Hormonal contraception and venous thrombosis An up-date

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University of Copenhagen

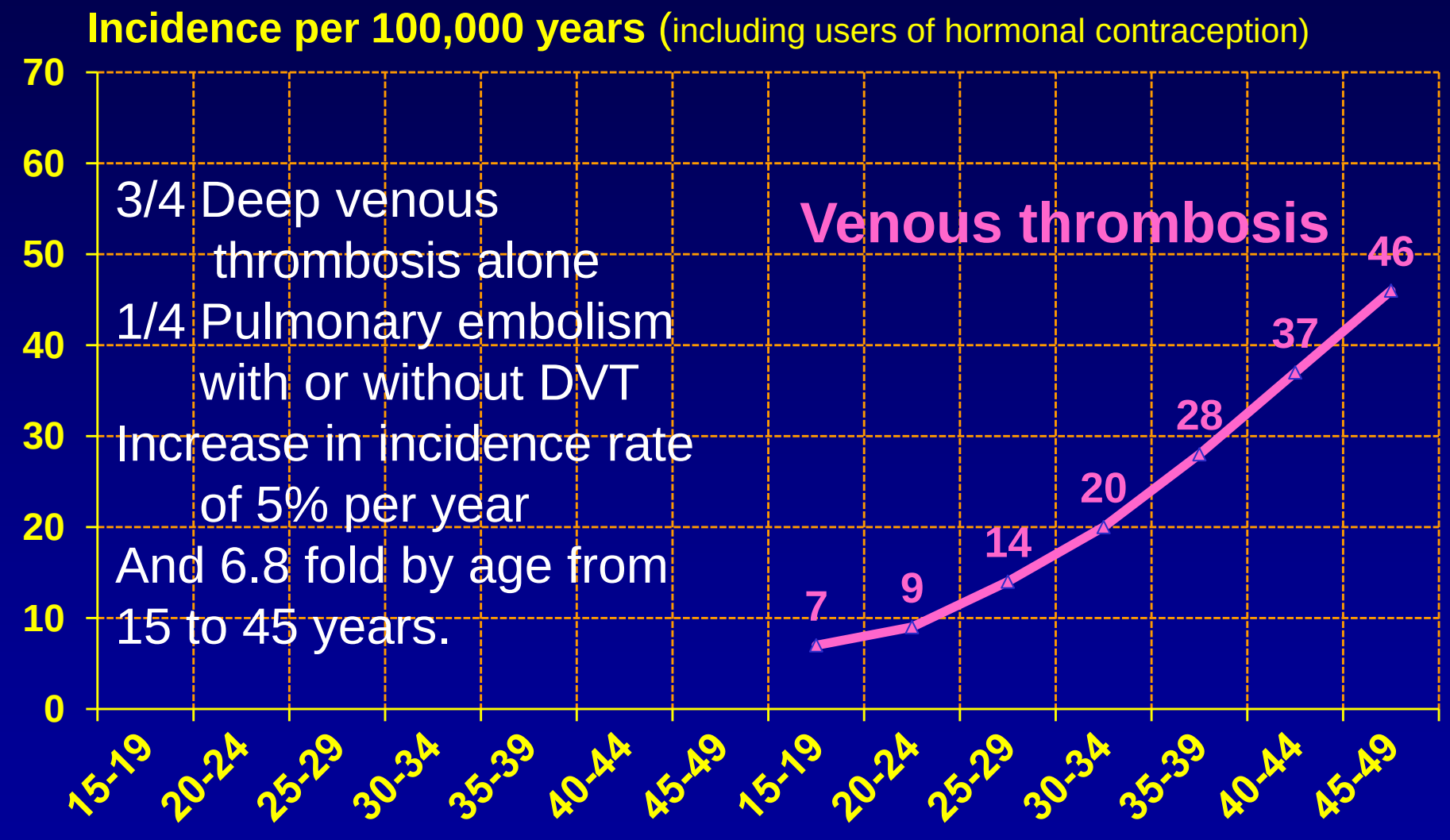
OC generations according to oestrogen dose and progestogen type

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	+	+		+		

Venous thrombosis in DK 2001-2009*

Pregnant and puerperal women excluded

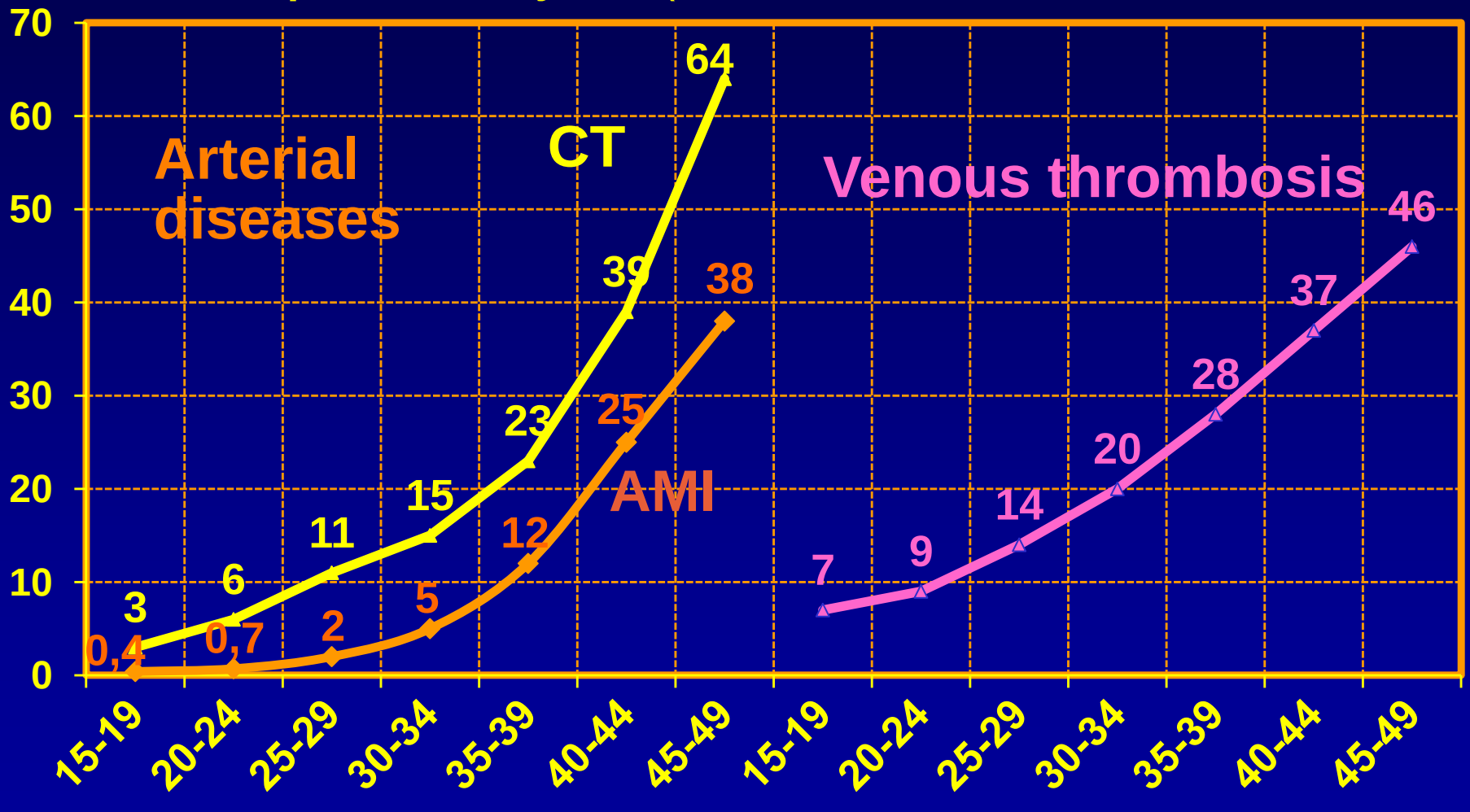


Lidegaard et al BMJ 2011

CT, AMI and VT in DK 2001-2009*

Pregnant and puerperal women excluded

Incidence per 100,000 years (including users of hormonal contraception)



Lidegaard et al 2012 (submitted) and BMJ 2011

VT: Genetic risk factors

Risk factor	Prevalence	RR
Leiden fact V hetero	6%	8
Leiden fact V homoz	0.2%	64
Protein C insufficiency	0.2%	15
Protein S insufficiency	<0.1%	>10
Antithrombin III insuff.	0.02%	50
Prothrombin 20210A	2%	3
Hyperhomocysteinaemia	3%	3

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
Oral contraceptives	30%	3-6
Medical diseases	5%?	2-5

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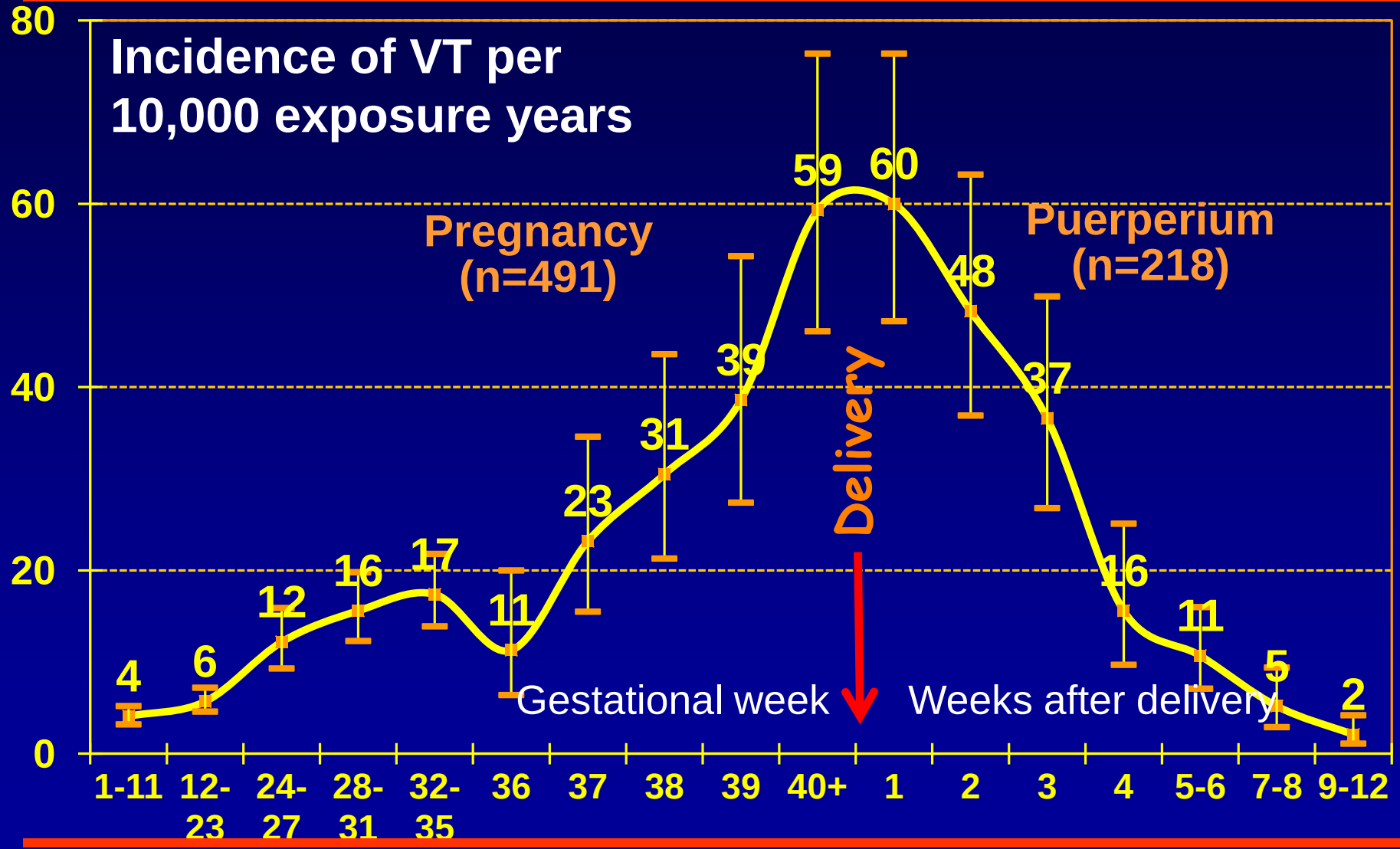
Venous thrombosis in pregnant and puerperal women, DK 1995-2005. N=709



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

Li/12

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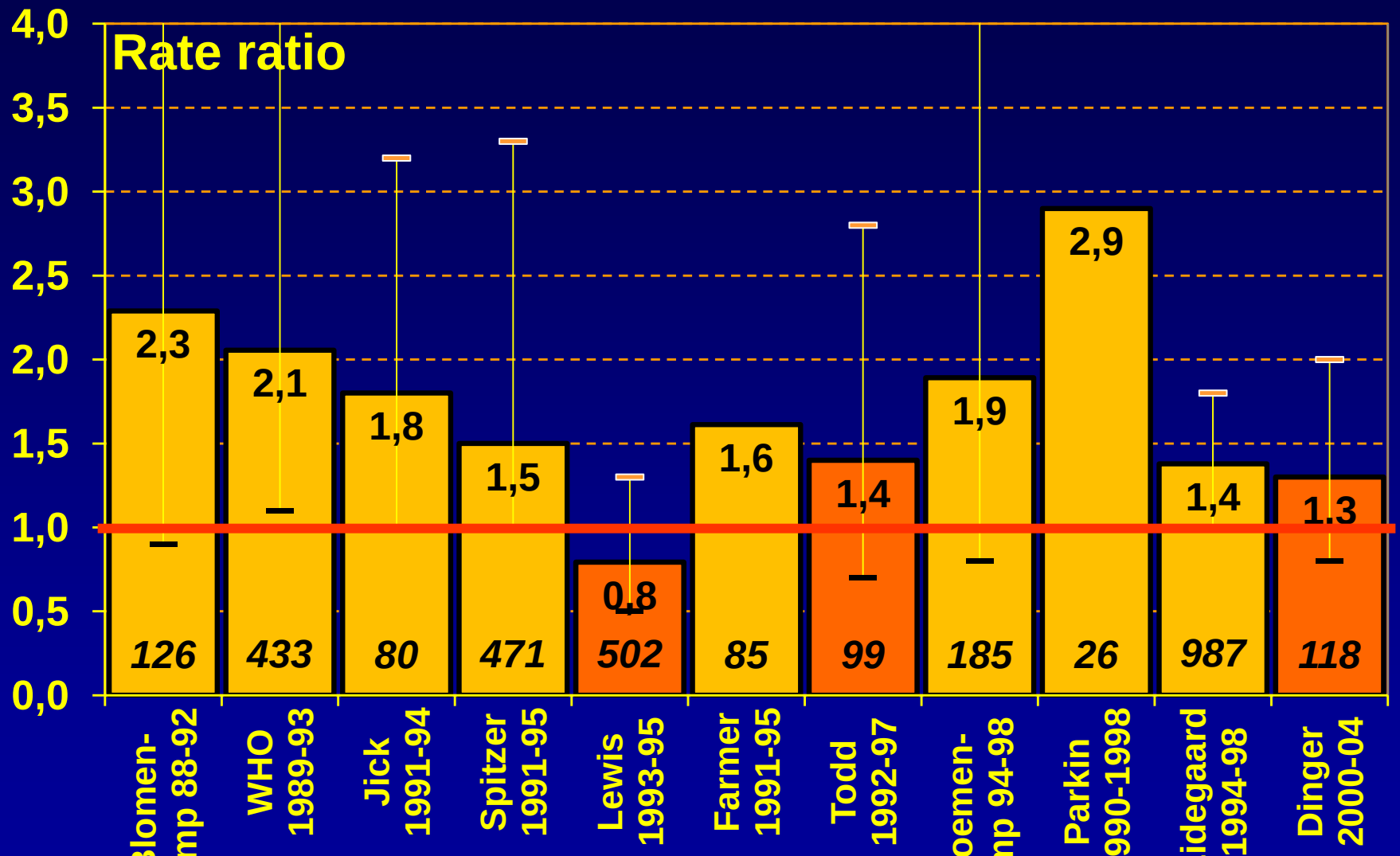
3rd versus 2nd generation COC



VT and COC drospirenone (4th)

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

OC and VT: Methods

National Registry of Patients (NRP)

VT diagnoses,

Previous CaVD/canc.

Pregnancies, surgery

National Registry of Medicinal products (NRM): OC use

Medication against

BP↑, DM, Hyperchol.

1995 → 2005

Cause of Deaths Registry

Lethal VT

Statistics of Denmark

PIN-codes, education

vital status, emigration

Lidegaard et al. BMJ 2009

OC and VT: Progestagen type adjusted for duration of use

ug EE	Neta	Lng	NGM	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

OC and VT; MEGA study

Design: Case-control study 1999-2004

Cases: 1,524

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

Controls: 1,760

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

Vlieg et al. BMJ 2009; 339; b2921

VT and drospirenone

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Research story

- 2010, Jan: Shapiro-Dinger critique*

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)

Research story

- 2010, Jan: Shapiro-Dinger critique*

Ref non users	LNG	DRSP	4th/2nd
< 1 year	1.9	7.9	4.1
1-4 years	2.2	2.7	1.2
> 4 years	1.9	3.3	1.7
All	2.0	4.0	1.6

- Lack of information on BMI and adiposity
  These variables were **not** confounders in any study with access to this information

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

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- 2010, Jan: EMA request
- 2010, March: Agreement PI, EMA, Bayer
- 2010, June: Steering Committee established
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- 2011, Jan: EMA report first draft.
- 2011, March: Final EMA report delivered
- 2011, March: Submission 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

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

OC and VT: Methods

National Registry of Patients (NRP)

VT diagnoses,

Previous CaVD/canc.

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National Registry of Medicinal products (NRM): OC use

Anticoagulation therapy

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1995 → 2001 → 2009

Cause of Deaths Registry

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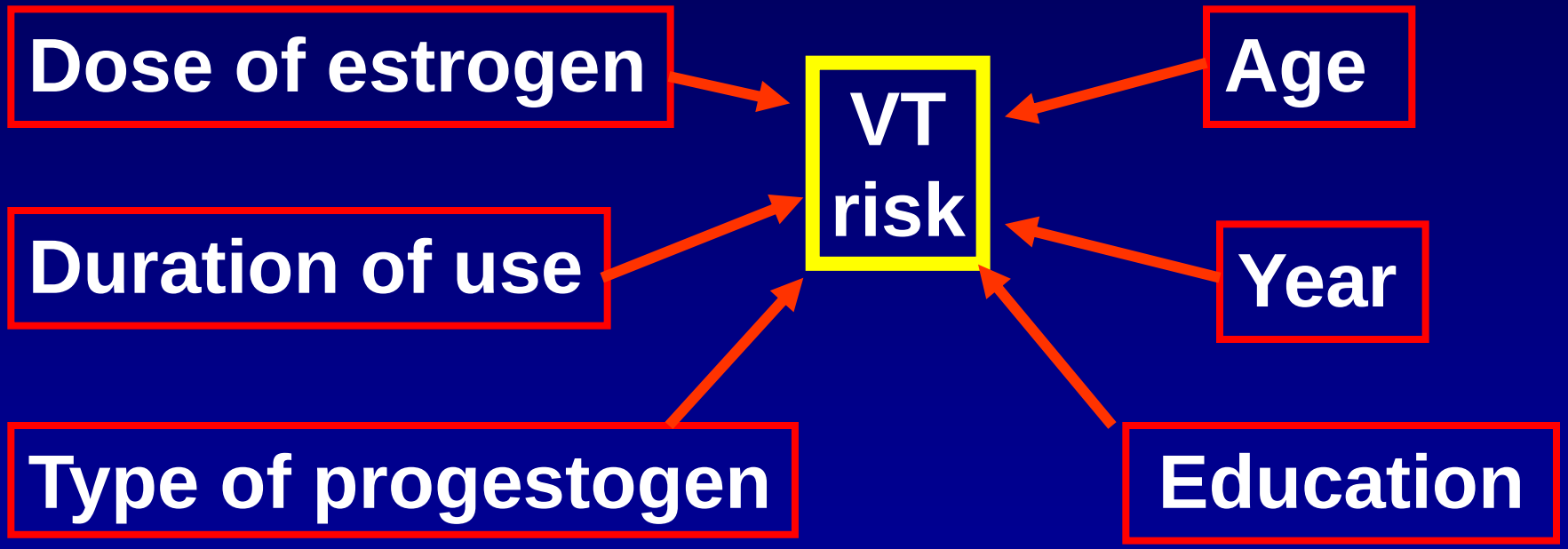
Lidegaard et al. 2011

Objectives

OC axes

Confounders



Lidegaard et al. BMJ 2011; 343: d6423

OC and VT: Progestogen type Confirmed versus non-use

ug EE	Neta	Lng	NGM	Deso	Gest	Drsp	Cypr
50	6.2 3.0-13.2	4.5 2.9-6.9	Patch	Vaginal Ring	na	na	na
30-40	2.2 1.1-4.5	3.0 2.4-4.0	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 5.4-7.5
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			
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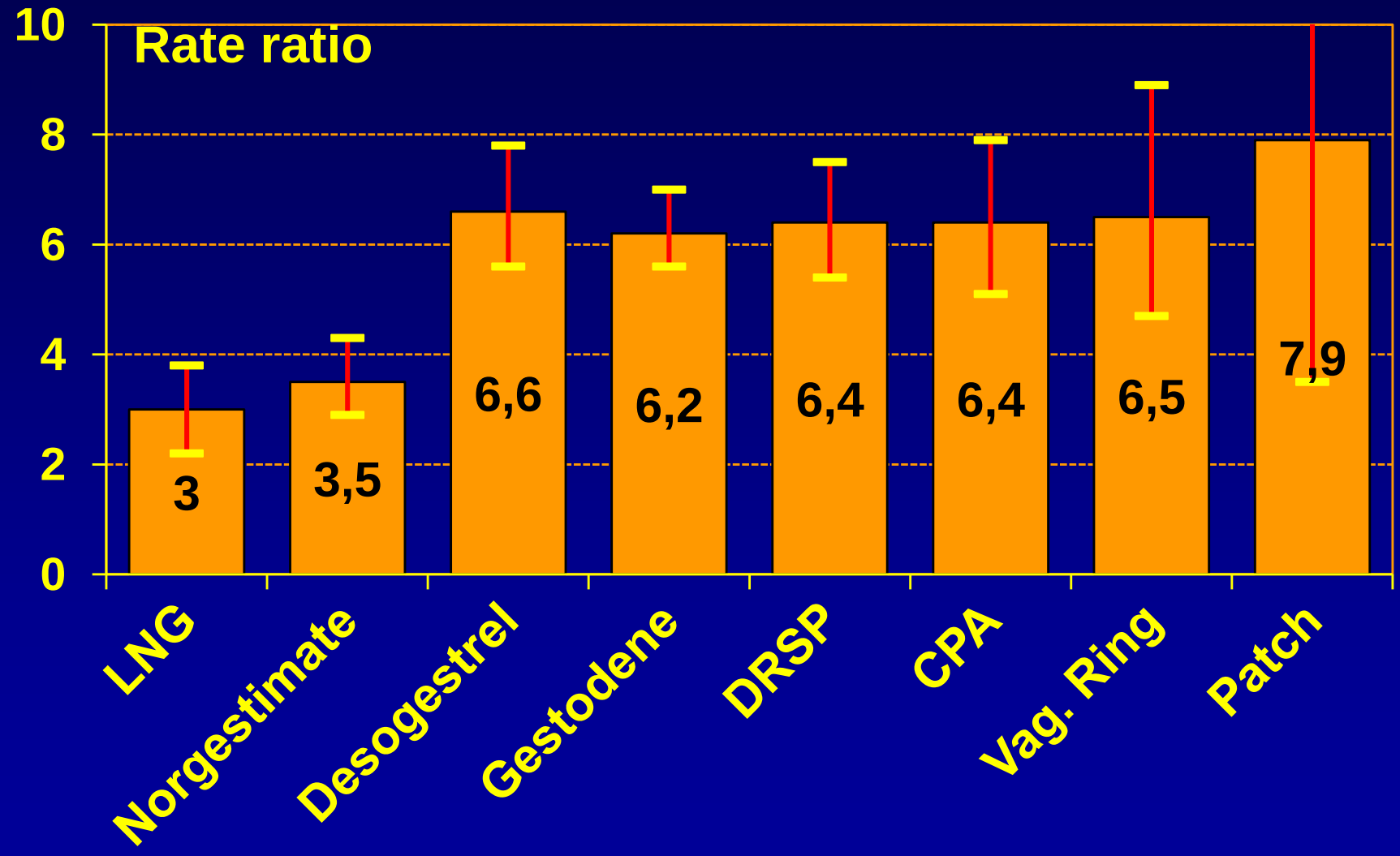
Lidegaard et al. BMJ 2011 and Lidegaard 2012 (submitted)

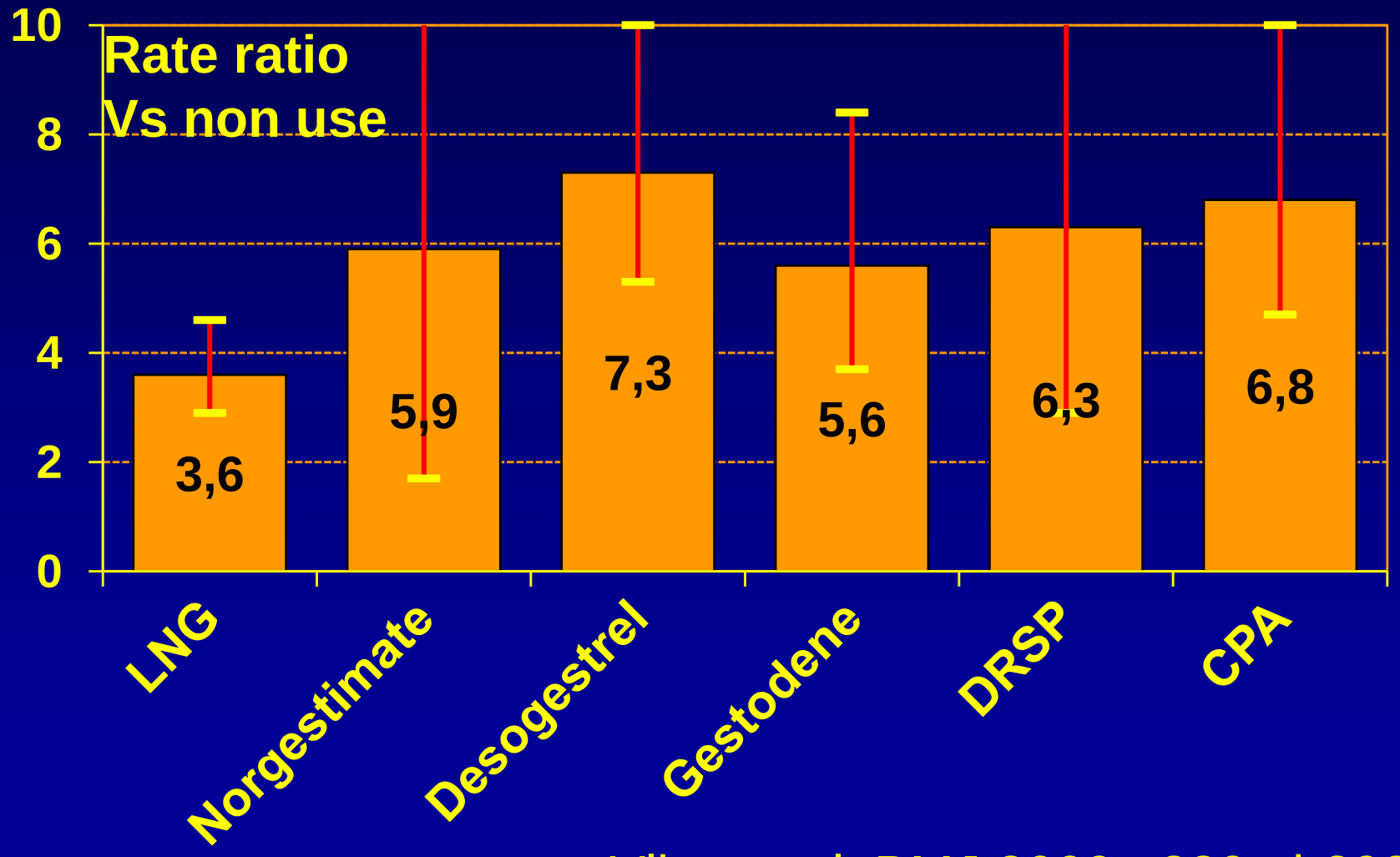
Relative risk versus non-use

Confirmed events only



Lidegaard et al. BMJ 2011; 343: d6423 + new submitted

Relative risk versus non-use



Vlieg et al. BMJ 2009; 339; b2921

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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

IR = incidence per 10,000 women years

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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
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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

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

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

VT and drospirenone

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

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HC and VT according to oestrogen dose and progestogen type

ug EE	Neta	Lng	Ngm	Deso	Gest	Drsp	Cypr
50	na	na	1.3* 0.9-1.7	1.5’ 1.0-2.3	na	na	na
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

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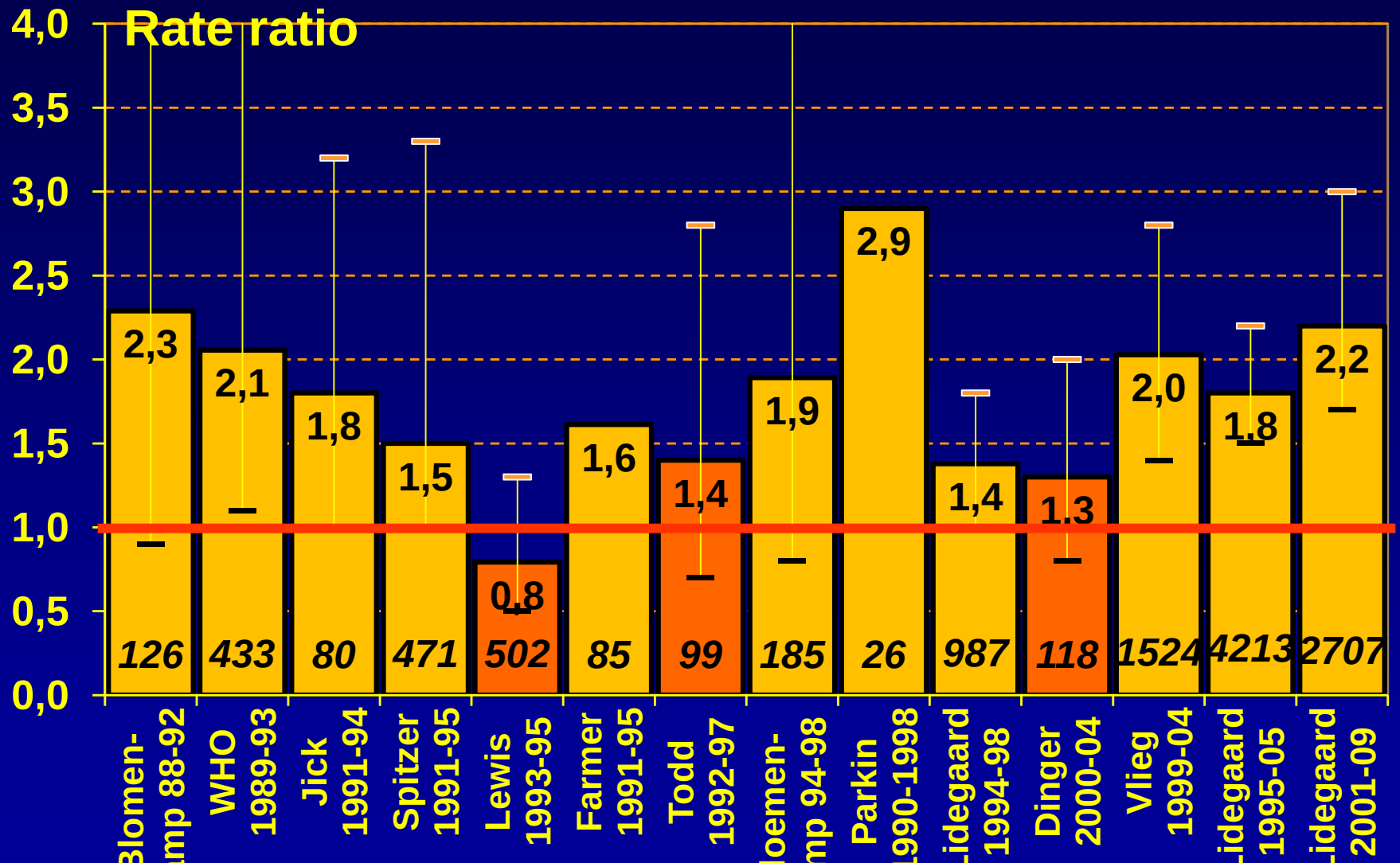
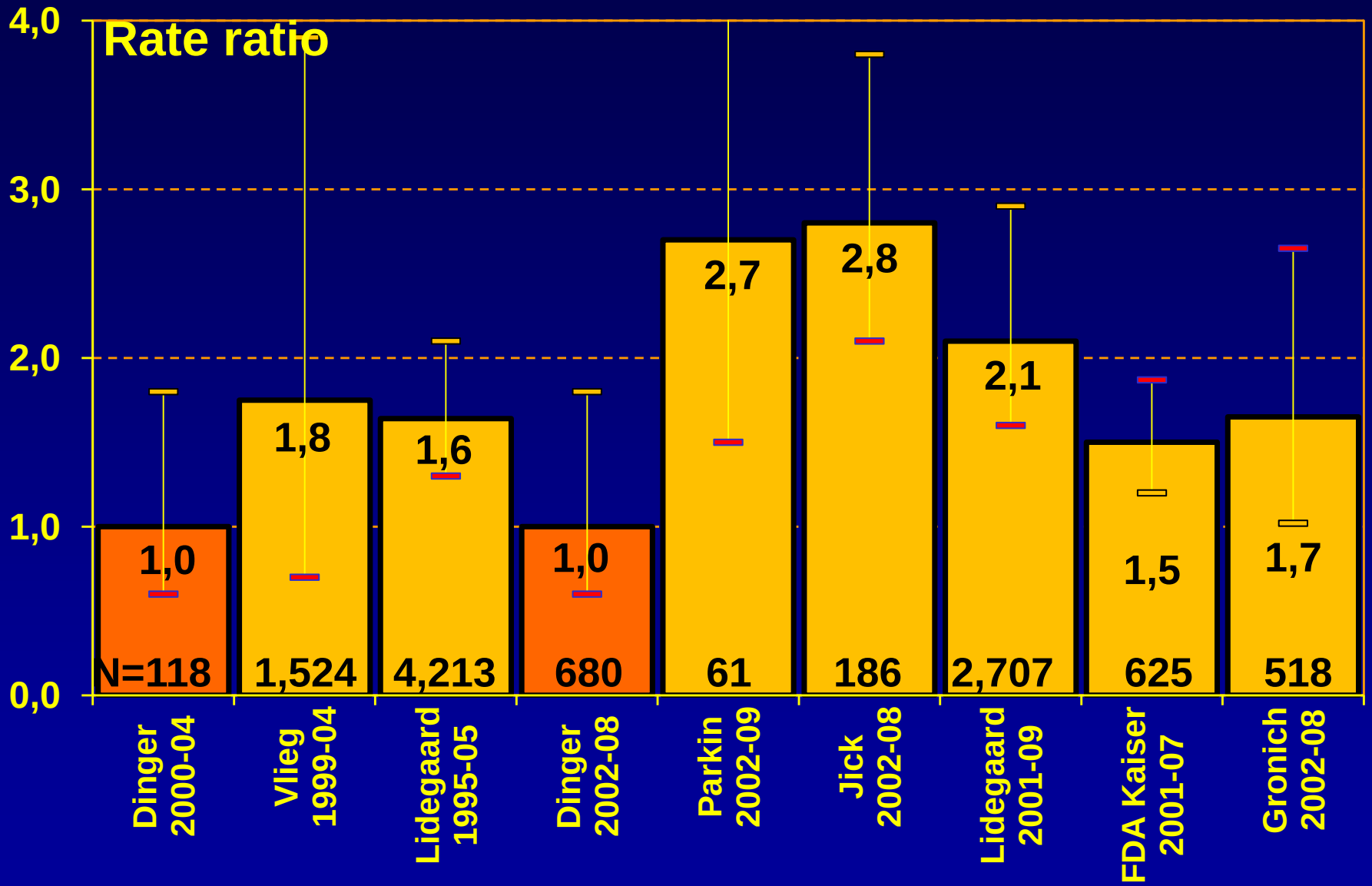
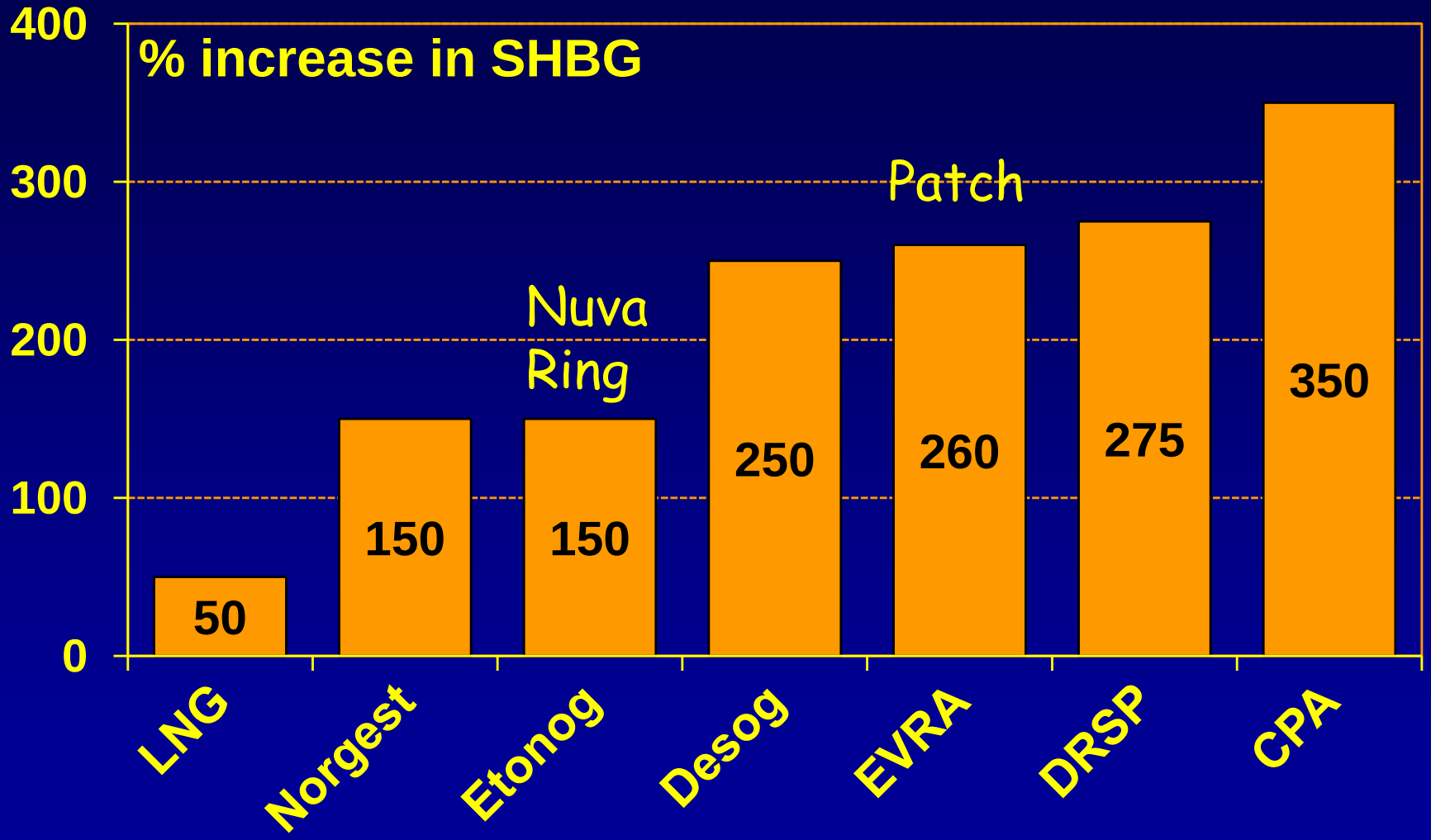
3rd versus 2nd generation COC



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 March 2012

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

Hvad skal praksislægen huske?

- Spørge ud om tromboemboliske kompl i fam
- First choice: 2. generations p-pille
- Informere om risikoen for venøs trombose samt symptomerne herpå!!
- Tænke på lungeemboli, når en ung kvinde henvender sig med dyspnø og/el smerter i brystet, specielt hvis tidligere rask

Hormonal contraception and venous thrombosis

Thanks for your attention

www.lidegaard.dk/slides