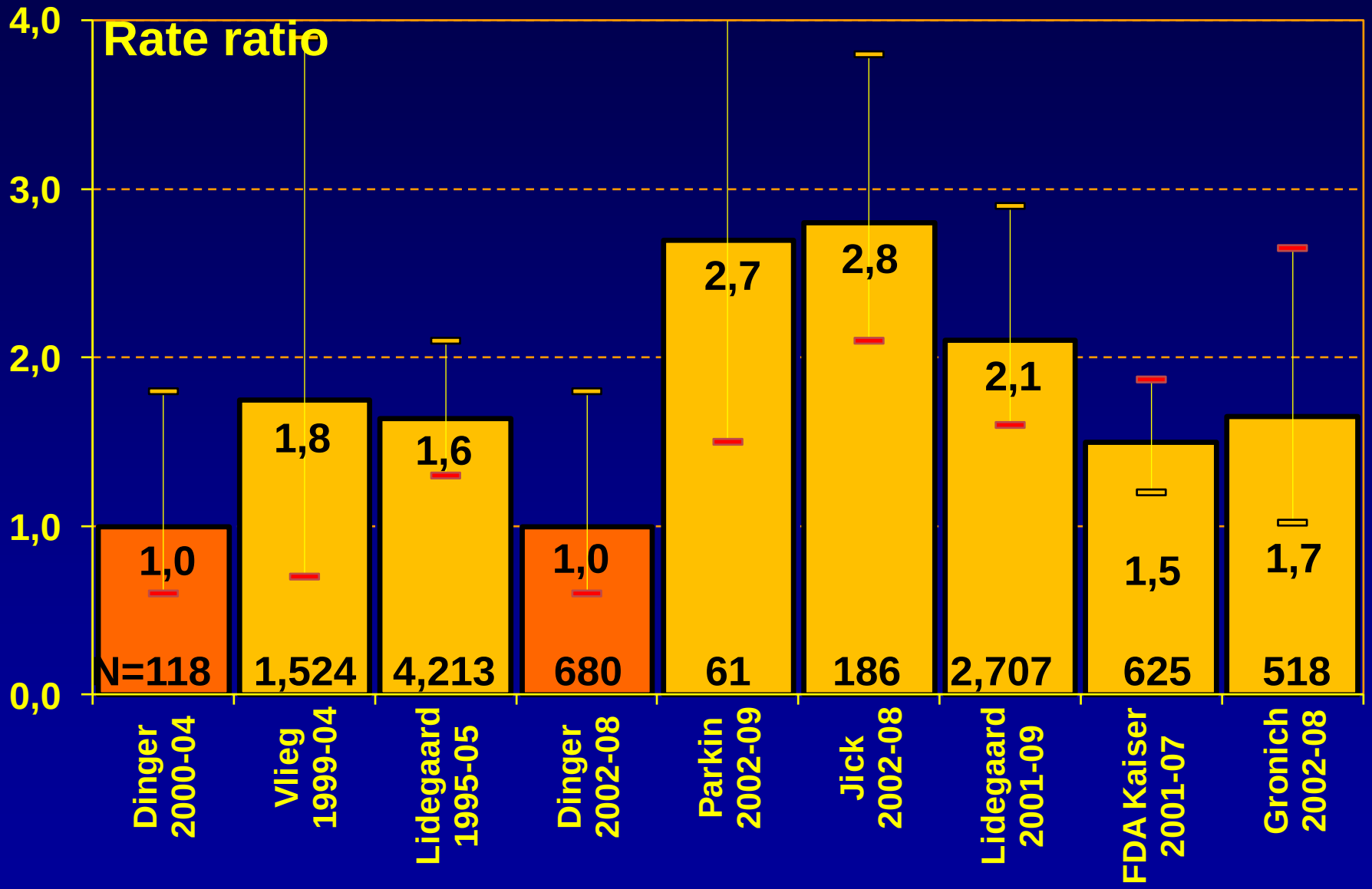
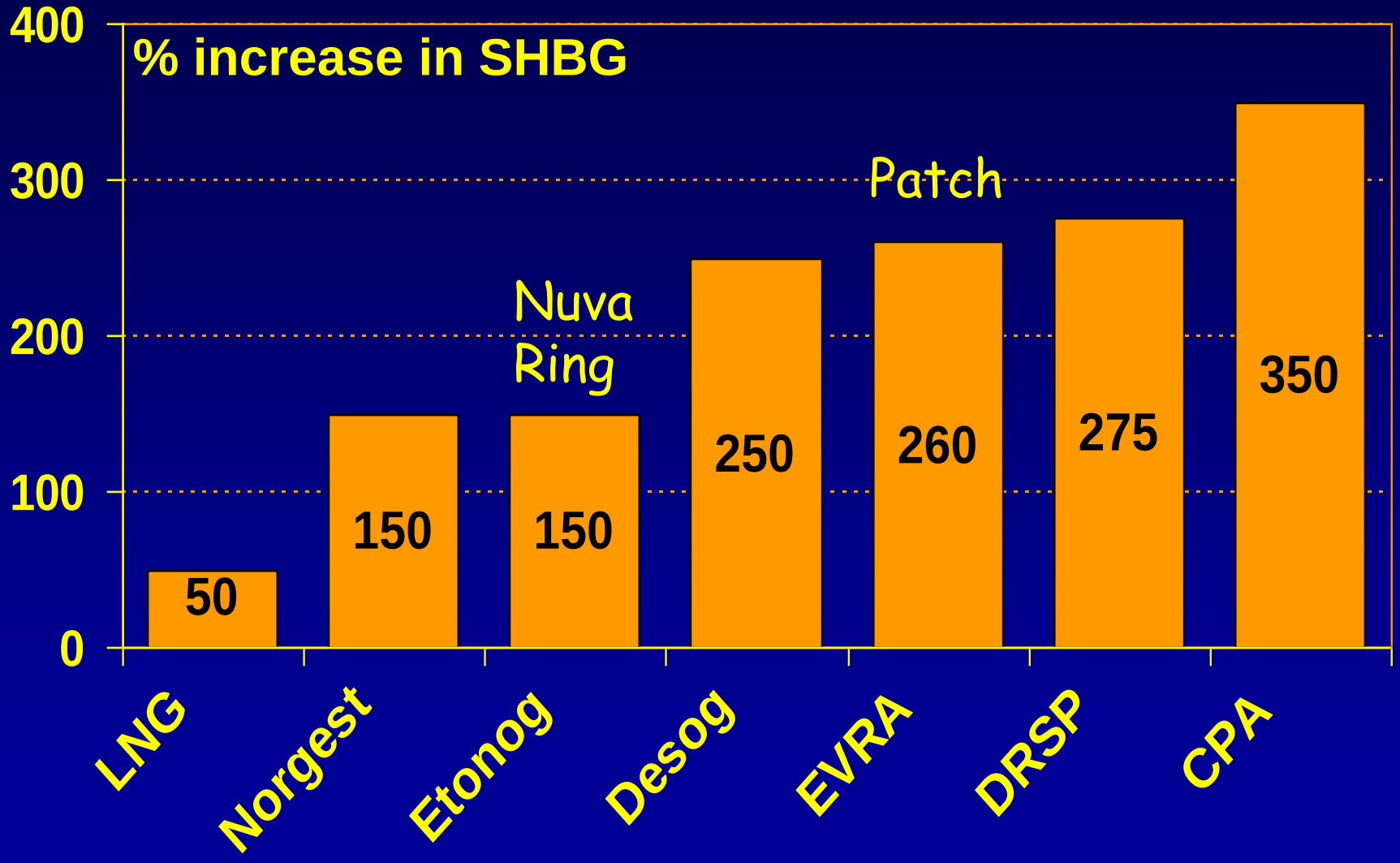
3rd versus 2nd generation COC



COC with DRSP vs LNG



OCs and SHBG changes



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

OCs and venous thrombosis

Current status October 2011

Non use	1
POP:	1
Hormone IUD:	1
2nd gen:	2 → 3
3rd gen:	4 → 6
4th gen:	4 → 6

COC and VTE: Conclusion

- COC increase the risk of VTE 3-6 fold

The risk with COC use is influenced by

- The progestogen type (~100 %)
- The oestrogen dose (~50 %)
- The length of use (~50 %)
- Other risk factors: Genetic predisposition, adiposity, varicose veins, immobilisation

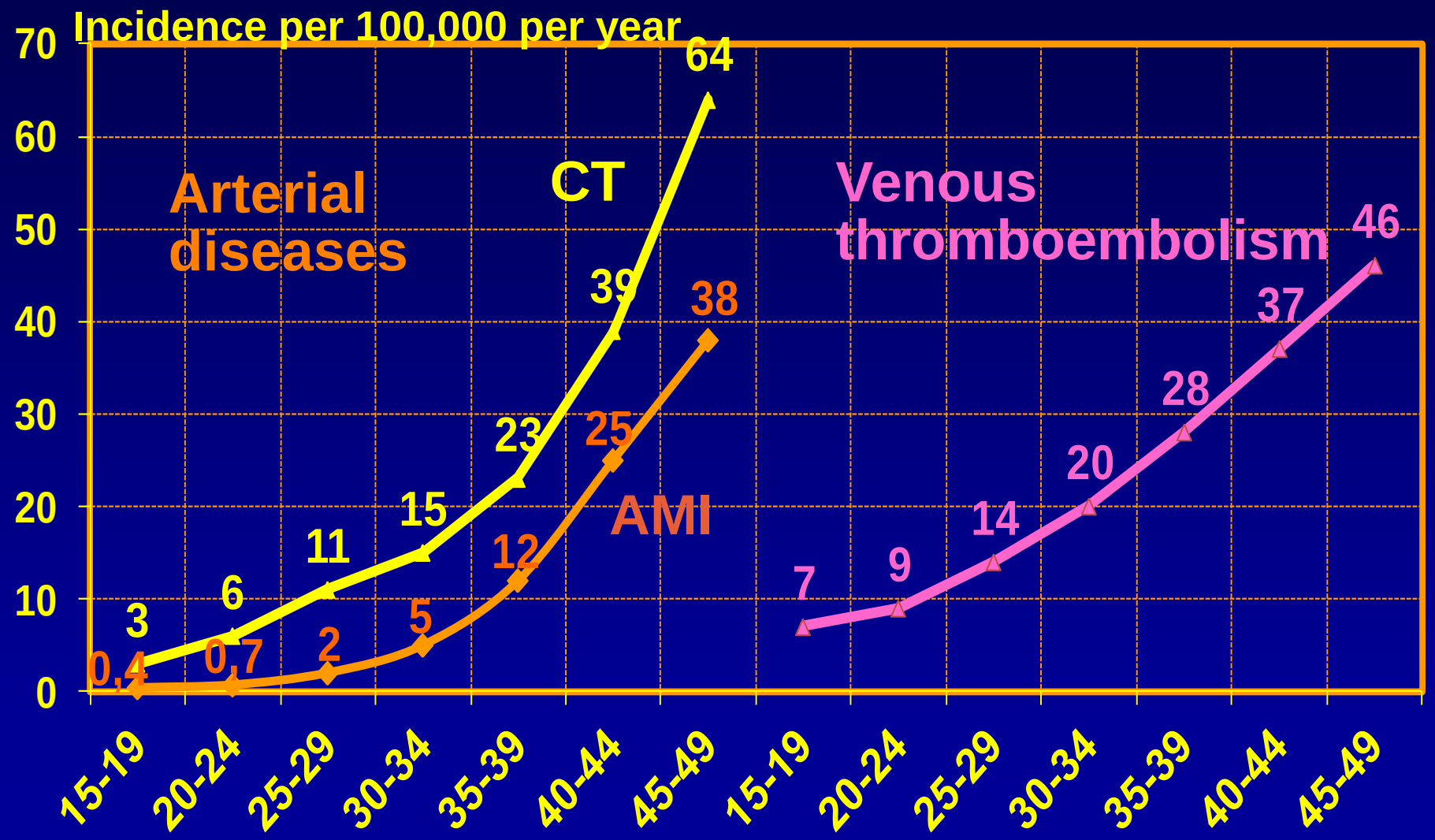
COC and VTE: Perspectives

- Parenteral hormonal contraception

  patch, implants, vaginal ring,
- New regimens: 24 vs 21 days active pills
- New hormones: Natural oestrogen (Qlaira)
- Arterial thromb. *urgently needed*: AMI, stroke

CT, AMI and VTE in DK 2001-2009

Pregnant and puerperal women excluded



Thrombotic diseases in women 15-49

Per 1 million in 2000-09	CT	AMI	VTE
Incidence	260	130	340
Non pregnant	230	120	280
Mortality	6	32	5
Non pregnant	5	30	4
Case-fatality rate	2.2%	25%	1.4%
Significant disability	30%	30%	5%
Long-term survival	↓	↓↓	→

After exclusions, DaHoRs 2011

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- Increased recruitment for law-suits
- New research opportunities (DK)

COC and VTE: Perspectives

Thanks

www.lidegaard.dk/slides