

# **The influence of progestogen types on the risk of venous thrombosis An up-date**

---

**Øjvind Lidegaard**

**European Congress on Menopause and  
Andropause. Athens March 2012**

**Gynaecological Clinic, Rigshospitalet  
University of Copenhagen**

---

# OC generations according to oestrogen dose and progestogen type

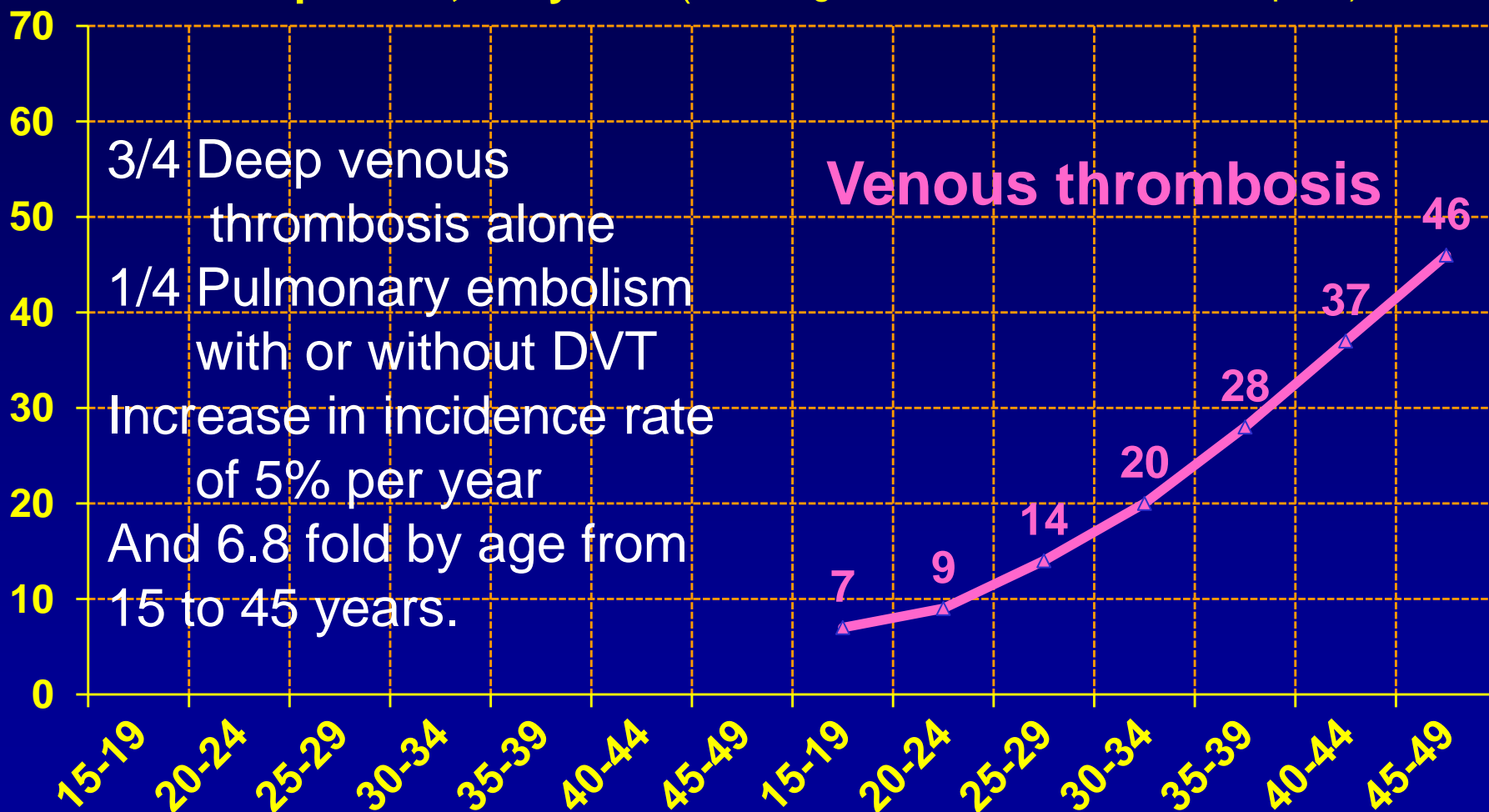
## Progestogen generation

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

# Venous thrombosis in DK 2001-2009\*

Pregnant and puerperal women excluded

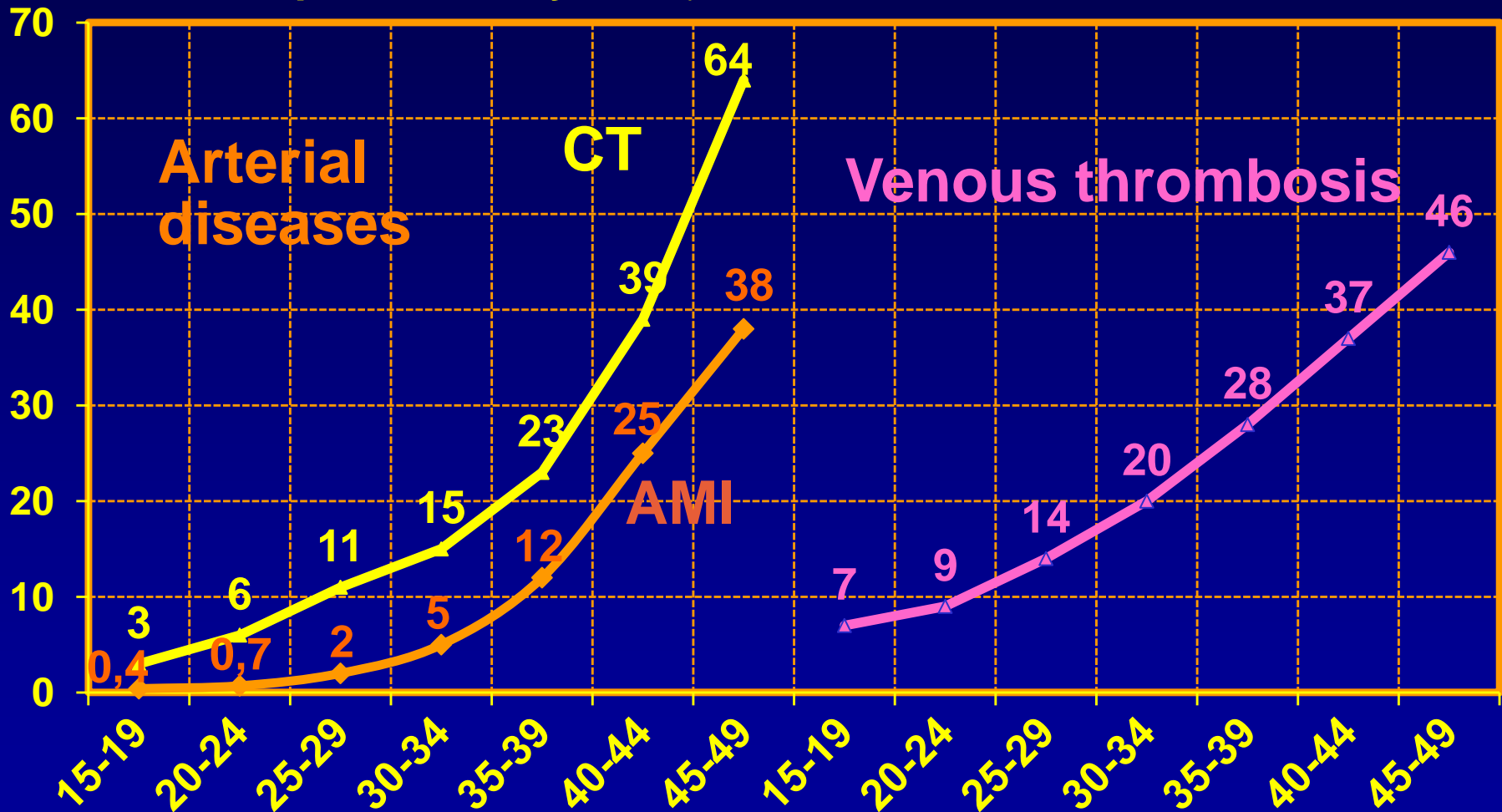
Incidence per 100,000 years (including users of hormonal contraception)



# CT, AMI and VT in DK 2001-2009\*

## Pregnant and puerperal women excluded

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



# VT: Genetic risk factors

---

<b>Risk factor</b>	<b>Prevalence</b>	<b>RR</b>
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 $\geq 30$ 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

---

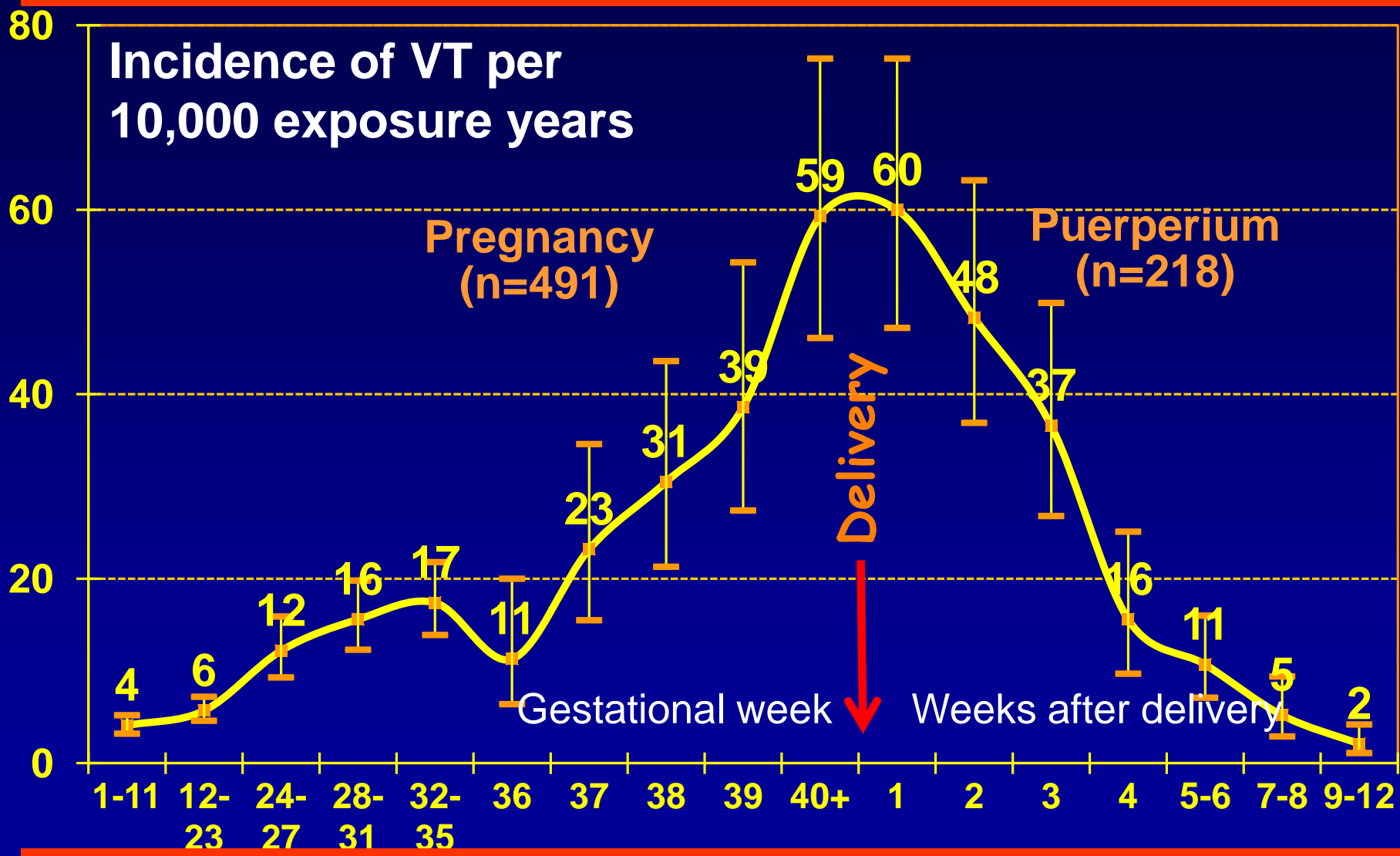
# VT: Acquired risk factors

---

	Prevalence	RR
Age $\geq 30$ vs $< 30$	50%	2.5
<b>Pregnancy</b>	<b>4%</b>	<b>8</b>
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





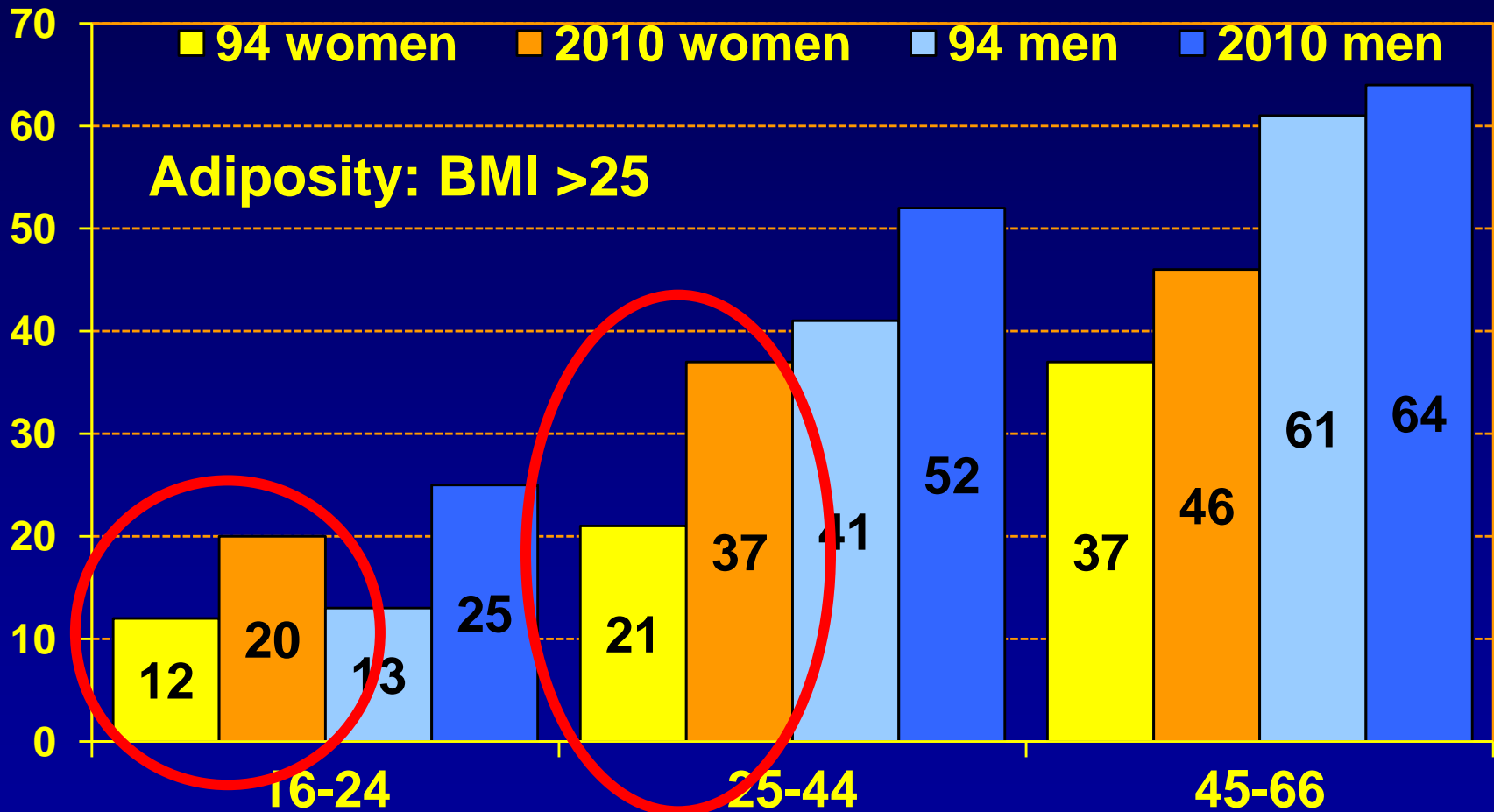
# VT: Acquired risk factors

---

	Prevalence	RR
Age $\geq 30$ vs $< 30$	50%	2.5
Pregnancy	4%	8
<b>Adiposity (BMI &gt; 25)</b>	<b>30%</b>	<b>2</b>
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



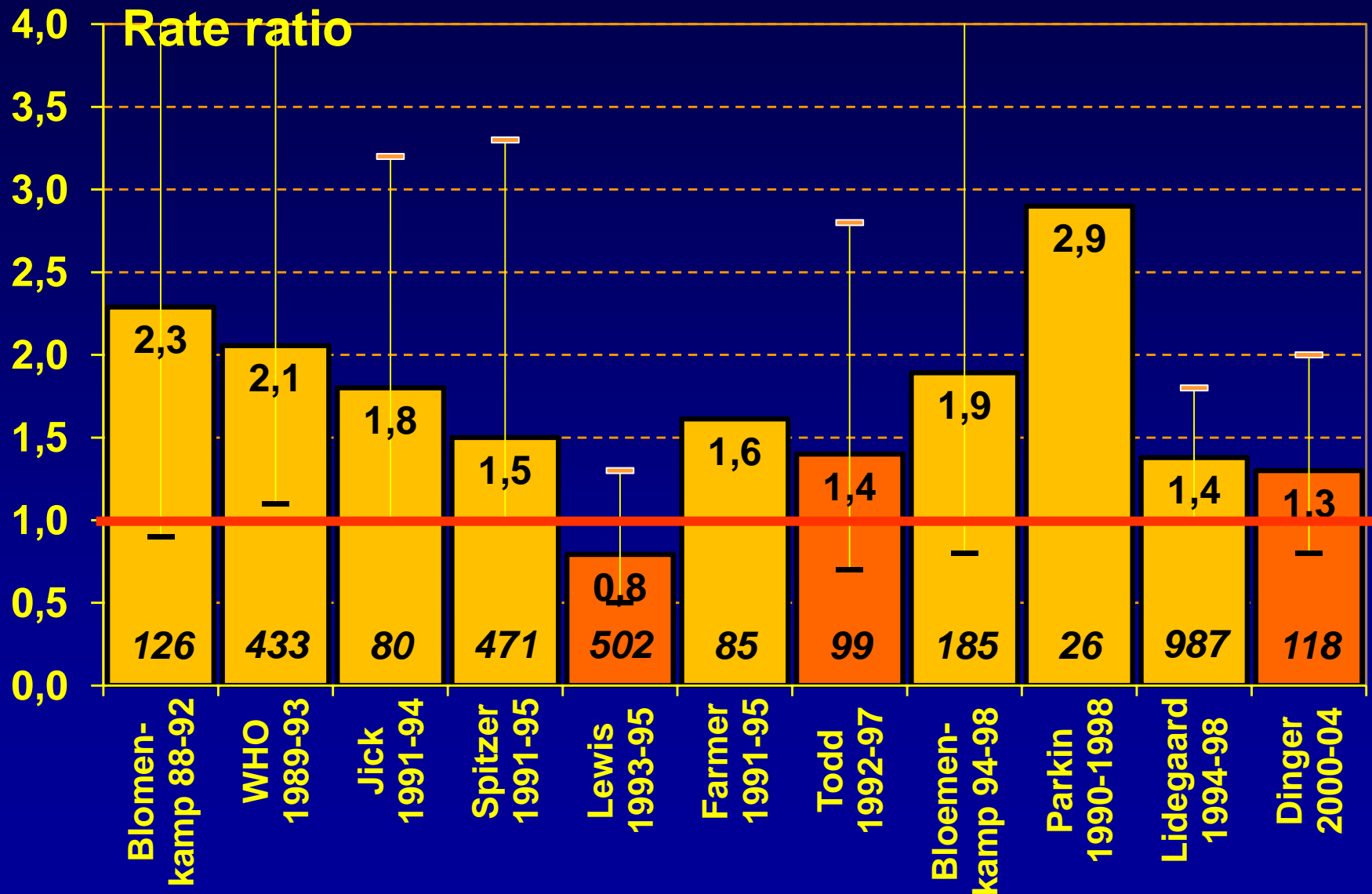
# VT: Acquired risk factors

---

	Prevalence	RR
Age $\geq 30$ 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

---

# 3<sup>rd</sup> versus 2<sup>nd</sup> generation COC



# VT and COC drospirenone (4<sup>th</sup>)

---

	VT no	Risk /10,000	Rate ratio DRSP/2nd gen
Dinger <sup>07</sup>	118	9.1	1.0 (0.6-1.8) 4th/2nd
Seeger <sup>07</sup>	57	13.0*	0.9 (0.5-1.6) 4th/???

---

# VT and COC drospirenone (4<sup>th</sup>)

---

	VT no	Risk /10,000	Rate ratio DRSP/2nd gen
Dinger <sup>07</sup>	118	9.1	1.0 (0.6-1.8) 4th/2nd
Seeger <sup>07</sup>	57	13.0*	0.9 (0.5-1.6) 4th/???

---

---

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

Øjvind Lidegaard, professor,<sup>1</sup> Ellen Løkkegaard, consultant,<sup>2</sup> Anne Louise Svendsen, statistician,<sup>3</sup> Carsten Agger, data manager<sup>4</sup>

### ABSTRACT

**Objective** To assess the risk of venous thrombosis in current users of different types of hormonal

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


RESEARCH

---

<sup>1</sup>Gynaecological Clinic, Rigshospitalet, Copenhagen University, DK-2100 Copenhagen, Denmark

---

## 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,<sup>1</sup>  Helmerhorst, professor of clinical epidemiology of fertility,<sup>1,2</sup> J P Vandenbroucke, professor of clinical epidemiology,<sup>1</sup> C J M Doggen, research fellow,<sup>1</sup> F R Rosendaal, professor of clinical epidemiology, head of department<sup>1,3,4</sup>

# VT and drospirenone

---

	VT no	Risk /10,000	Rate ratio DRSP/2nd gen
Dinger <sup>07</sup>	118	9.1	1.0 (0.6-1.8) 4th/2nd
Seeger <sup>07</sup>	57	13.0*	0.9 (0.5-1.6) 4th/???
Vlieg <sup>09</sup>	1,524	na	1.7 (0.7-3.9) 4th/2nd
Lidegaard <sup>09</sup>	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 of Denmark

PIN-codes, education  
vital status, emigration

# 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	<b>1</b> <b>Ref</b>	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					

# VT and drospirenone

---

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

# Research story

---

- 2010, Jan: Shapiro-Dinger critique\*
  - 2010, Jan: EMA request
  - 2010, March: Agreement PI, EMA, and MH
  - 2010, June: Steering Committee established
  - 2010, Oct: Protocol agreement
  - 2010, New case-control study by Dinger
-

# VT and drospirenone

---

	<b>VT no</b>	<b>Risk /10,000</b>	<b>Rate ratio DRSP/2nd gen</b>
Dinger <sup>07</sup>	118	9.1	1.0 (0.6-1.8) 4th/2nd
Seeger <sup>07</sup>	57	13.0*	0.9 (0.5-1.6) 4th/???
Vlieg <sup>09</sup>	1,524	na	1.7 (0.7-3.9) 4th/2nd
Lidegaard <sup>09</sup>	4,213	7.8	1.6 (1.3-2.1) 4th/2nd
Dinger <sup>10</sup>	680	na	1.0 (0.5-1.8) 4th/2nd

---

# Research story

---

- 2010, Jan: Shapiro-Dinger critique\*
  - 2010, Jan: EMA request
  - 2010, March: Agreement PI, EMA, Bayer
  - 2010, June: Steering Committee established
  - 2010, Oct: Protocol agreement
  - 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

1.3 million women

2005



2009

**Cause of Deaths Registry (>1977)**


Lethal VT

**Statistics Denmark**

PIN-codes, education  
vital status, emigration

## 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*<sup>1</sup>, Lars Hougaard Nielsen *statistician*<sup>1</sup>, Charlotte Wessel Skovlund *data manager and scientific assistant*<sup>1</sup>, Finn Egil Skjeldstad *professor of clinical medicine*<sup>2</sup>, Ellen Løkkegaard *senior registrar in obstetrics and gynaecology*<sup>3</sup>

<sup>1</sup>Gynaecological Clinic 4232, Rigshospitalet, University of Copenhagen, Denmark; <sup>2</sup>Department of Obstetrics and Gynaecology, Institute of Clinical Medicine, University of Tromsø, Norway; <sup>3</sup>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

# 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%)

# 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			
Mirena		0.7 0.5-1.1					

Lidegaard et al. BMJ 2011; 343: d6423

# OC and VT: Progestogen type

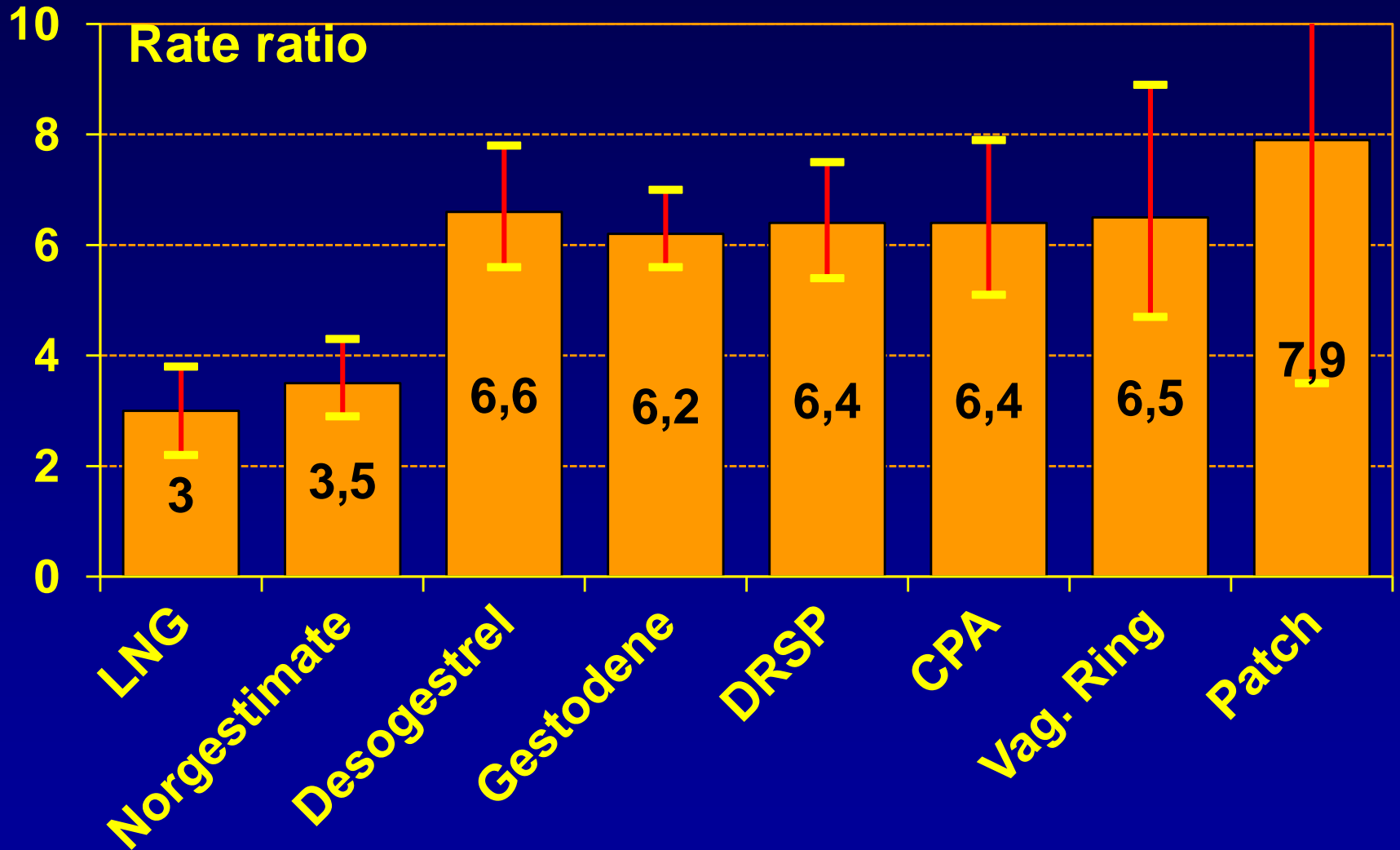
## Confirmed versus non-use

ug EE	Neta	Lng	NGM	Deso	Gest	Drsp	Cypr
50	6.2 3.0-13.2	4.5 2.9-6.9	<b>7.9</b> ← Patch 3.5-17.7	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
				<b>6.5</b> 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					

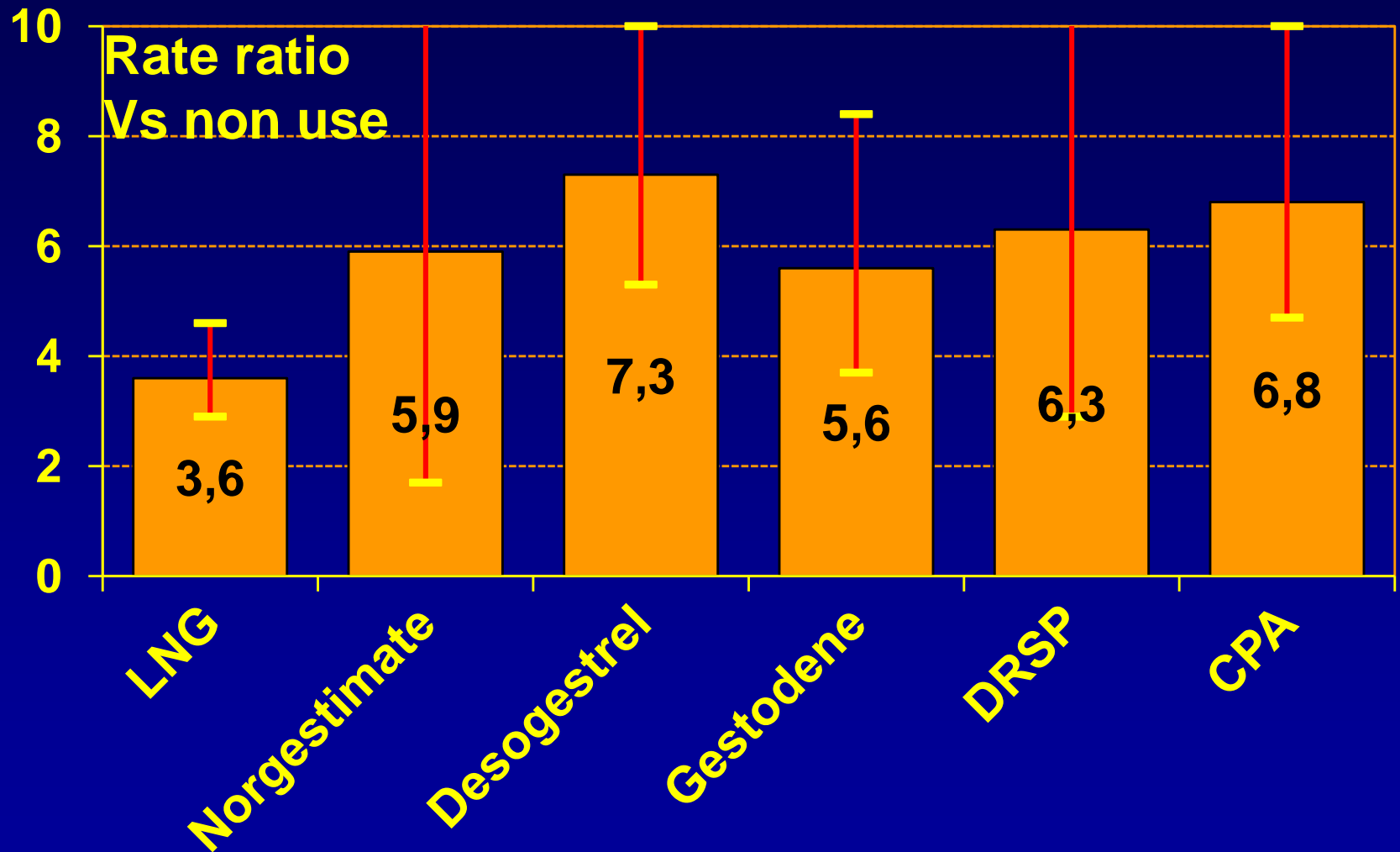
Lidegaard et al. In press

# Relative risk versus non-use

## Confirmed events only



# Relative risk versus non-use



# VT and drospirenone

	VT no	Risk /10,000	Rate ratio DRSP/2nd gen
Dinger <sup>07</sup>	118	9.1	1.0 (0.6-1.8) 4th/2nd
Seeger <sup>07</sup>	57	13.0*	0.9 (0.5-1.6) 4th/???
Vlieg <sup>09</sup>	1,524	na	1.7 (0.7-3.9) 4th/2nd
Lidegaard <sup>09</sup>	4,213	7.8	1.6 (1.3-2.1) 4th/2nd
Dinger <sup>10</sup>	680	na	1.0 (0.5-1.8) 4th/2nd
Lidegaard <sup>11</sup>	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 <sup>07</sup>	118	9.1	1.0 (0.6-1.8) 4th/2nd
Vlieg <sup>09</sup>	1,524	na	1.7 (0.7-3.9) 4th/2nd
Lidegaard <sup>09</sup>	4,213	7.8	1.6 (1.3-2.1) 4th/2nd
Dinger <sup>10</sup>	680	na	1.0 (0.5-1.8) 4th/2nd
Parkin <sup>11</sup>	61	2.3	2.7 (1.5-4-7) 4th/2nd
Jick <sup>11</sup>	186	3.1	2.8 (2.1-3.8) 4th/2nd
Lidegaard <sup>11</sup>	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 <sup>07</sup>	118	9.1	1.0 (0.6-1.8)	4th/2nd
Vlieg <sup>09</sup>	1,524	na	1.7 (0.7-3.9)	4th/2nd
Lidegaard <sup>09</sup>	4,213	7.8	1.6 (1.3-2.1)	4th/2nd
Dinger <sup>10</sup>	680	na	1.0 (0.5-1.8)	4th/2nd
Parkin <sup>11</sup>	61	2.3	2.7 (1.5-4-7)	4th/2nd
Jick <sup>11</sup>	186	3.1	2.8 (2.1-3.8)	4th/2nd
Lidegaard <sup>11</sup>	4,246	9.3	2.1 (1.6-2.8)	4th/2nd
FDA Kaiser <sup>11</sup>	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		

# VT and drospirenone

	VT	IR	Rate ratio	
Dinger <sup>07</sup>	118	9.1	1.0 (0.6-1.8)	4th/2nd
Vlieg <sup>09</sup>	1,524	na	1.7 (0.7-3.9)	4th/2nd
Lidegaard <sup>09</sup>	4,213	7.8	1.6 (1.3-2.1)	4th/2nd
Dinger <sup>10</sup>	680	na	1.0 (0.5-1.8)	4th/2nd
Parkin <sup>11</sup>	61	2.3	2.7 (1.5-4-7)	4th/2nd
Jick <sup>11</sup>	186	3.1	2.8 (2.1-3.8)	4th/2nd
Lidegaard <sup>11</sup>	4,246	9.3	2.1 (1.6-2.8)	4th/2nd
FDA Kaiser <sup>11</sup>	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 <sup>07</sup>	118	9.1	1.0 (0.6-1.8)	4th/2nd
Vlieg <sup>09</sup>	1,524	na	1.7 (0.7-3.9)	4th/2nd
Lidegaard <sup>09</sup>	4,213	7.8	1.6 (1.3-2.1)	4th/2nd
Dinger <sup>10</sup>	680	na	1.0 (0.5-1.8)	4th/2nd
Parkin <sup>11</sup>	61	2.3	2.7 (1.5-4.7)	4th/2nd
Jick <sup>11</sup>	186	3.1	2.8 (2.1-3.8)	4th/2nd
Lidegaard <sup>11</sup>	4,246	9.3	2.1 (1.6-2.8)	4th/2nd
FDA Kaiser <sup>11</sup>	625	7.6	1.5 (1.2-1.9)	4th/2nd
Gronich <sup>11</sup>	518	8.6	1.7 (1.0-2.7)	4th/2nd

IR = incidence per 10,000 women years

# VT and drospirenone

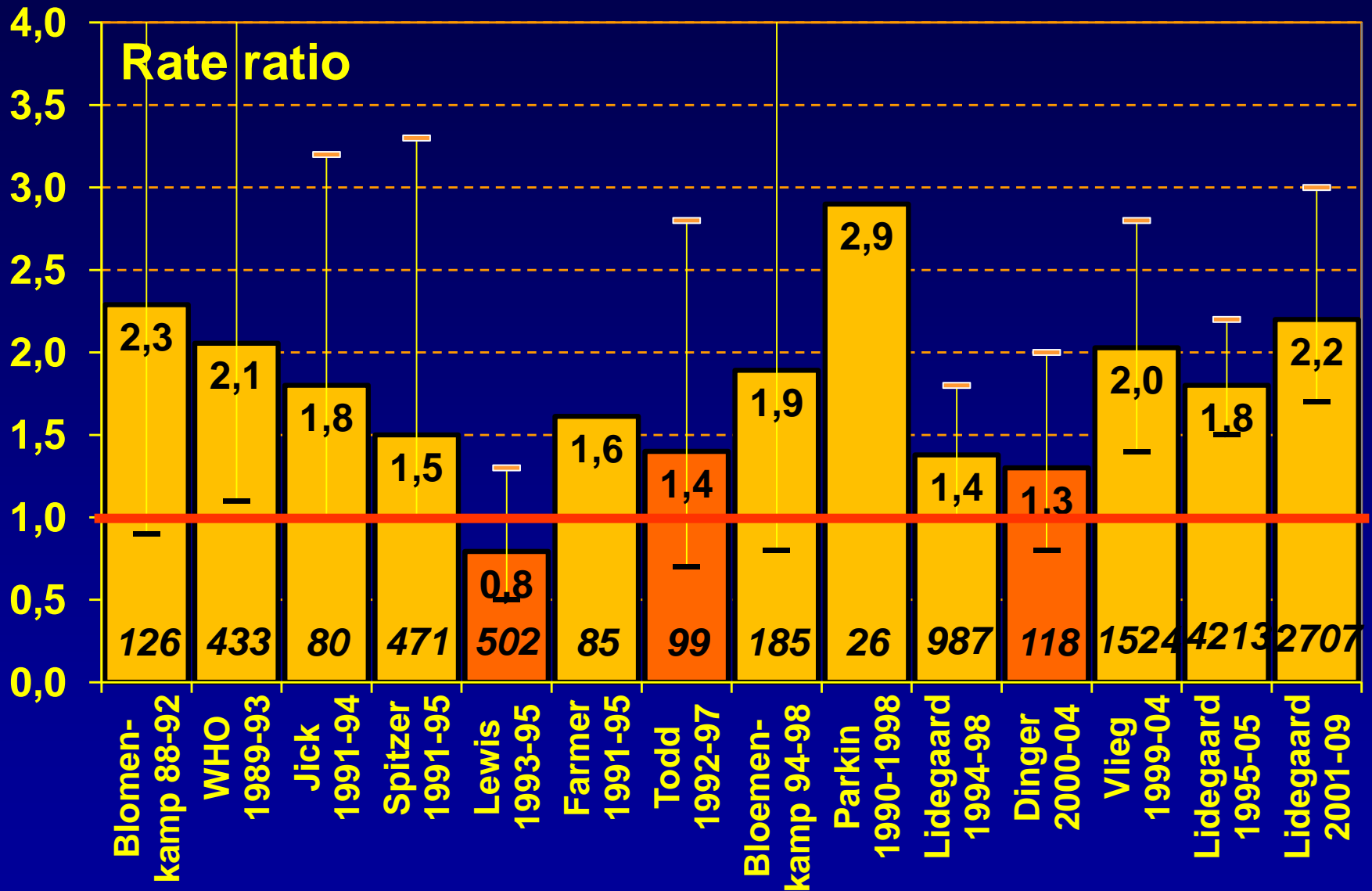
---

	VT	IR	Rate ratio	
Dinger <sup>07</sup>	118	9.1	1.0 (0.6-1.8)	4th/2nd
Vlieg <sup>09</sup>	1,524	na	1.7 (0.7-3.9)	4th/2nd
Lidegaard <sup>09</sup>	4,213	7.8	1.6 (1.3-2.1)	4th/2nd
Dinger <sup>10</sup>	680	na	1.0 (0.5-1.8)	4th/2nd
Parkin <sup>11</sup>	61	2.3	2.7 (1.5-4-7)	4th/2nd
Jick <sup>11</sup>	186	3.1	2.8 (2.1-3.8)	4th/2nd
Lidegaard <sup>11</sup>	4,246	9.3	2.1 (1.6-2.8)	4th/2nd
FDA Kaiser <sup>11</sup>	625	7.6	1.5 (1.2-1.9)	4th/2nd
Gronich <sup>11</sup>	518	8.6	1.7 (1.0-2.7)	4th/2nd

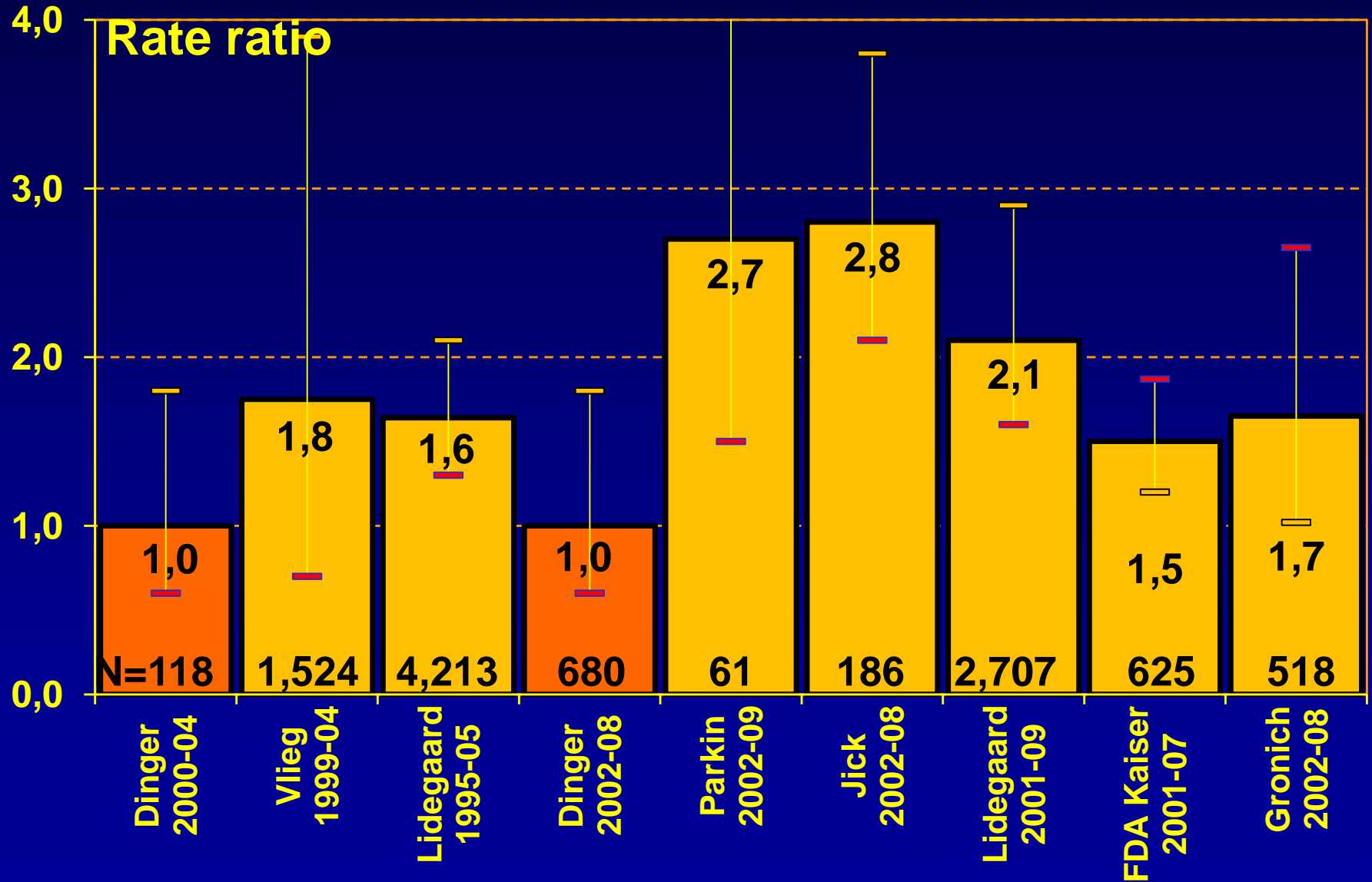
---

IR = incidence per 10,000 women years

# 3<sup>rd</sup> versus 2<sup>nd</sup> generation COC

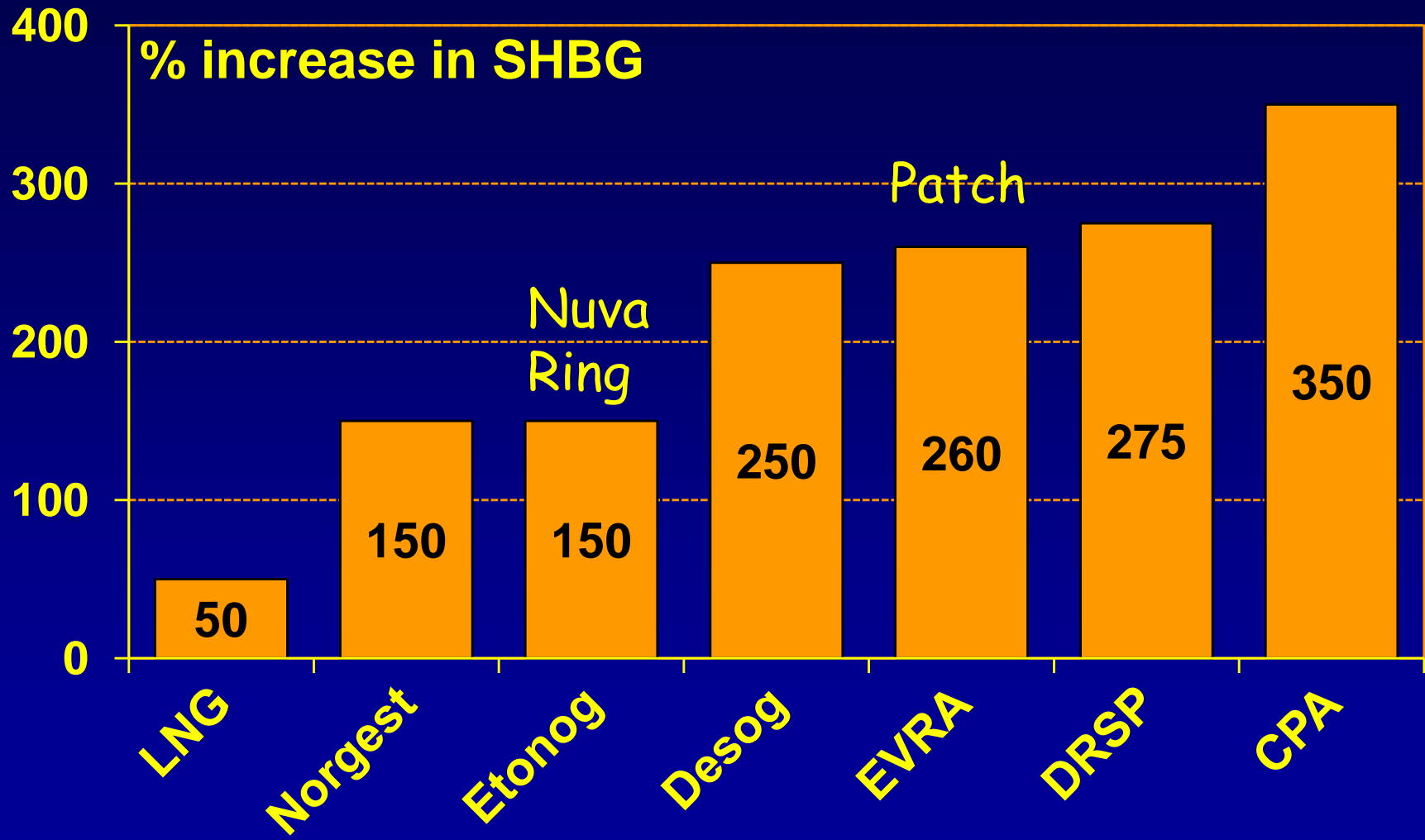


# COC with DRSP vs LNG





# OCs and SHBG changes



# 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

---

# 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%)
- The length of use (~50 %)

**We need low-dose oral contraceptives  
with 1<sup>st</sup> and 2<sup>nd</sup> generation progestogens  
and low-dose pills with natural oestrogen**

---

# Hormonal contraception and venous thrombosis

---

Thanks for your attention

[www.lidegaard.dk/slides](http://www.lidegaard.dk/slides)

From tomorrow

---