European Society of Gynecology

9th Congress of the European Society of Gynecology
9éme Congress de la Société Européenne de Gynécologie

Copenhagen, Denmark 8 - 11 September 2011

- Øjvind Lidegaard
- **Oral contraception and venous thrombosis: Significance of the progestogen type.**
- 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	1st	+ 2nd +		+	+	+ 4th
20 low	-	-	-	3rd	+	+
E2/DNG	+	-	-	-	-	
POP	+	+		+		

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
Lidegaard[09]	4,213	7.8	1.6 (1.3-2.1) 4th/2nd
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Reliability of epidemiological studies on OC and VTE

1. Valid exposure information (OC)

Valid exposure information

- Correct date of initiation of OC use
- Correct date of end of use
- Correct type of OC taken in order to specify oestrogen dose and progestogen type

This information can be achieved from

- Medical charts (incomplete)
- Questionnaires retrospectively (recall bias)
- Questionnaires prospectively (switch bias)
- Prescription registries (most reliable)

Reliability of epidemiological studies on OC and VTE

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Reliability of epidemiological studies on OC and VTE

1. Valid exposure information (OC)
2. Appropriate user definition (current user)

Reliability of epidemiological studies on OC and VTE

1. Valid exposure information (OC)
2. Appropriate user definition (current user)
3. Standardised definition of end point (VTE)
4. Valid end point: VTE (confirmation)

Standardised VTE definition and validation of end point

- Strict criteria should be applied in deciding whether or not a VTE event occurred
- Validation could be done according to
  - Venography, ultrasound, scintigraphy
  - Succeeding anticoagulation therapy
- Appropriate selection of diagnosis codes
- Voting is an unreliable way to validate VTE

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3. Standardised definition of end point (VTE)
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5. Exclusion of predisposed

Exclusion of predisposed

- Pregnant women
- Puerperal women (12 weeks after delivery)
- Women with previous thrombosis
- Women with previous cancer
- Women with known coagulation disorders
- Women undergoing fertility treatment

Reliability of epidemiological studies on OC and VTE

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5. Exclusion of predisposed
6. Confounder control (age, education)

Confounder control

- Age (by far the most important confounder)
- Length of education

Risk factors are not the same as confounders

- BMI
- Family disposition
- Smoking

Reliability of epidemiological studies on OC and VTE

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7. Control for length of use

Control for length of use

- The relative risk of VTE in current users of COC decreases by time
- The risk is 50% higher during the first year
- After the first year is the risk almost constant
- Therefore new users of new products will appear to have higher risk of VTE than users of older products typically with long-term use

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8. Control for oestrogen dose

VTE and drospirenone

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OC and VTE: Methods

National Registry of Patients (NRP)

VTE 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 VTE

Statistics of Denmark

PIN-codes, education

vital status, emigration

Lidegaard et al. BMJ 2009

OC and VTE: Progestagen type adjusted for duration of use

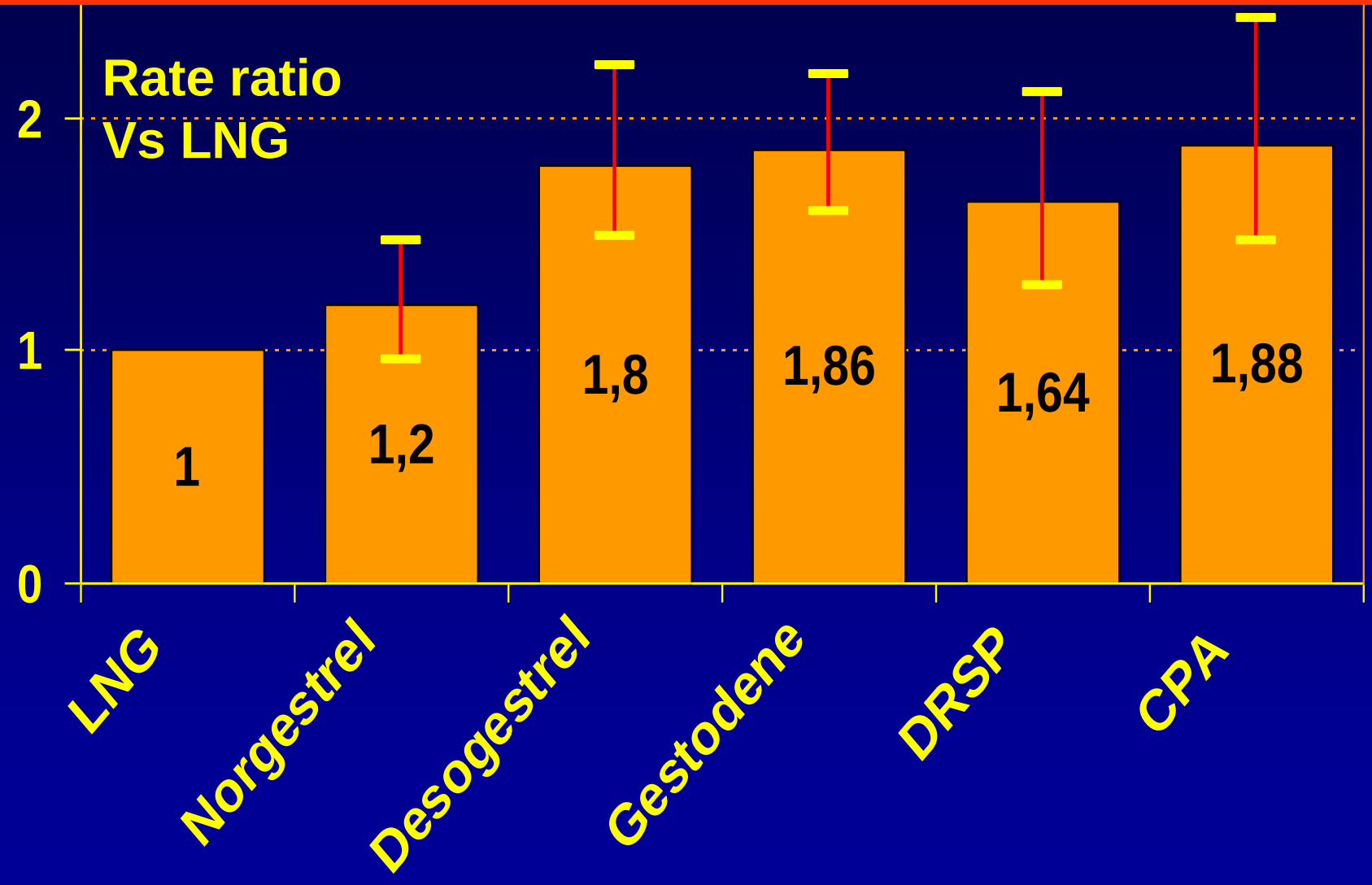
ug EE	Neta	Lng	Norg	Deso	Gest	Drsp	CPA
50	1.4 1.0-2.1	1.2 0.9-1.7	na	na	na	na	na
30-40	1.0 0.7-1.4	1 Ref	1.2 1.0-1.5	1.8 1.5-2.2	1.9 1.6-2.2	**1.64** 1.3-2.1	1.9 1.5-2.4
20	na	na	na	1.5 1.3-1.8	1.5 1.2-1.9	na	na
POP	na	0.3 0.2-0.5		0.5 0.2-1.7			
Mirena	na	0.4 0.3-0.6					

Lidegaard et al. BMJ 2009; 339; b2890

Li/09

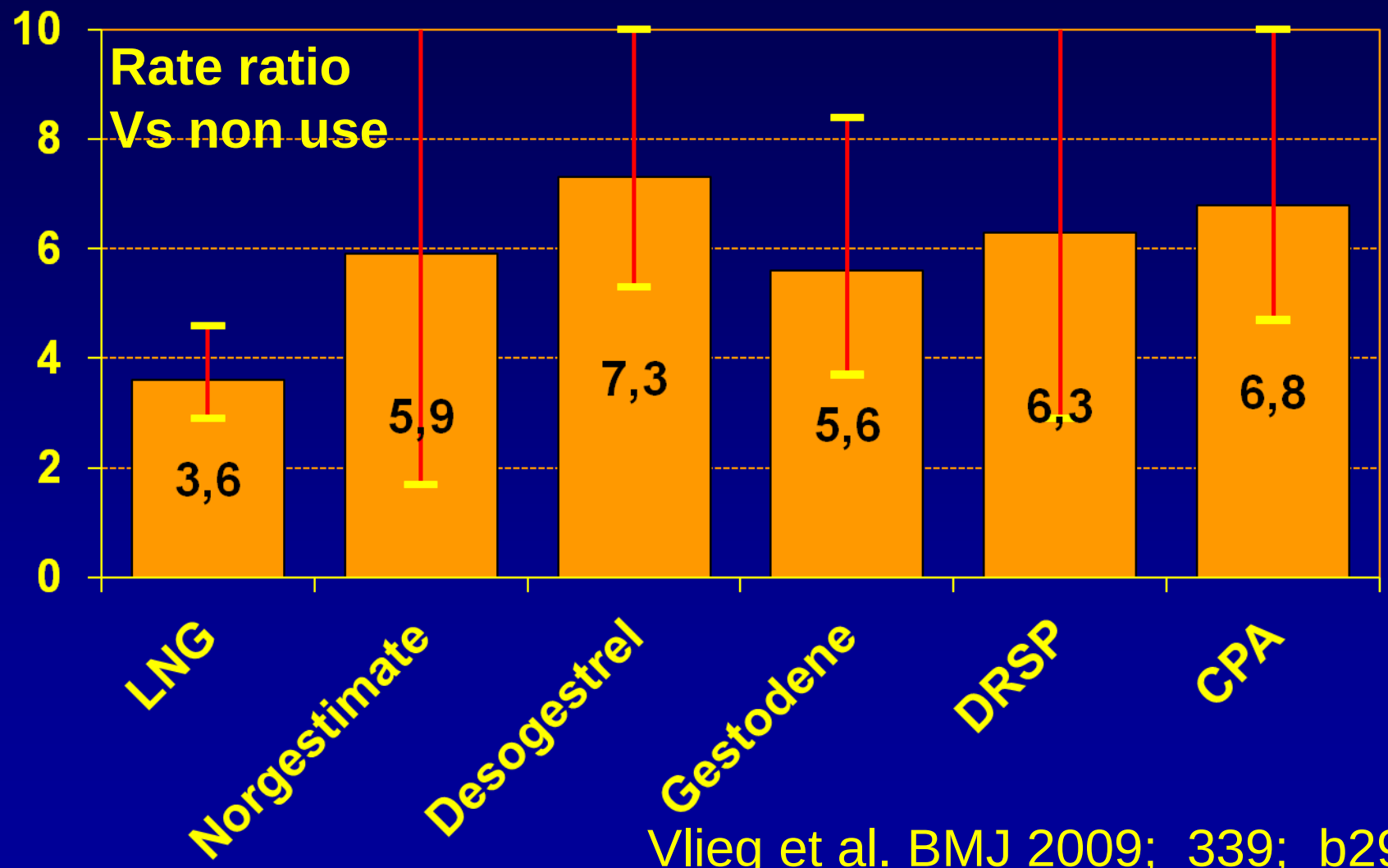
Risk versus levonorgestrel

with same length of use and same dose of oestrogen



Lidegaard et al. BMJ 2009; 339; b2890

Relative risk versus non-use



Vlieg et al. BMJ 2009; 339; b2921

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VTE and drospirenone

	VTE	Methodological quality								
	no	1	2	3	4	5	6	7	8	Total
EURAS[07]	118	↓	↓	↓	↑	↓	↑	↓	↓	2
Vlieg[09]	1,524	↓	↑	↑	↑	↑	↑	↑	↑	7
Lidegaard[09]	4,213	↑	↑	↑	↓	↑	↑	↑	↑	7
Dinger[10]	680	↓	↓	↓	↑	↓	↑	↓	↓	2
Parkin[11]	61	↑	↑	↑	↑	↑	↑	↑	↑	8
Jick[11]	186	↑	↑	↑	↑	↑	↑	↑	↑	8

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Lidegaard[09]	4,213	↑	↑	↑	↓	↑	↑	↑	↑	7
Dinger[10]	680	↓	↓	↓	↑	↓	↑	↓	↓	2
Parkin[11]	61	↑	↑	↑	↑	↑	↑	↑	↑	8
Jick[11]	186	↑	↑	↑	↑	↑	↑	↑	↑	8

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

Øjvind Lidegaard, Rigshospitalet

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Charlotte Wessel Skovlund, Rigshospitalet

All University of Copenhagen

OC and VTE: Methods

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1995 → 2009

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Lethal VTE

Statistics of Denmark

PIN-codes, education

vital status, emigration

Lidegaard et al. 2011

OC and VTE: Progestogen type Reference: non-users

ug EE	NETA	LNG	Norg	Deso	Gest	DRSP
30-40	1.6	2.2	2.6	4.2	4.2	**4.5**
	0.8-29	1.7-2.8	2.2-3.0	3.6-4.9	3.9-4.6	3.9-5.1

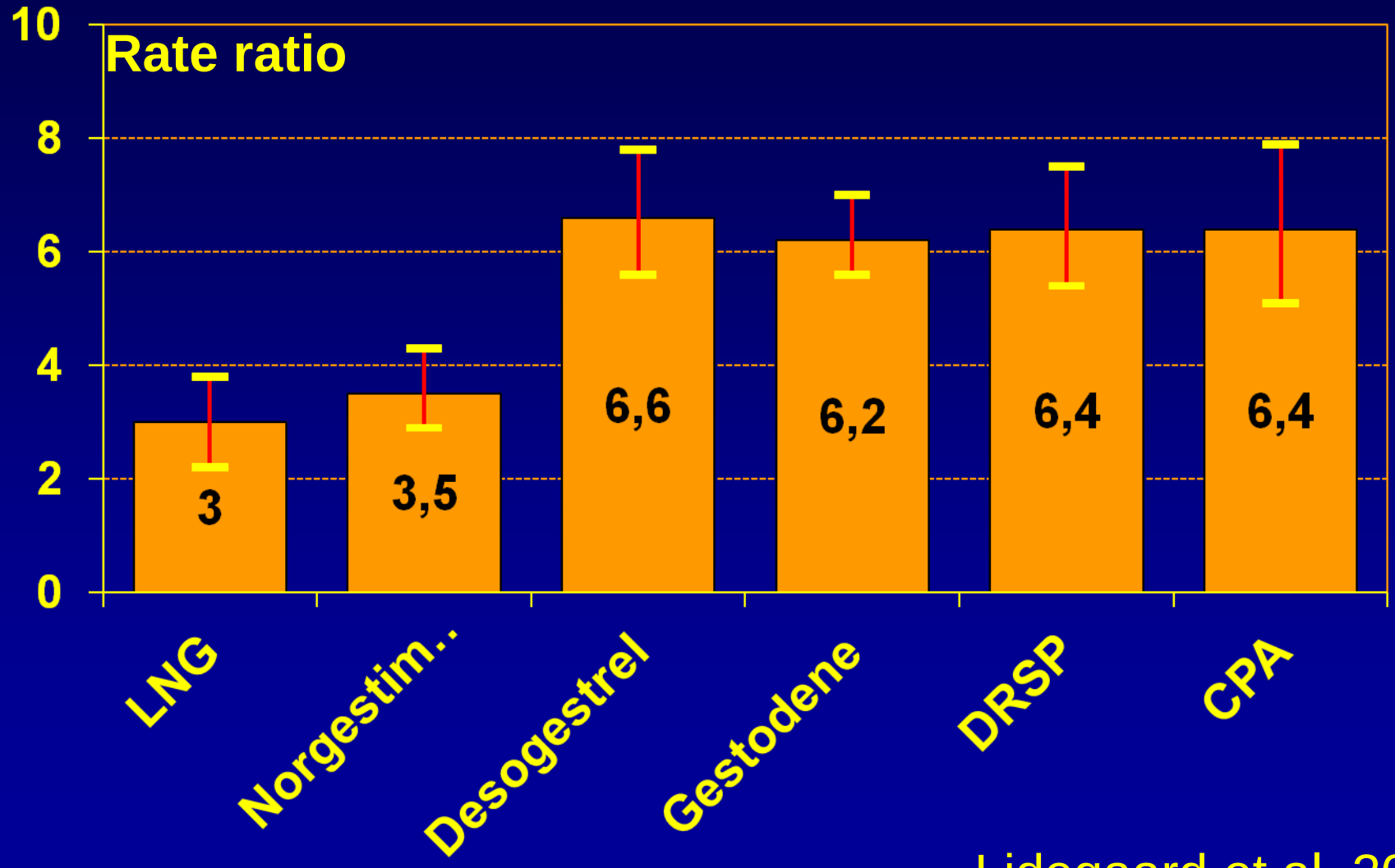
Confirmed only:

30-40	2.2	3.0	3.5	6.6	6.2	**6.4**
	1.1-4.5	2.2-3.8	2.9-4.3	5.6-7.8	5.6-7.0	5.4-7.5

Lidegaard et al. 2011

Relative risk versus non-use

Confirmed events only



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VTE and drospirenone

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Vlieg[09]	1,524	↓	↑	↑	↑	↑	↑	↑	↑	7
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Dinger[10]	680	↓	↓	↓	↑	↓	↑	↓	↓	2
Parkin[11]	61	↑	↑	↑	↑	↑	↑	↑	↑	8
Jick[11]	186	↑	↑	↑	↑	↑	↑	↑	↑	8
Lidegaard[11]	2,707	↑	↑	↑	↑	↑	↑	↑	↑	8

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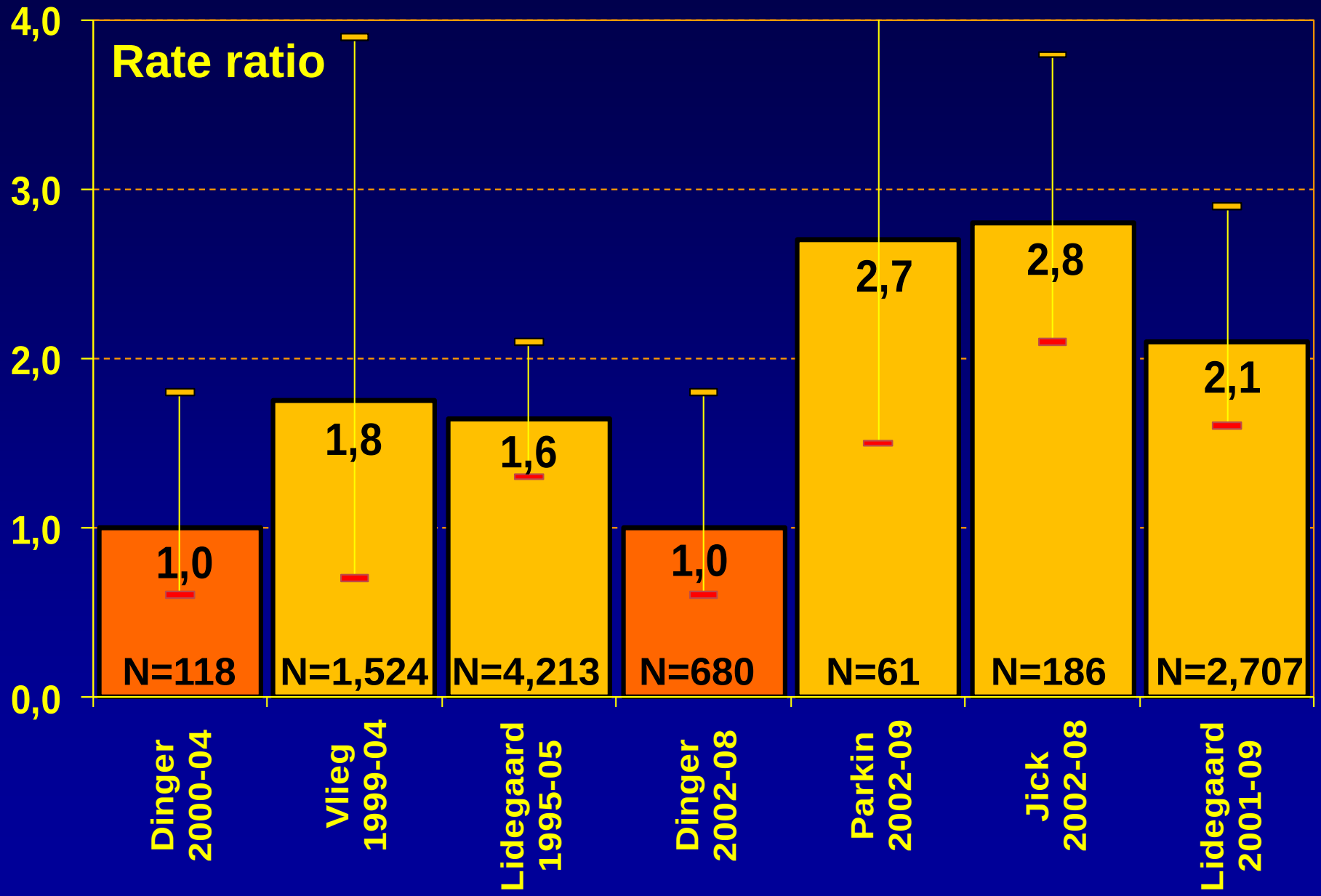
Jick[11]	186	↑	↑	↑	↑	↑	↑	↑	↑	8
Lidegaard[11]	2,707	↑	↑	↑	↑	↑	↑	↑	↑	8

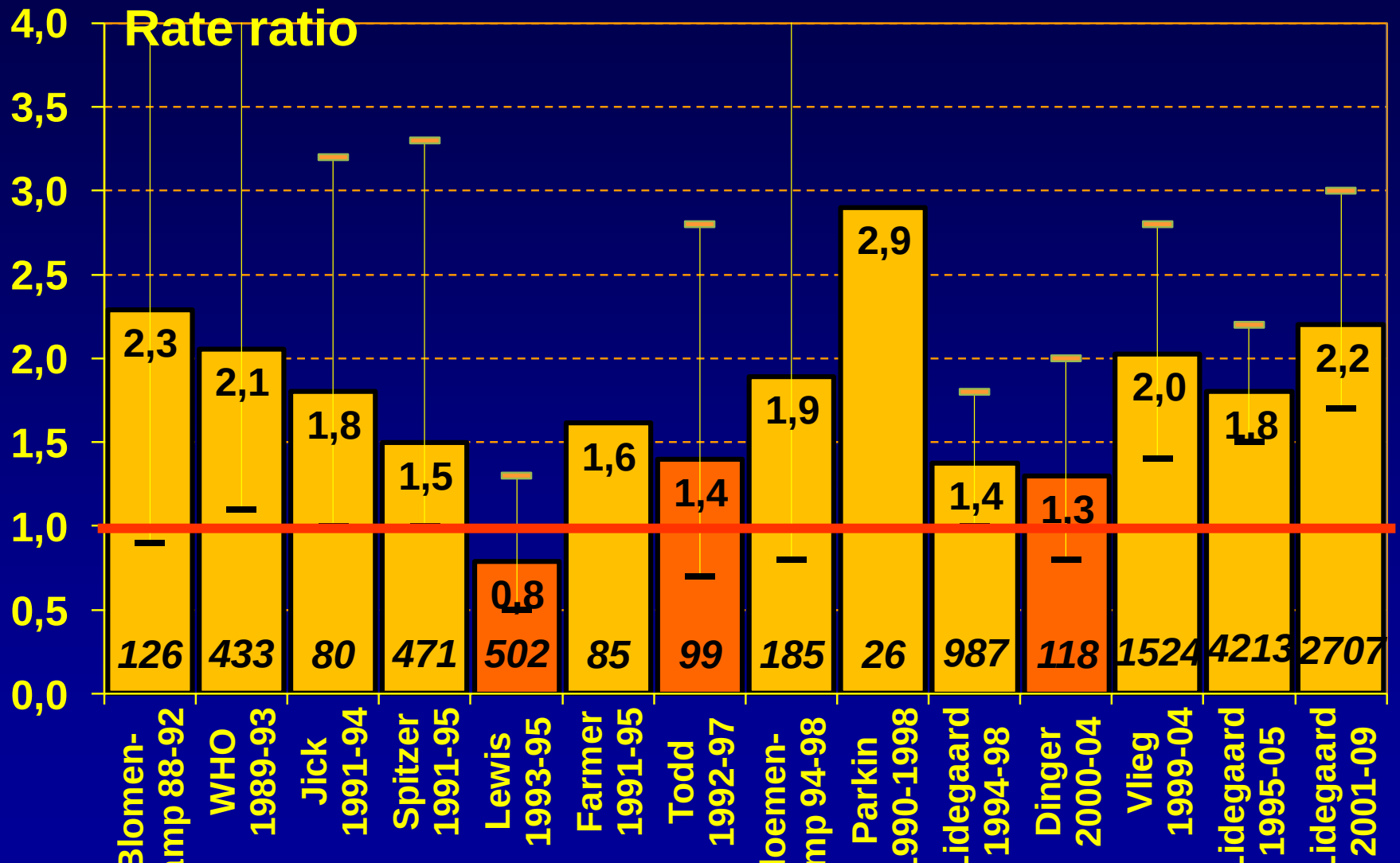
VTE and drospirenone

	VTE no	Quality index	Rate ratio DRSP/2nd gen
EURAS[07]	118	2	1.0 (0.6-1.8) 4th/2nd
Vlieg[09]	1,524	7	1.7 (0.7-3.9) 4th/2nd
Lidegaard[09]	4,213	7	1.6 (1.3-2.1) 4th/2nd
Dinger[10]	680	2	1.0 (0.5-1.8) 4th/2nd
Parkin[11]	61	8	2.7 (1.5-4-7) 4th/2nd
Jick[11]	186	8	2.8 (2.1-3.8) 4th/2nd
Lidegaard[11]	2,707	8	2.1 (1.7-2.7) 4th/2nd

COC with DRSP vs LNG



3rd versus 2nd generation COC



OCs and venous thrombosis

Current status September 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 %)
- Rate ratio OC DRSP / OC LNG at least 2

Thanks for your attention