Oral contraceptives and venous thromboembolism. Dose reduction matters.

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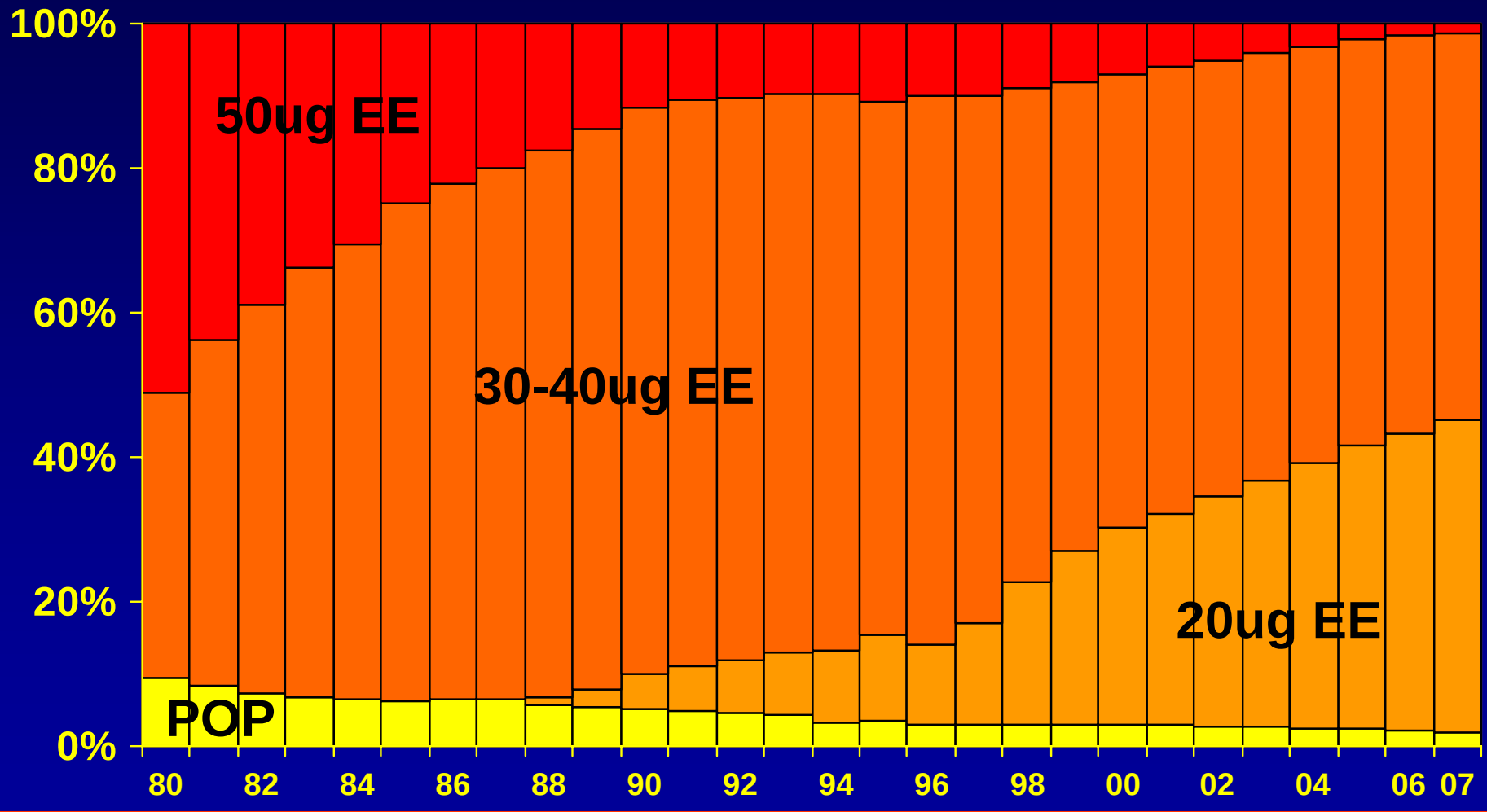
OC generations according to estrogen dose and progestagen type

Progestagen generation

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

OC types in DK according to estrogen dose during the period 1980-2007



Sale statistics. Dansk Lægemiddelstatistik

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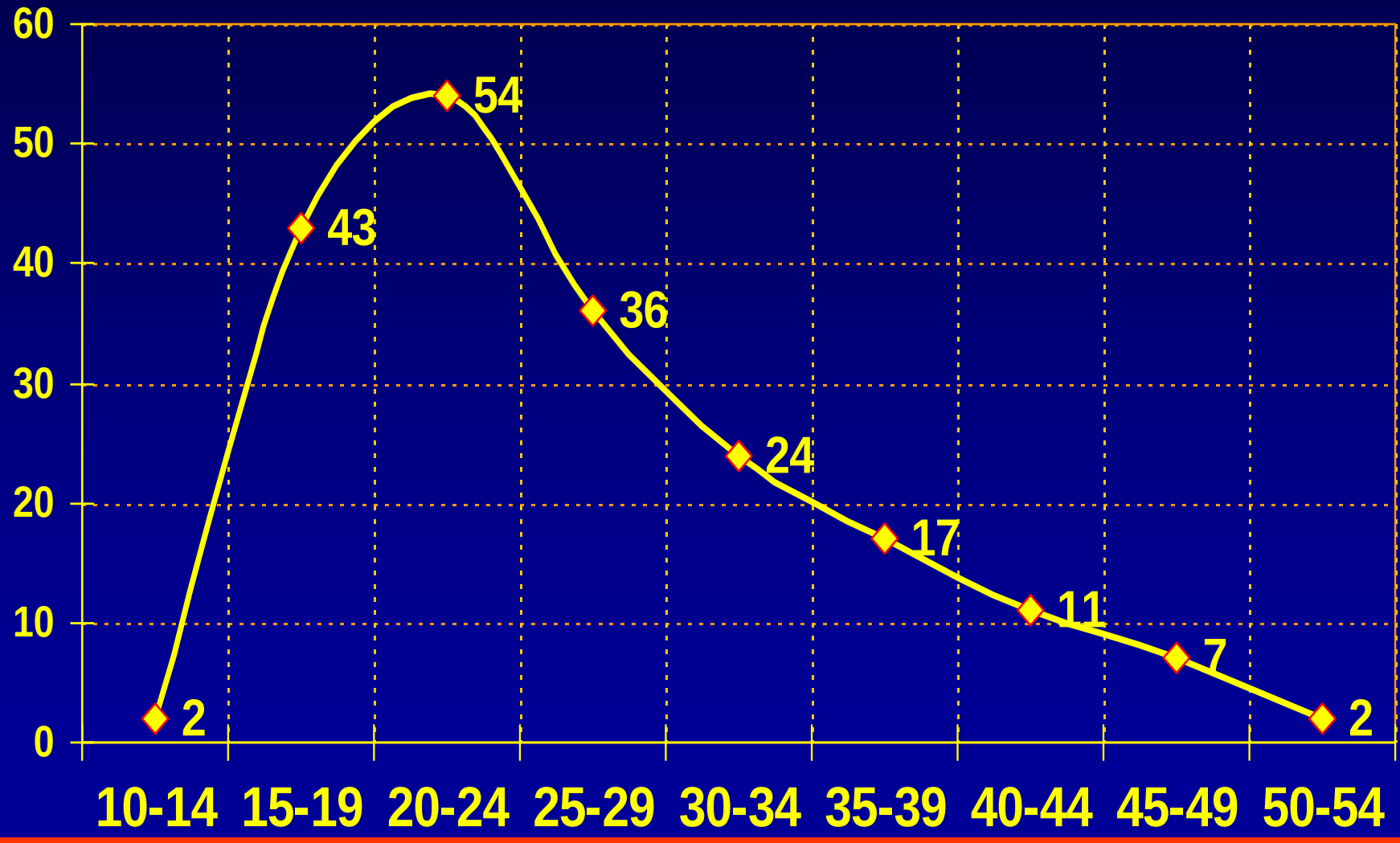
Use of oral contraceptives in DK

DDD/100 women/day at different ages



www.laegemiddelstyrelsen.dk

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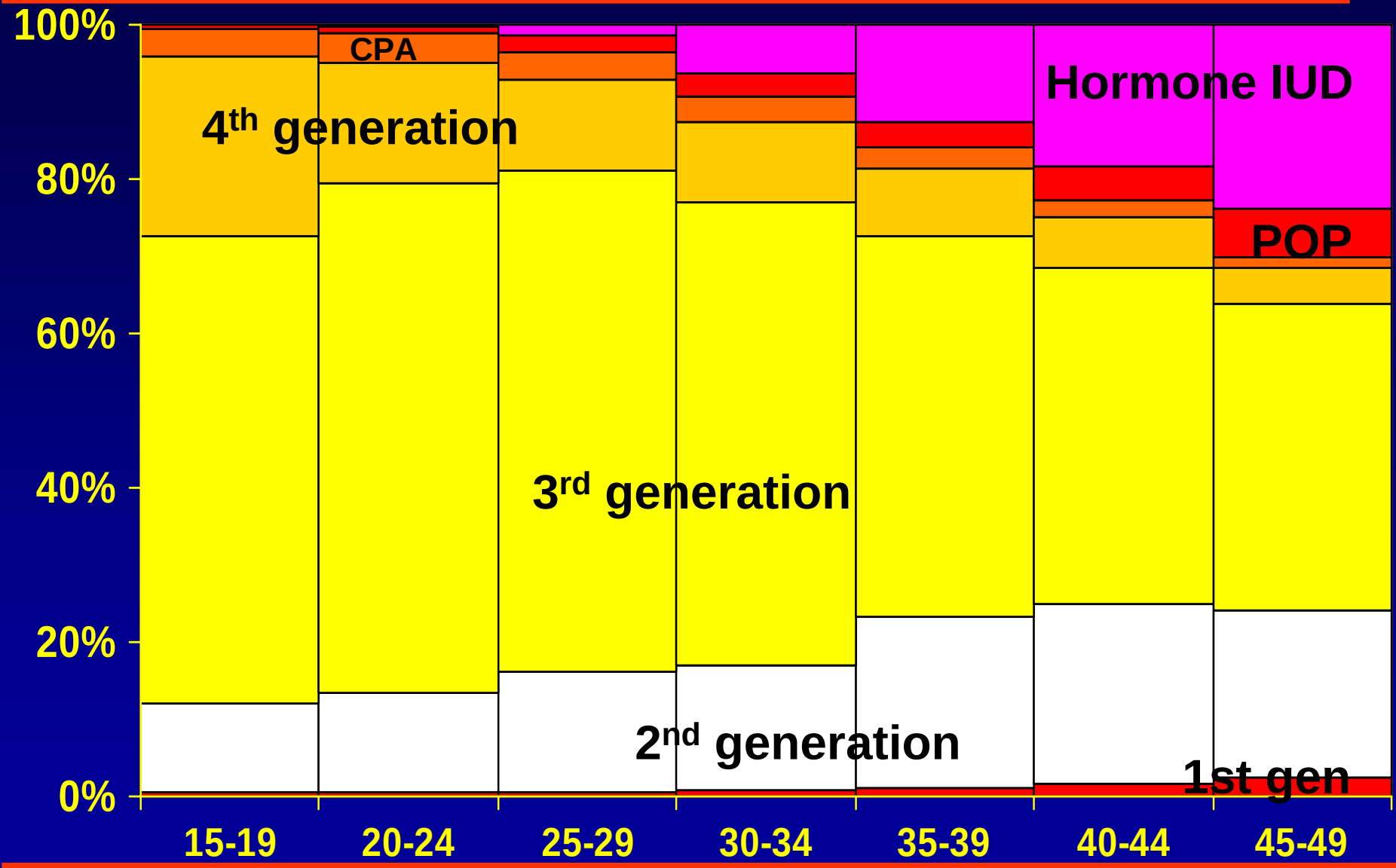
Hormonal contraception DK 2005



Sale statistics. www.laegemiddelstyrelsen.dk

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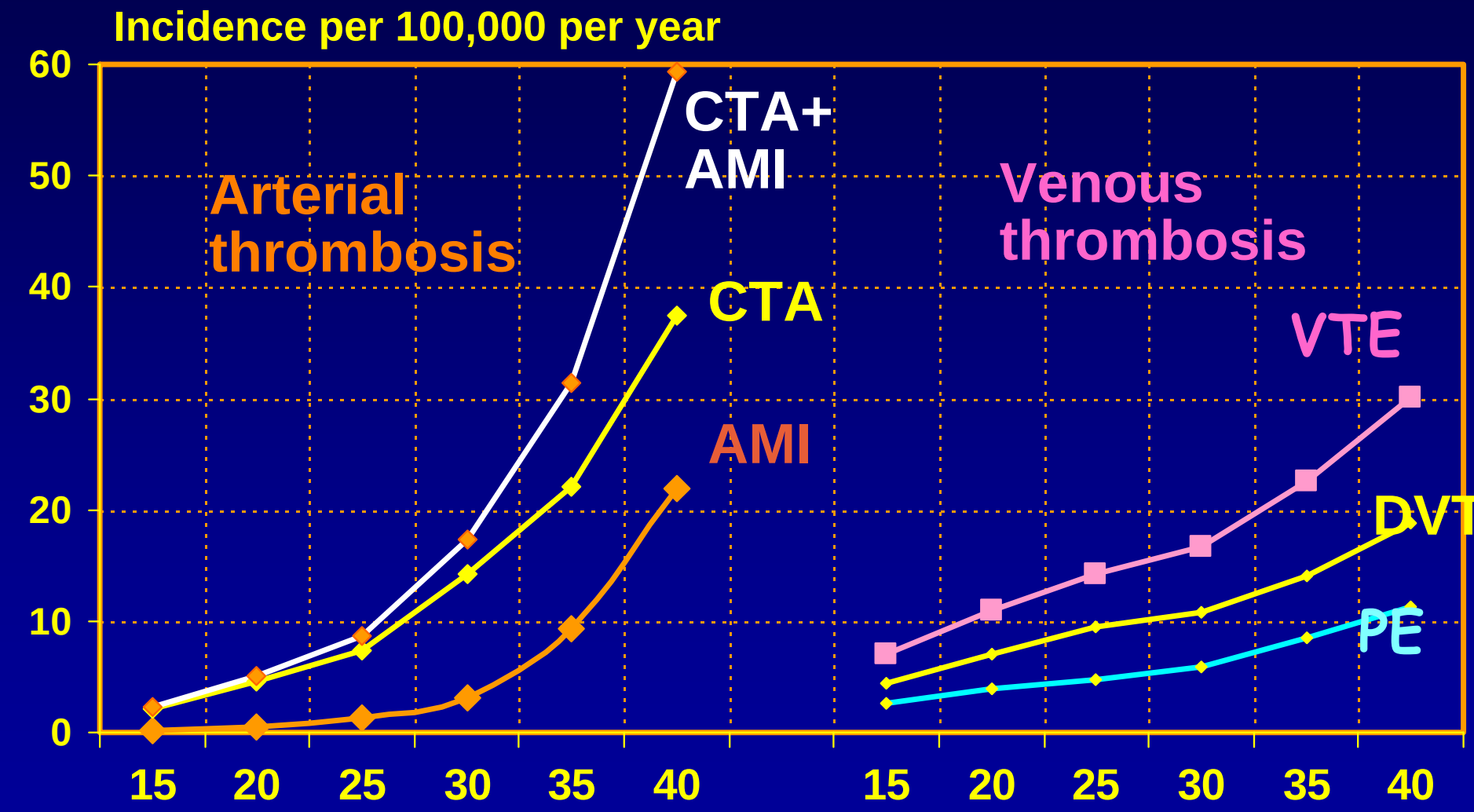
CTA, AMI & VTE in DK according to age

Pregnant and puerperal women excluded



Lidegaard Ø. Am J Obstet Gynecol 1998; 179: S62-7.

Li/04

Thrombotic diseases in young women

Per 1 million per year	CTA	AMI	VTE
Incidence	170	62	230
Non pregnant	150	60	170
Mortality	3	15	2.7
Non pregnant	3	15	2.3
Case-fatality rate	2.3%	25%	1.3%
Significant disability	30%	30%	5%
Long-term survival	↓	↓↓	→

Lidegaard. Am J Obstet Gynecol 1998; 179: s62-7

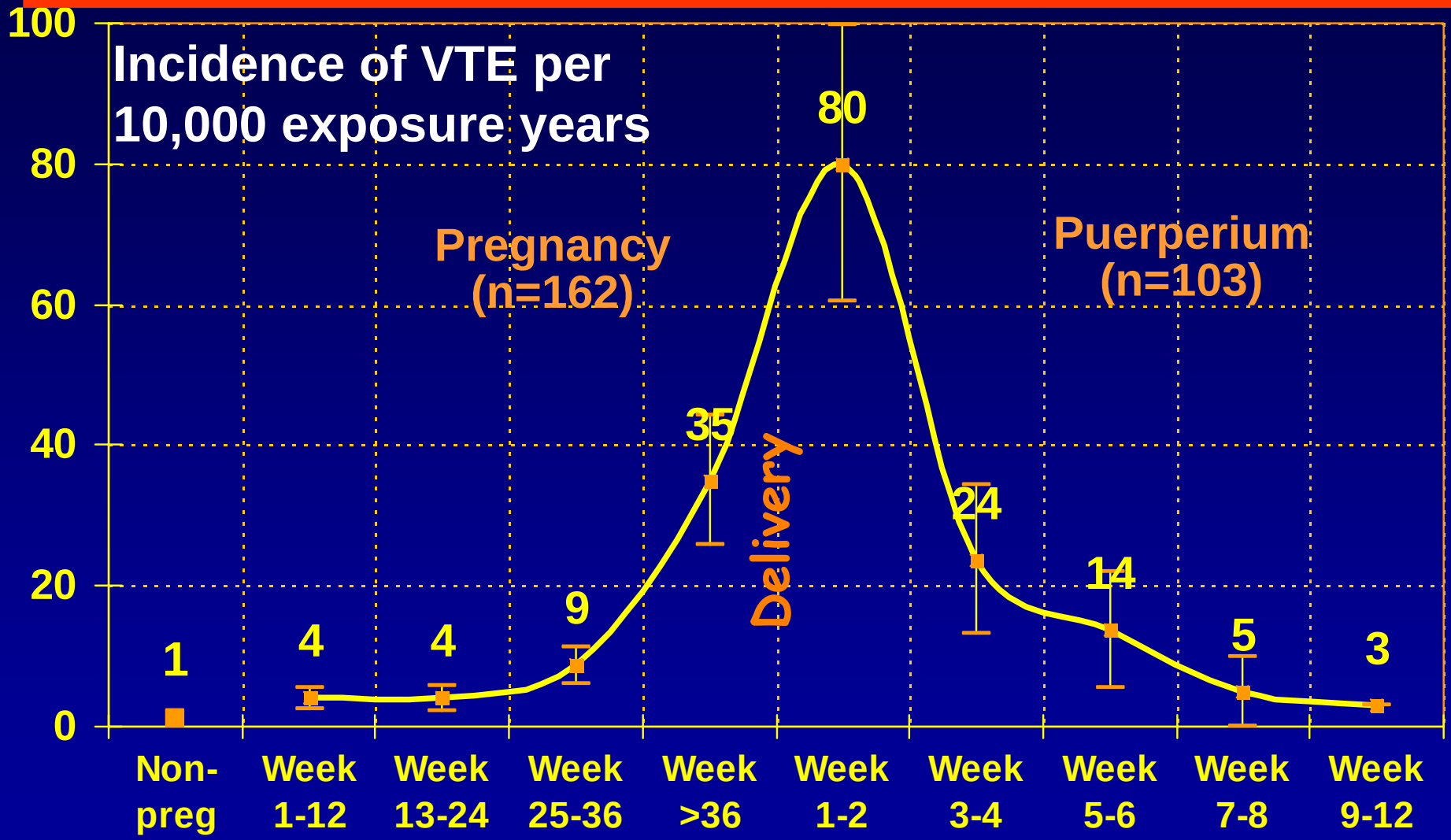
VTE: Genetic risk factors

Risk factor	Prevalence	RR
Leiden fact V hetero	5%	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

VTE: Acquired risk factors

	Prevalence	RR
Age ≥30 vs <30	50%	2.5
Pregnancy	4%	8
Adiposity (BMI>25)	36%	2
Varicose veins	8%	2
Immobilisation/trauma	?	2-10
Oral contraceptives	33%	3-4
Medical diseases	5%?	2-5

Incidence rate of VTE among pregnant and puerperal women, DK 1994-96. N=265



Hormonal contraception and VTE Denmark 1995-2005

Danish Sex Hormone Register Study DaHoRS

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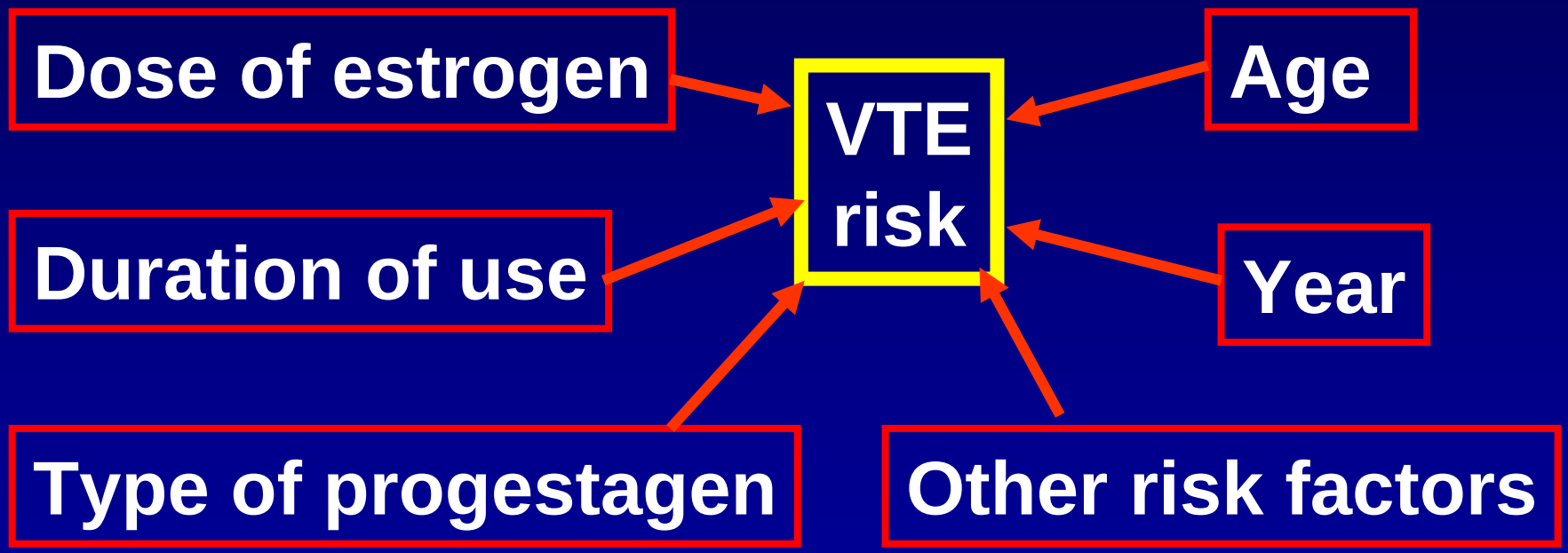
Ellen Løkkegaard, Glostrup Hospital
Anne Louise Svendsen, Copenhagen University
Carsten Agger,
Research Centre for Prevention and Health

OC and VTE: Objectives

OC axes

Confounders



OC and VTE: Material

Inclusion

- All women in Denmark 15-49 years old during the period January 1995 through December 2005 (11 years)

Exclusion

- Pregnant women
- Women with previous VTE or cancer
- Women censored at their first VTE

OC and VTE: Methods

National Registry of Patients (NRP)

VTE diagnoses,
Previous CaVD/canc.
Pregnancies

National Registry of Medicinal products (NRM): OC use
Medication against
BP↕, DM, Hyperchol.

1995 → 2005

Statistics of Denmark

Education, PIN-codes,
address, vital status

OC and VTE: Results

- Observation years: 10.4 million
- Current user years: 3.3 million
- Former user years: 2.3 million
- Never user years: 4.8 million
- Number of included VTE: 4,213
- VTE in current users of OC: 2,045
- VTE in former users of OC: 667
- VTE in never users of OC: 1,467

OC and VTE: Axes of significance

	Correlation to VTE risk
• Estrogen dose	Positive
• Progestagen generation	Positive
• Length of use	Negative
• Age of the woman	Positive
• Year (1995-2005)	Positive
• Education	Negative

OC and VTE: Results

	Crude IR/10,000wy	Rate ratio*
• Non use	3.1	1 ref.
• OC all	6.3	2.8 (2.7-3.0)
• Comb OC <1 yr	6.5	4.2 (3.7-4.7)
• Comb OC 1-4yrs	5.4	3.0 (2.7-3.3)
• Comb OC >4 yrs	7.7	2.8 (2.5-3.0)
• 1st generation OC	7.8	2.7 (2.1-3.4)
• 2nd generation OC	5.5	2.0 (1.8-2.3)
• 3rd generation OC	6.8	3.6 (3.3-3.8)
• 4th generation OC	7.8	4.0 (3.3-4.9)

***) Adjusted for age, year, education**

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OC and VTE: Results

	Crude IR/10,000wy	Rate ratio*
• Non use	3.1	reference
• POP, 30ug levo	1.8	0.6 (0.3-1.0)
• POP, 75ug deso	3.3	1.1 (0.4-3.4)
• Hormone-IUD	3.4	0.9 (0.6-1.3)

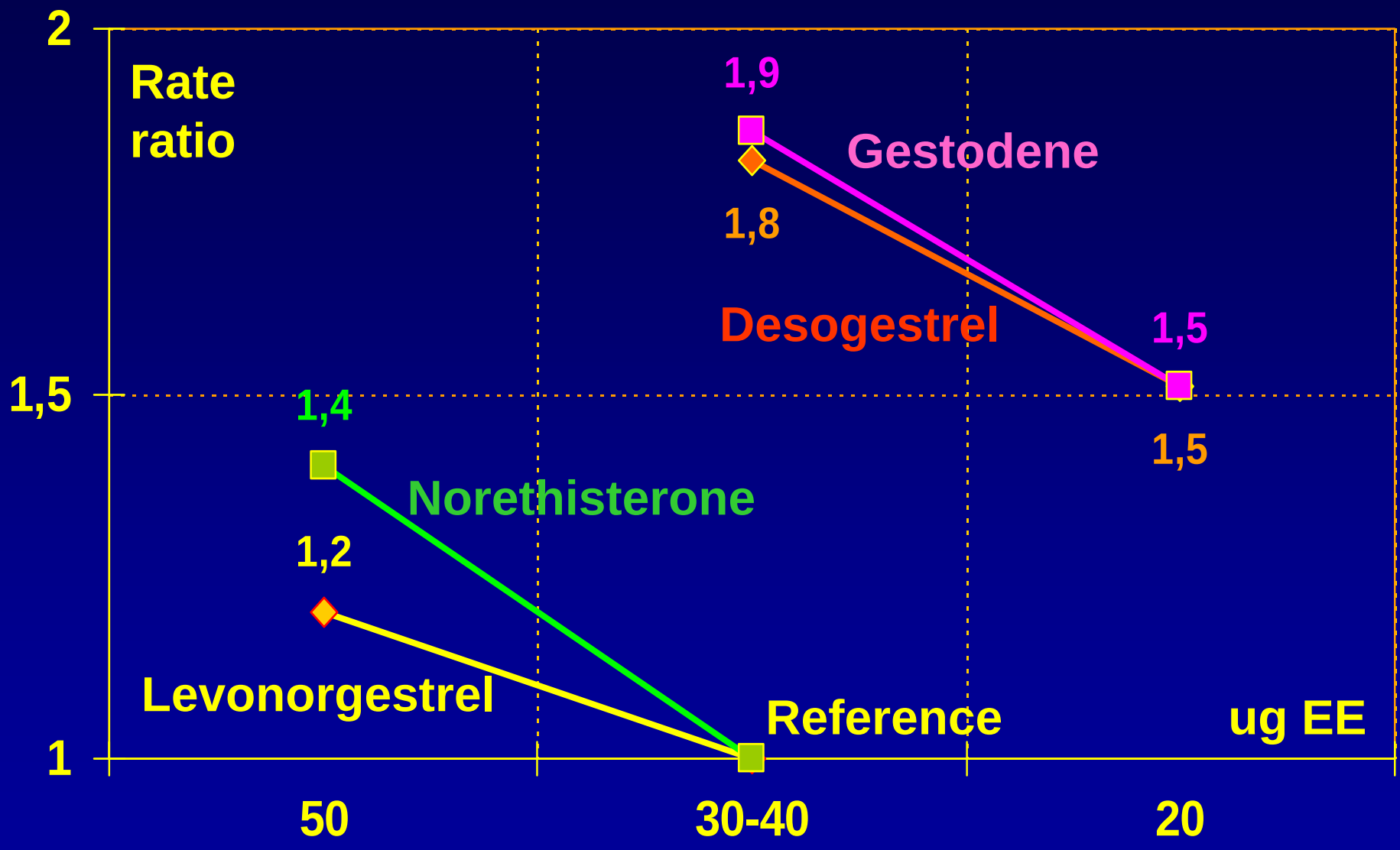
- Year: Risk increases by 1.05 per year
- Age: 15-19 years: 1.8 per 10.000 years
  45-49 years: 6.6 per 10.000 years

***) Adjusted for age, year, education**

OC and VTE: Progestagen type adjusted for duration of use

ug EE	Neta	Levo	Norg	Deso	Gest	Dros	Cypr
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	Ref	1.2 1.0-1.5	1.8 1.5-2.2	1.9 1.6-2.2	1.6 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					

Risk of VTE according to estrogen dose



Adjusted for age, year, education and length of use

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EURAS: Design

- European Active Surveillance Study (EURAS), part of phase IV commitment
- Prospective multinational cohort study
- Recruitment: 2000-2004
- 142,475 womenyears of OC use, age 25 yrs.
- Users stratified into DRSP, LNG, Other OCs
- In total 118 VTE events
  - 92 (78%) DVT
  - 26 (22%) PE

Dinger et al. Contraception 2007; 75: 344-54

EURAS vs Lidegaard

	EURAS	Lidegaard
VTE	118	4.213
Non use	2.3 /10^4 wy	3.1 /10^4 wy
1st gen:	na	7.8 /10^4 wy
2nd gen:	8.0 /10^4 wy	5.5 /10^4 wy
3rd gen:	9.9 /10^4 wy	6.8 /10^4 wy
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Preferential prescribing

Are adipose women more likely to take 4th gengeneration OCs?

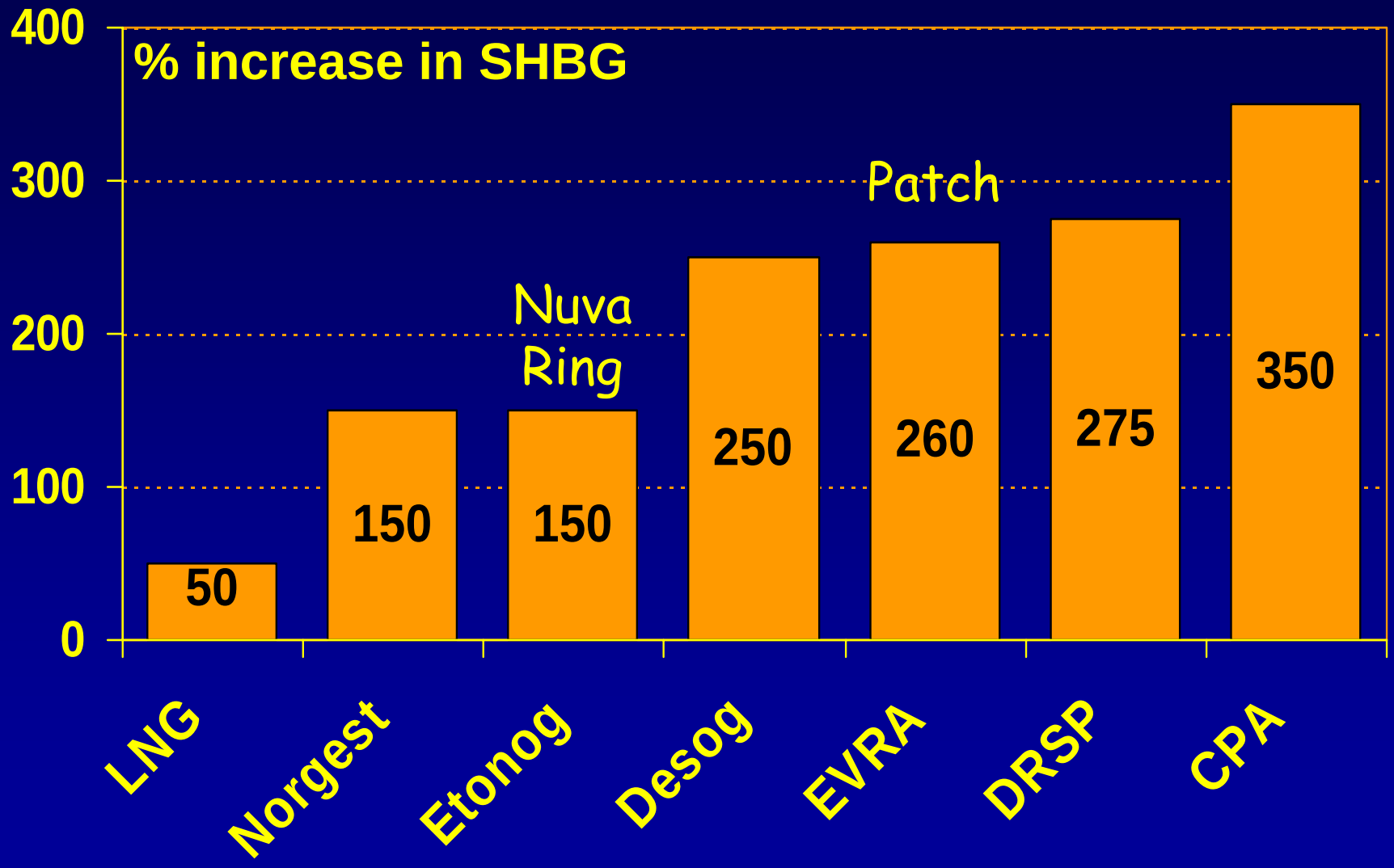
EURAS:

- BMI Mean: Levo 22.0, 4th gen: 22.9
- BMI >30: Levo: 4.4%, 4th gen: 7.0%
- Mean age: Levo: 25.2 yrs. 4th gen 26.3 yrs

"The differences were small and the preferential prescribing pattern identified here could only slightly increase the incidence of VTE in the DRSP cohort"

Heinemann & Dinger. Drug safety 2004; 27: 1001-1018
Dinger et al. Contraception 2007; 75: 344-54

OCs and SHBG changes



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

OCs and activated protein C (APC) sensitivity test

Background

- Protein C has an anticoagulant effect
- Activated protein C (APC) enhances the degradation of coagulation factors.
- APC resistance can be inherited (Leiden V) or acquired: pregnancy and OCs
- APC resistance = reduced sensitivity for APC
- Normalised APC sensitivity ratio (nAPCsr) is a quantitave test for APC resistance.

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

OCs and activated protein C (APC) resistance test: Results

	nAPCsr	Shift 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
Norgest	5.2	DRSP	4.6	4.9
NETA	3.6	DRSP	3.7	2.4

Conclusion: nAPCsr for DRSP is of same magnitude as for 3. generation progestagens

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

OC and VTE: Conclusion

Conclusion

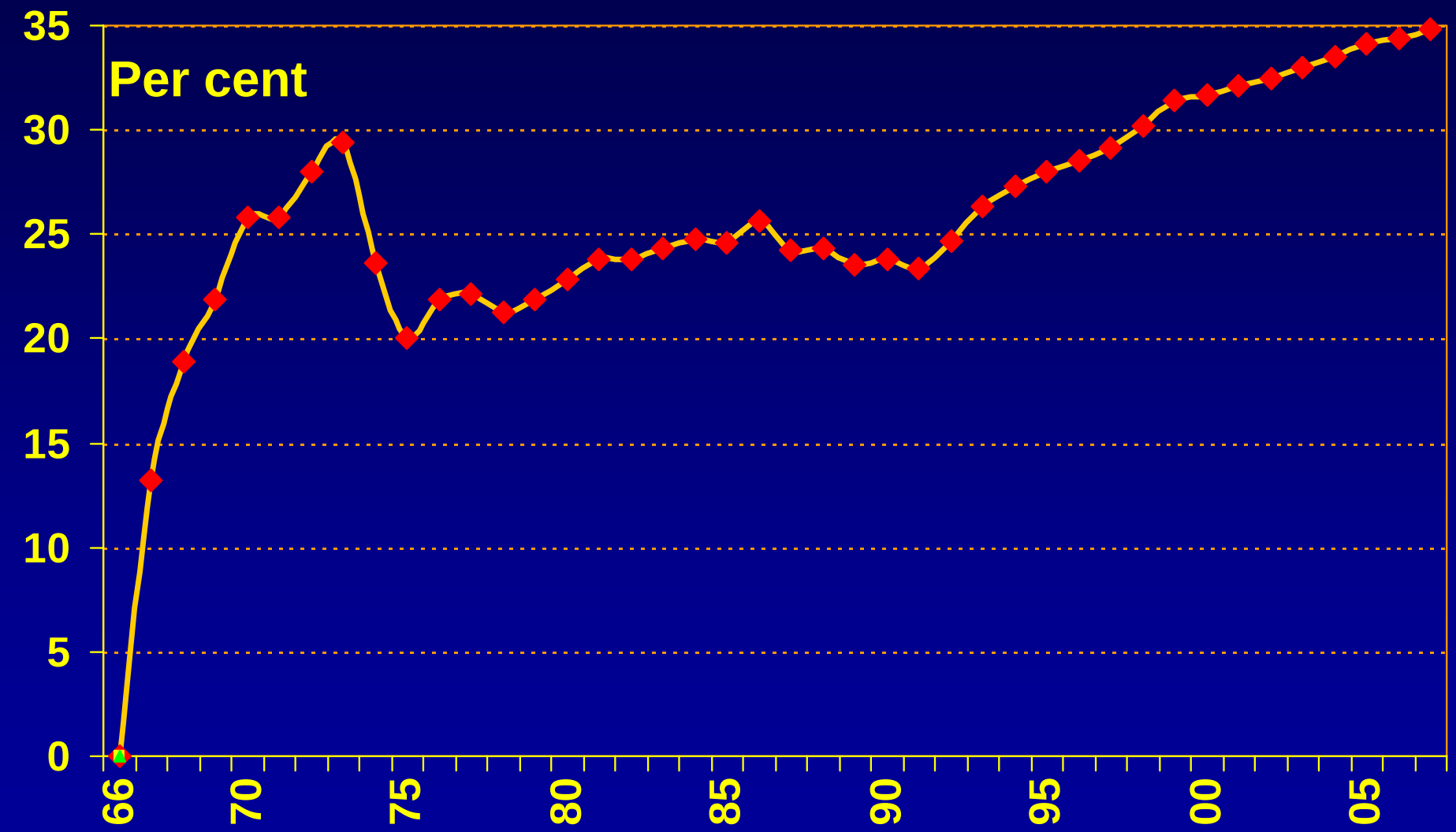
- Risk of VTE about 50% higher the first year
- 30-40 → 20ug EE: 18% reduction in risk
- Norgestimate same risk as 2nd generation.
- 4th generation same risk as 3rd generation
- 3rd/4th generation higher risk than 2nd gen
- POP: No risk (low/middle dose)
- Hormone IUD: No risk

OCs and thrombosis

Current status April 2008

	CTA	AMI	VTE
Non use	1	1	1
2nd gen:	2.5	1.5	2.5
3rd gen:	1.5	1.5	4.0
4th gen:	na	na	4.0

OC use in Denmark 1966-2007



Calculated from total sale in DDD/fem pop 15-44 years.

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Thank you for your attention
Presentation at:
www.Lidegaard.dk