La contraception hormonale et la thrombose veineuse Une mise à jour

Øjvind Lidegaard

Symposium Salon de Gynécologie Pratique, Paris, Mars, 2012

Gynaecological Clinic, Rigshospitalet
University of Copenhagen

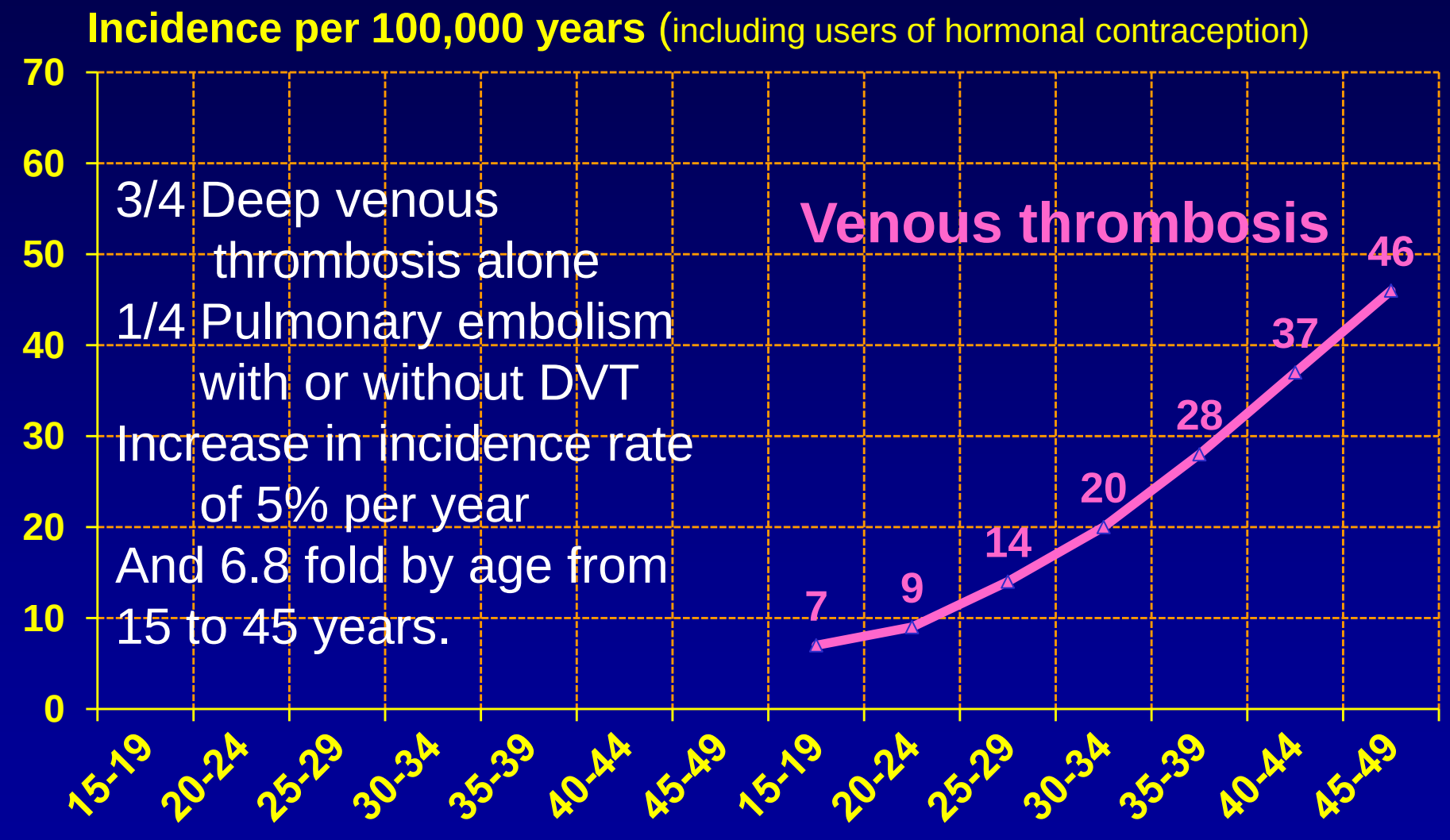
OC generations according to oestrogen dose and progestogen type

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	-	-	-
30-40^{mid}	1st	+	2nd +	+	+	+ 4th
20^{low}	-	-	-	3rd	+	+
E2/DNG	+	-	-	VaginalRing	-	-
POP	+	+		+		

Venous thrombosis in DK 2001-2009*

Pregnant and puerperal women excluded

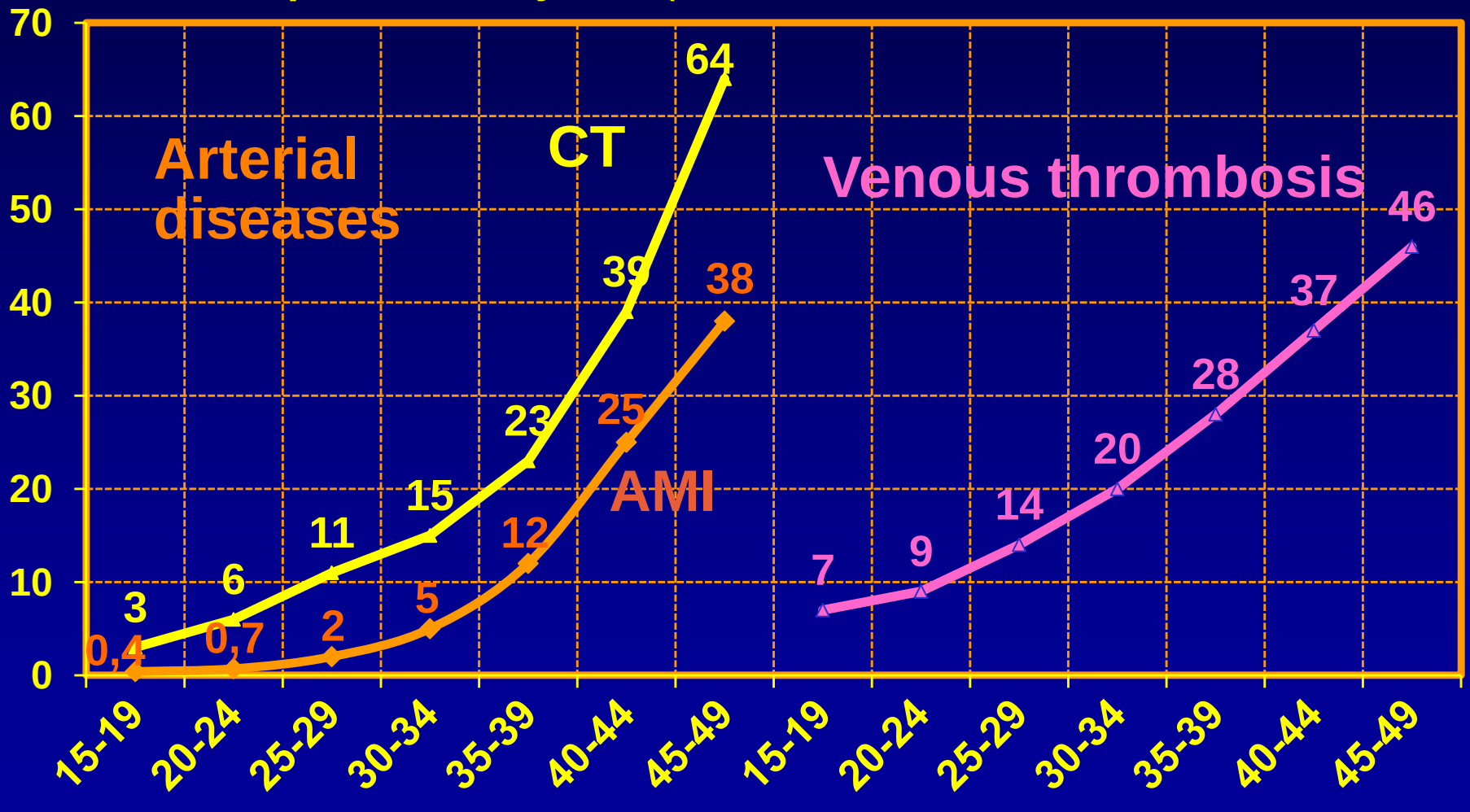


Lidegaard et al BMJ 2011

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

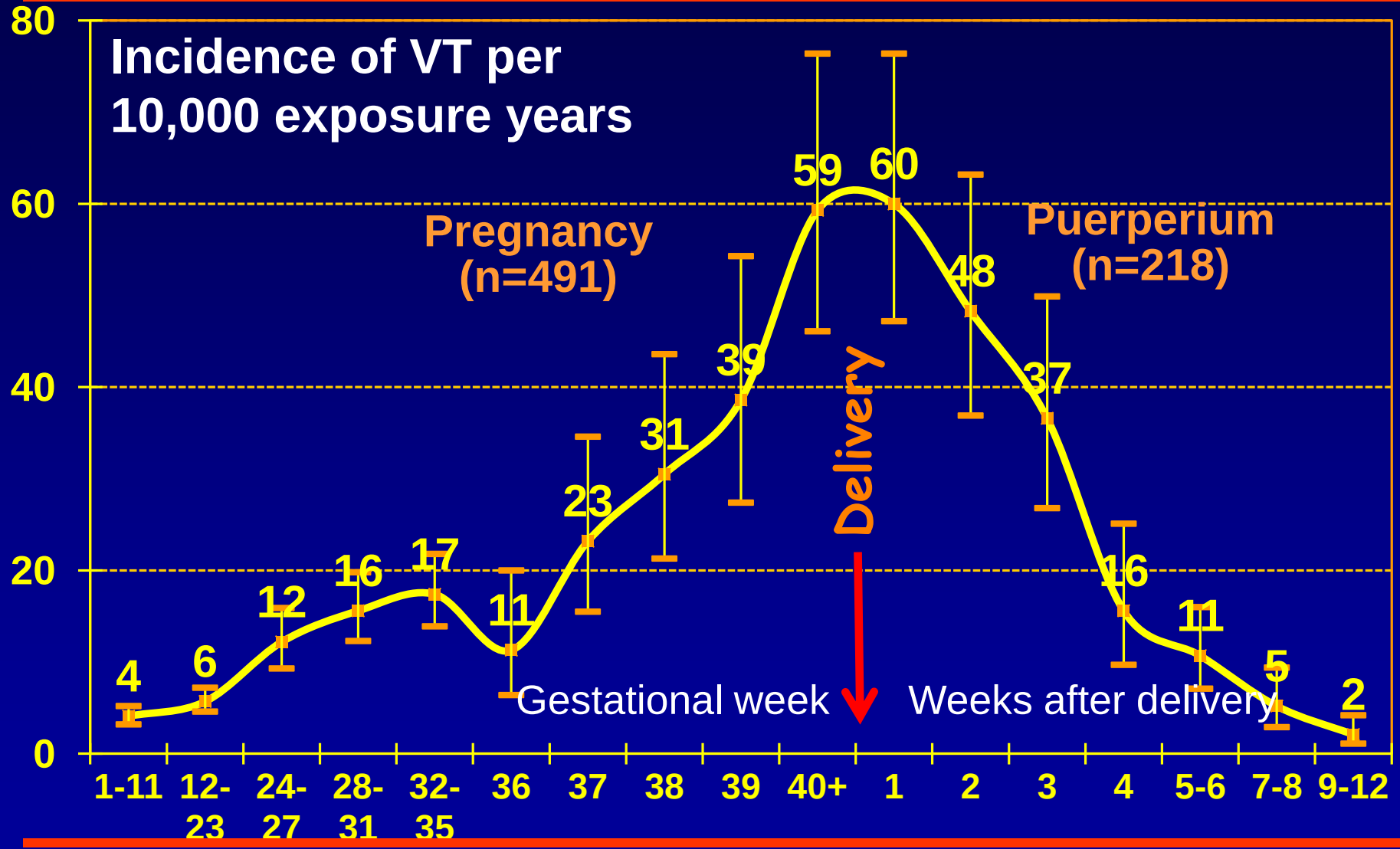
VT: Acquired risk factors

	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

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

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



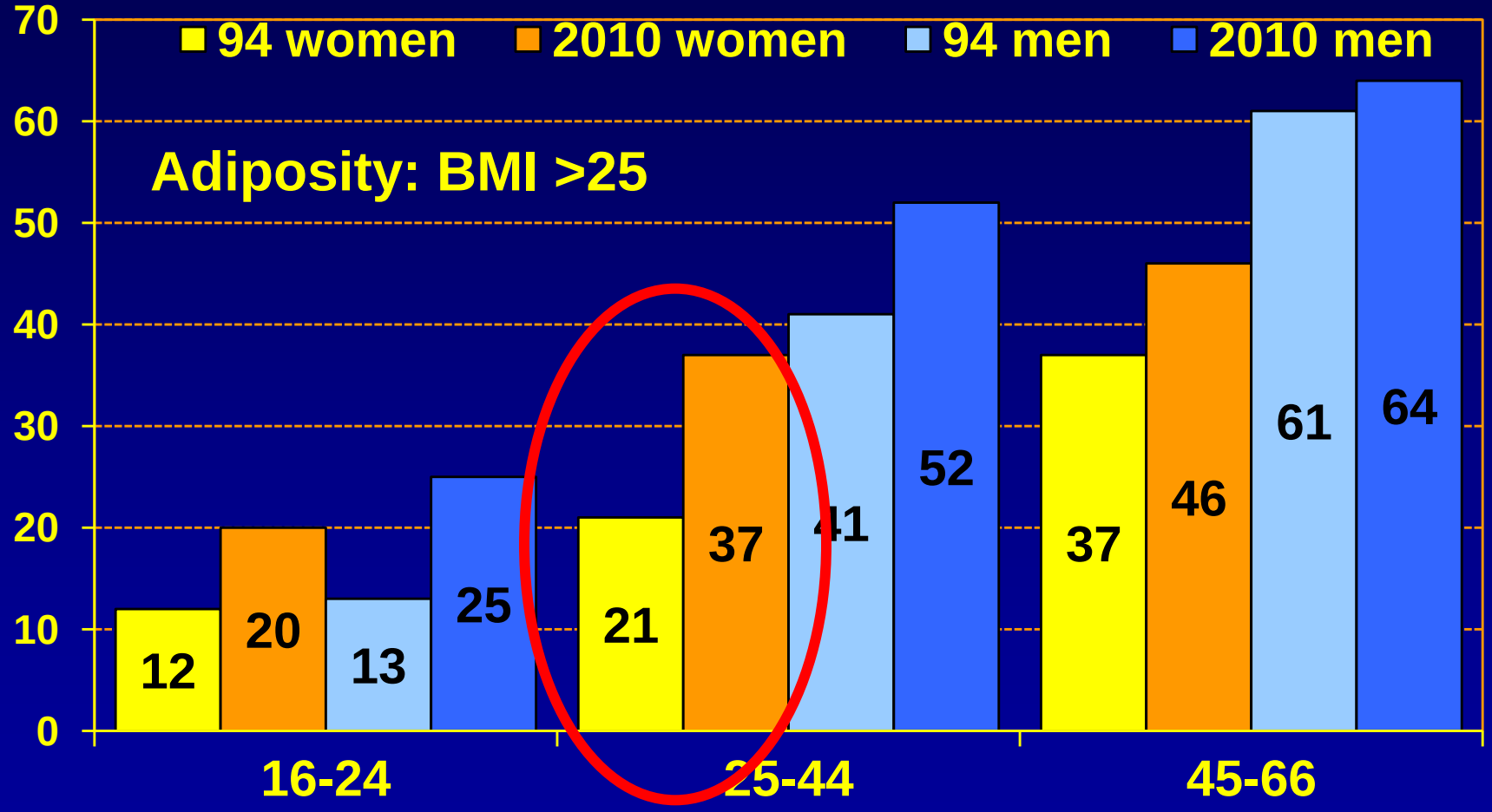
Virkus et al. Thromb Haemost 2011; 106: 304-9

Li/12

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

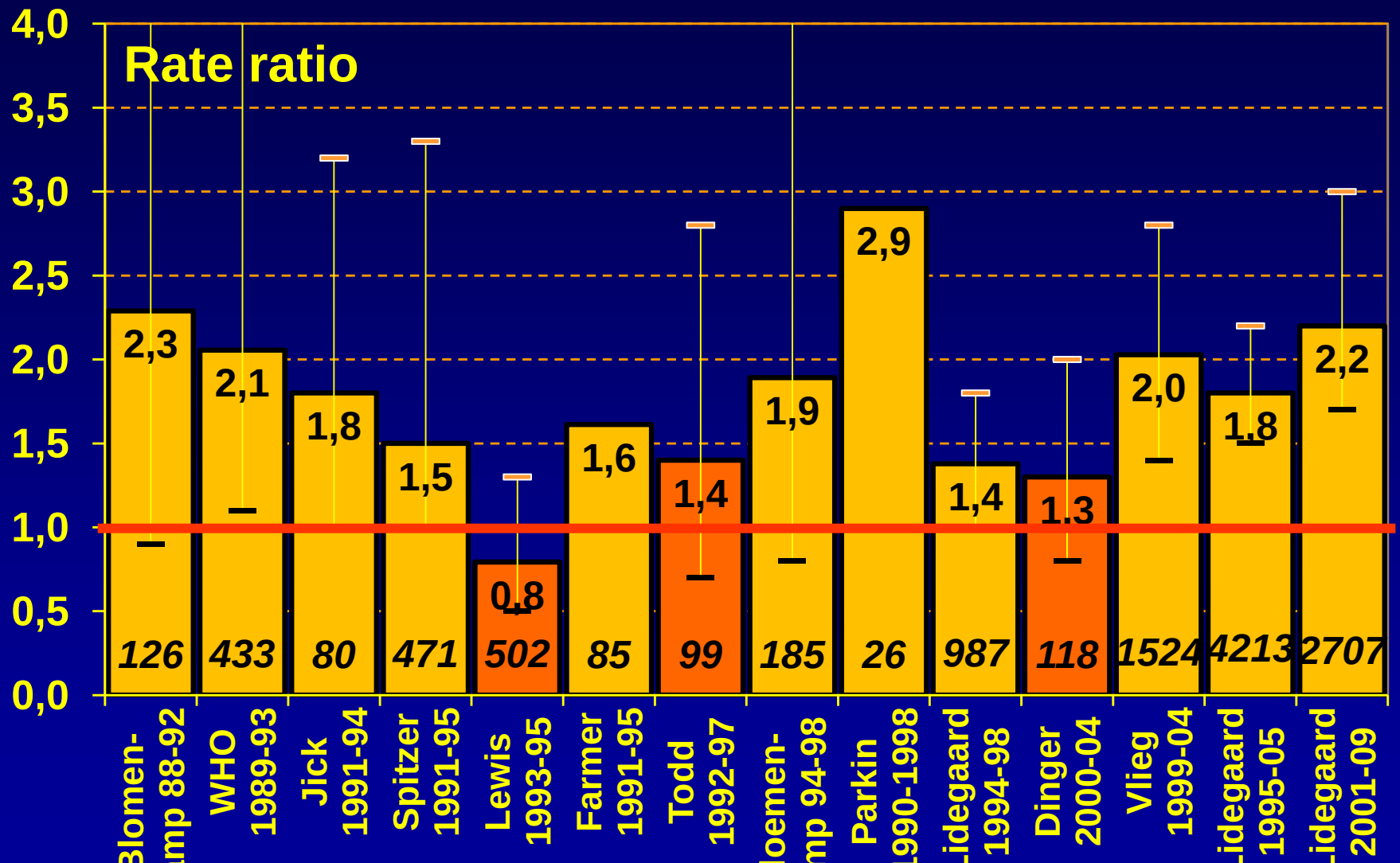
Adiposity in Danish women and men in 1994 and 2010



VT: Acquired risk factors

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

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
Seeger[07]	57	13.0*	0.9 (0.5-1.6)	4th/???

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
Seeger[07]	57	13.0*	0.9 (0.5-1.6)	4th/???

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

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

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

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

VT and drospirenone

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

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.

1995 → 2005

Cause of Deaths Registry (>1977)

Lethal VT

Statistics 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			
Lng-IUS	na	0.4 0.3-0.6					

Lidegaard et al. BMJ 2009; 339; b2890

Li/09

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

Research story

- 2010, Jan: Shapiro-Dinger critique

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.

1995 → 2005

Cause of Deaths Registry (>1977)

Lethal VT

Statistics Denmark

PIN-codes, education

vital status, emigration

Lidegaard et al. BMJ 2009

Research story

- 2010, Jan: Shapiro-Dinger critique*
- 2010, Jan: EMA request
- 2010, New case-control study by Dinger

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

Research story

- 2010, Jan: Shapiro-Dinger critique*
- 2010, Jan: EMA request
- 2010, New case-control study by Dinger

Research story

- 2010, Jan: Shapiro-Dinger critique*
- 2010, Jan: EMA request
- 2010, New case-control study by Dinger
- 2011, March: Submission BMJ

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

Results 2001-2009

- Identified 15-49 years: 1,436,130 women
- Excluded: 140,010 women
- Included in analysis: 1,296,120 women
- Observation years: 8,010,290 womenyrs
- First time VT (all): 4,307 events

  First time DVT: 2,738 (64%)

  First time PE: 1,130 (26%)

  First time other VT: 357 (10%)

Lidegaard et al. BMJ 2011; 343: d6423

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

OPEN ACCESS

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

[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: 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	na	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

		Vg. Ring
POP	0.7 0.3-1.5	0.6 0.2-1.9
Lng-IUS	0.7 0.5-1.1	

Lidegaard et al. BMJ 2011; 343: d6423

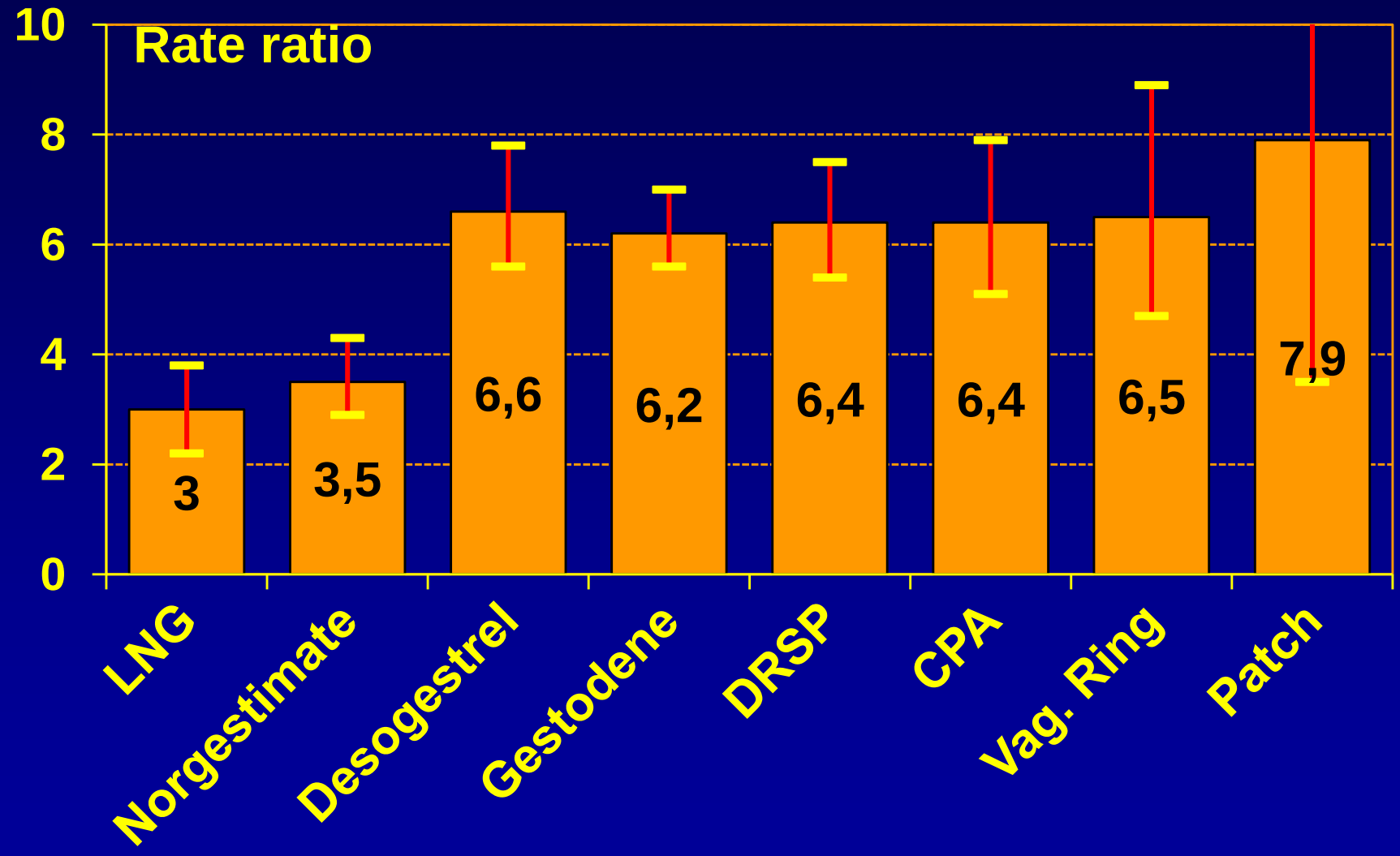
OC and VT: Progestogen type Confirmed versus non-use

ug EE	Neta	Lng	NGM	Deso	Gest	Drsp	Cypr
50	6.2 3.0-13.2	4.5 2.9-6.9	7.9 3.5-17.7 ← Patch	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
				6.5 4.5-8.9 Vaginal Ring			
POP	0.7 0.3-1.5			0.6 0.2-1.9			
Lng-IUS		0.7 0.5-1.1					

Lidegaard et al. In press

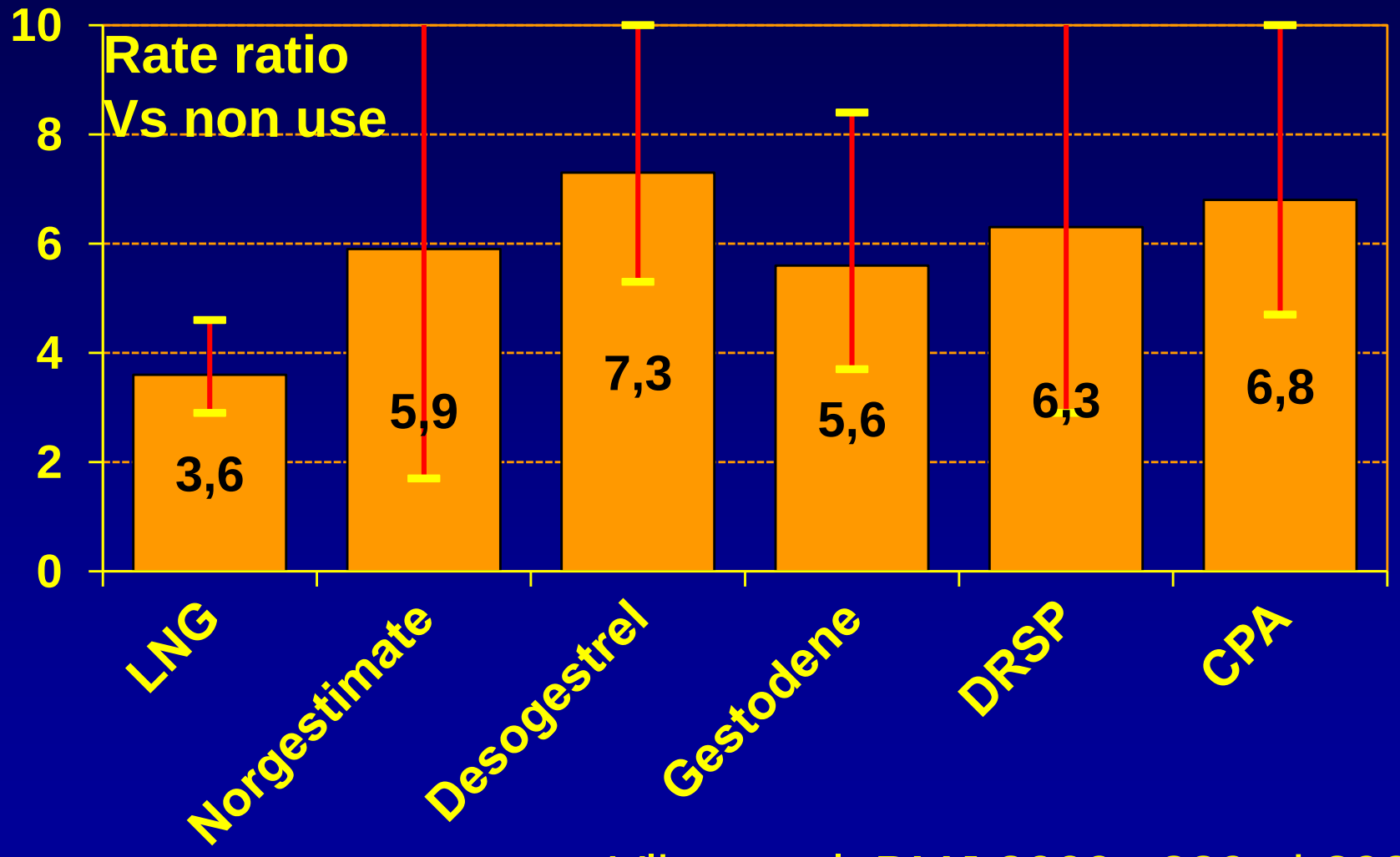
Relative risk versus non-use

Confirmed events only



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

Relative risk versus non-use



Vlieg et al. BMJ 2009; 339; b2921

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
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

	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

VT and drospirenone

	VT	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

IR = incidence per 10,000 women years

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	na	na	na	na
30-40	na	1 Ref	(ref)	1.5’ 1.0-2.3	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

VT and drospirenone

	VT	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

IR = incidence per 10,000 women years

VT and drospirenone

	VT	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

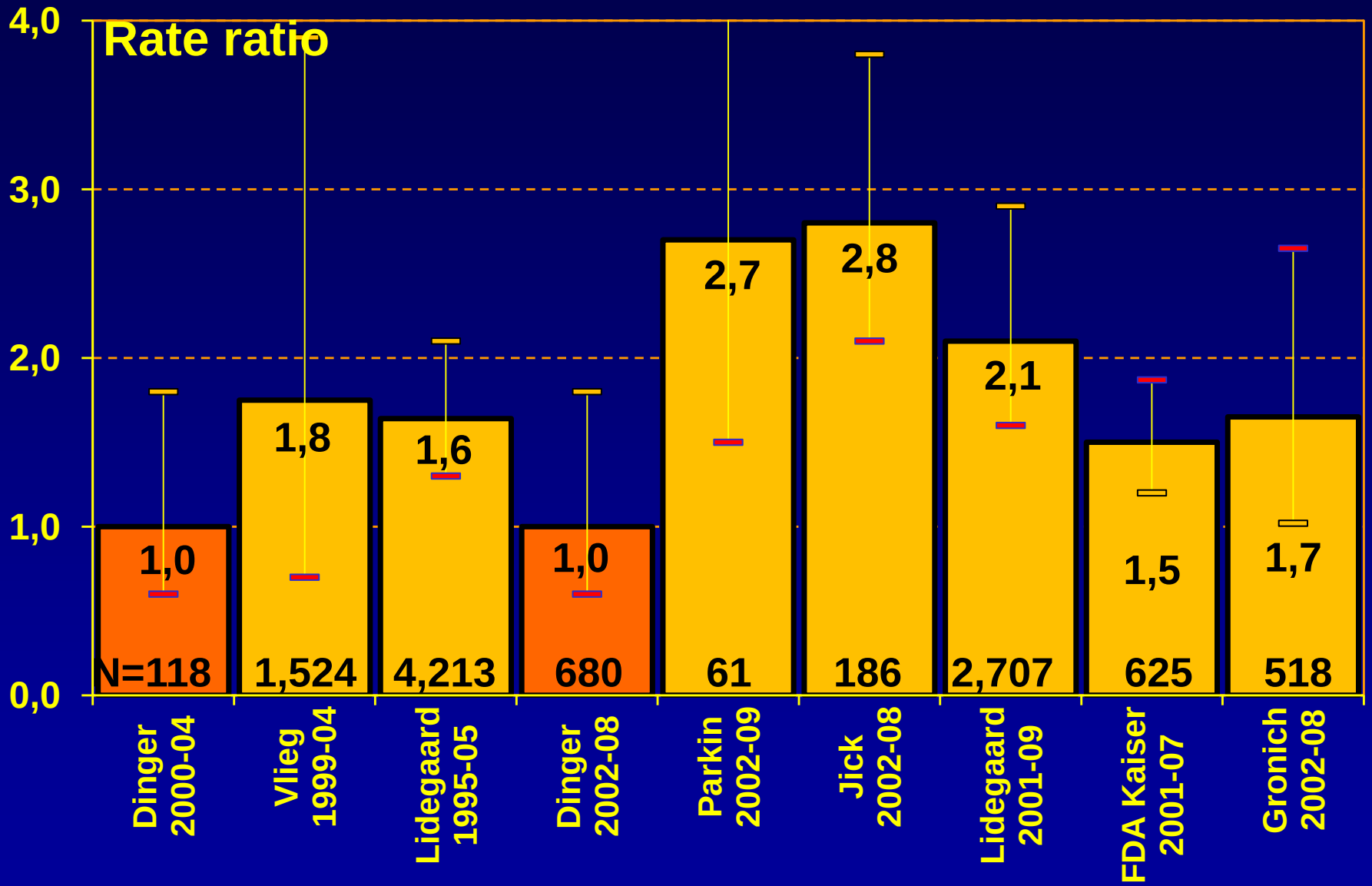
IR = incidence per 10,000 women years

VT and drospirenone

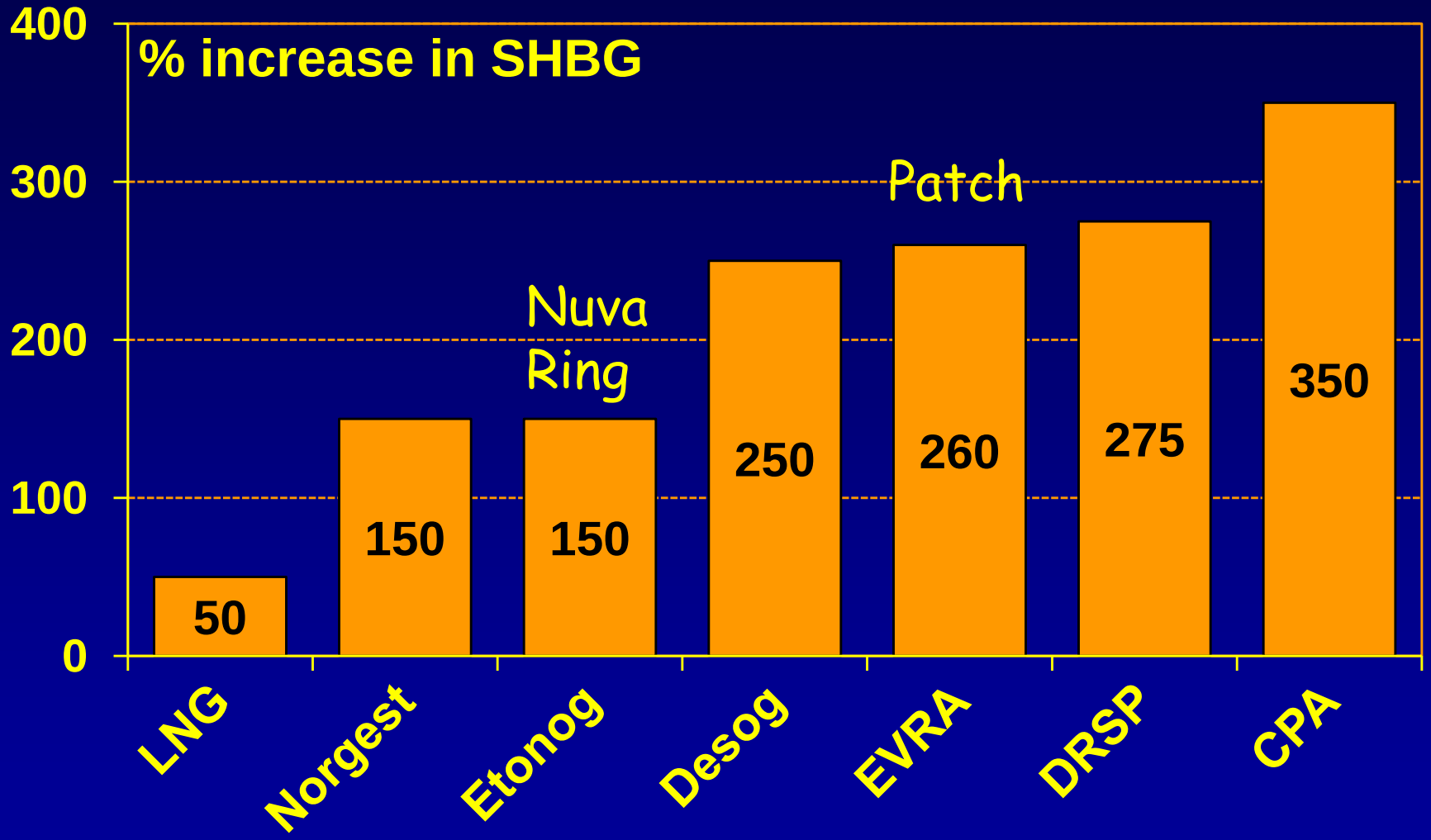
	VT	IR	Rate ratio	
Dinger[07]	118	9.1	1.0 (0.6-1.8)	4th/2nd
Vlieg[09]	1,524	na	1.7 (0.7-3.9)	4th/2nd
Lidegaard[09]	4.213	7.8	1.6 (1.3-2.1)	4th/2nd
Dinger[10]	680	na	1.0 (0.5-1.8)	4th/2nd
Parkin[11]	61	2.3	2.7 (1.5-4-7)	4th/2nd
Jick[11]	186	3.1	2.8 (2.1-3.8)	4th/2nd
Lidegaard[11]	4,246	9.3	2.1 (1.6-2.8)	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

COC with DRSP vs LNG



OCs and SHBG changes



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

OC use and activated protein C (APC) sensitivity test

Background

- Protein C is an anticoagulant
- Activated protein C (APC) exerts a proteolytic cleavage of coagulation factors
- APC resistance can be inherited (Leiden V) or be acquired; pregnancy or OC use.
- APC resistance = reduced sensitivity to APC
- Normalised APC sensitivity ratio (nAPCsr) is a quantification test of APC resistance.

Van Vliet et al. J Thromb Haemost 2004; 2: 2060-2

OC use and activated protein C (APC) sensitivity test: Results

	nAPCsr	Switch to	before	after
LNG	3.0	DRSP	3.1	3.6
DRSP	4.1	LNG	3.6	2.7
Desoges	4.1	DRSP	3.8	4.0
Gestod.	3.7	DRSP	2.8	2.8

Conclusion: nAPCsr for DRSP is of same magnitude as for 3. gen. progestogens

Van Vliet et al. J Thromb Haemost 2004; 2: 2060-2

OCs and venous thrombosis

Current status March 2012

Non use ref.	Relative risk
POP:	1
Hormone IUD:	<1
2nd generation	3
3rd generation	6
4th generation	6

COC and VT: Conclusion

- COC increase the risk of VT 3-6 fold

The risk with COC use is influenced by

- The progestogen type (~100 %)
- The oestrogen dose (~50 % -> 20%)
- Length of use (~50 %)

We need low-dose oral contraceptives with 1st and 2nd generation progestogens and low-dose pills with natural oestrogens

La contraception hormonale et la thrombose veineuse

Je vous remercie de votre attention

La présentation peut être trouvée à

ma page d’accueil

www.lidegaard.dk/slides