Hormones and cardiovascular disease

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Danish Cardiovascular Research Academy, June 13, 2009

Hormones and CaVD

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OC, HT, and CaVD

- OC and HT in Denmark
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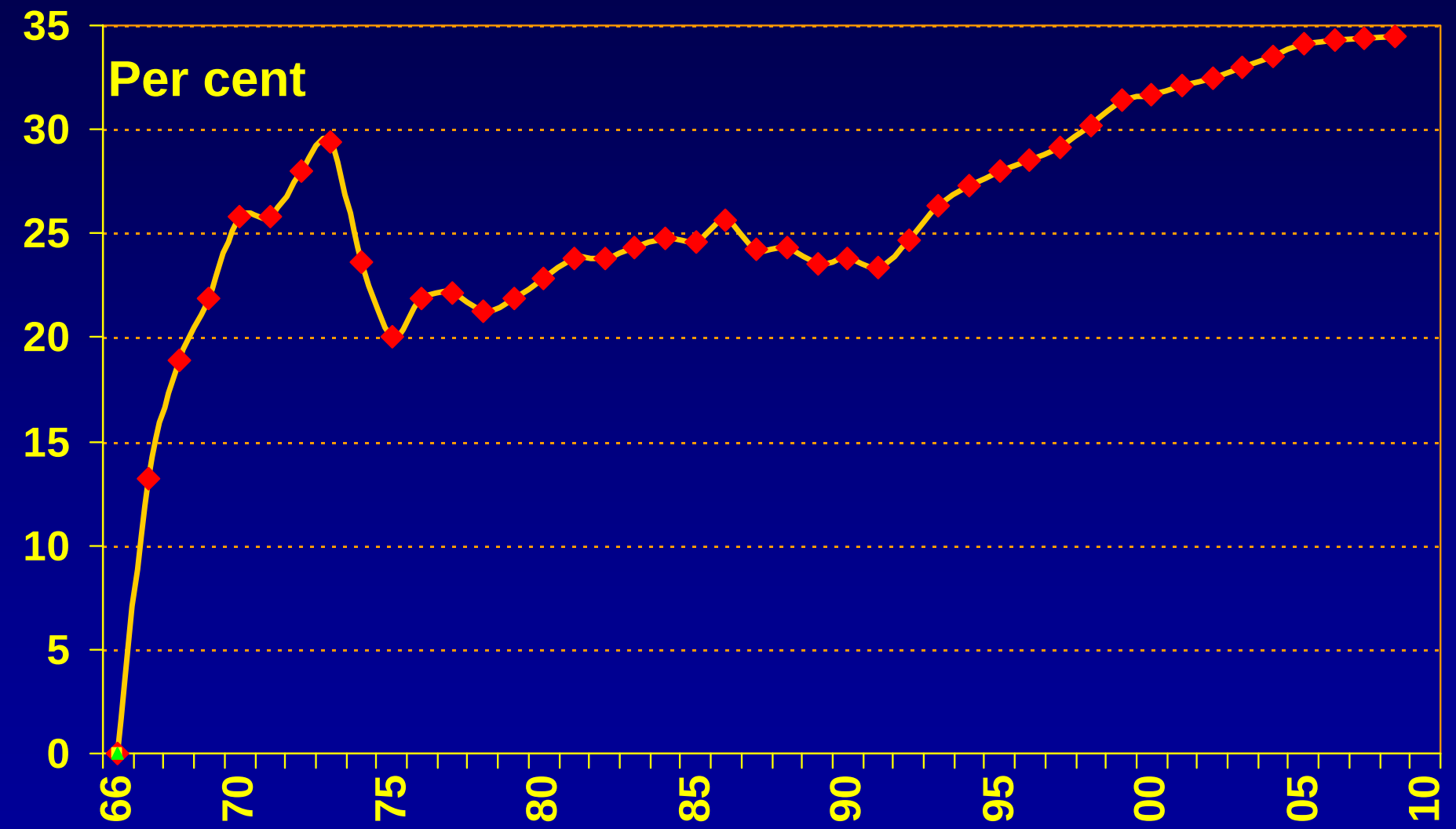
OC use in Denmark 1966-2008



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

Li/05

OC generations according to estrogen dose and progestagen type

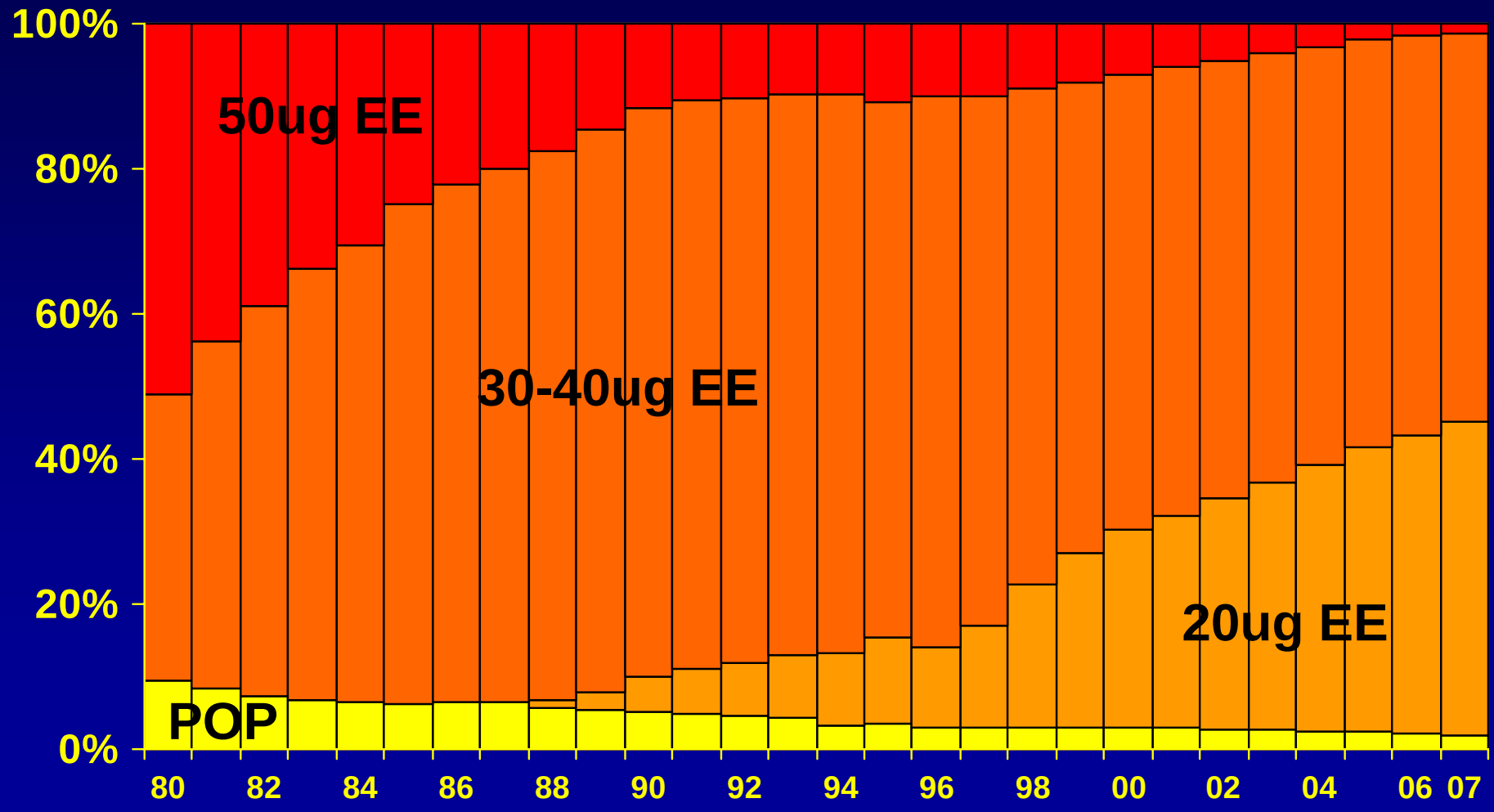
Progestagen generation

	1 Estrans NETA	2 Levonor-gestrel	"2" Norges-timate	3 Deso-gestrel	3 Gesto-dene	4 Dros-pirenon
50	-	1st+	EVRA	-	-	-
30-40	-	+	2nd +	+	+	+4th
20	-	-	-	Nuvaring	+	+
POP	+	+	-	+	-	-

3rd

Low dose = 20-40ug EE

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

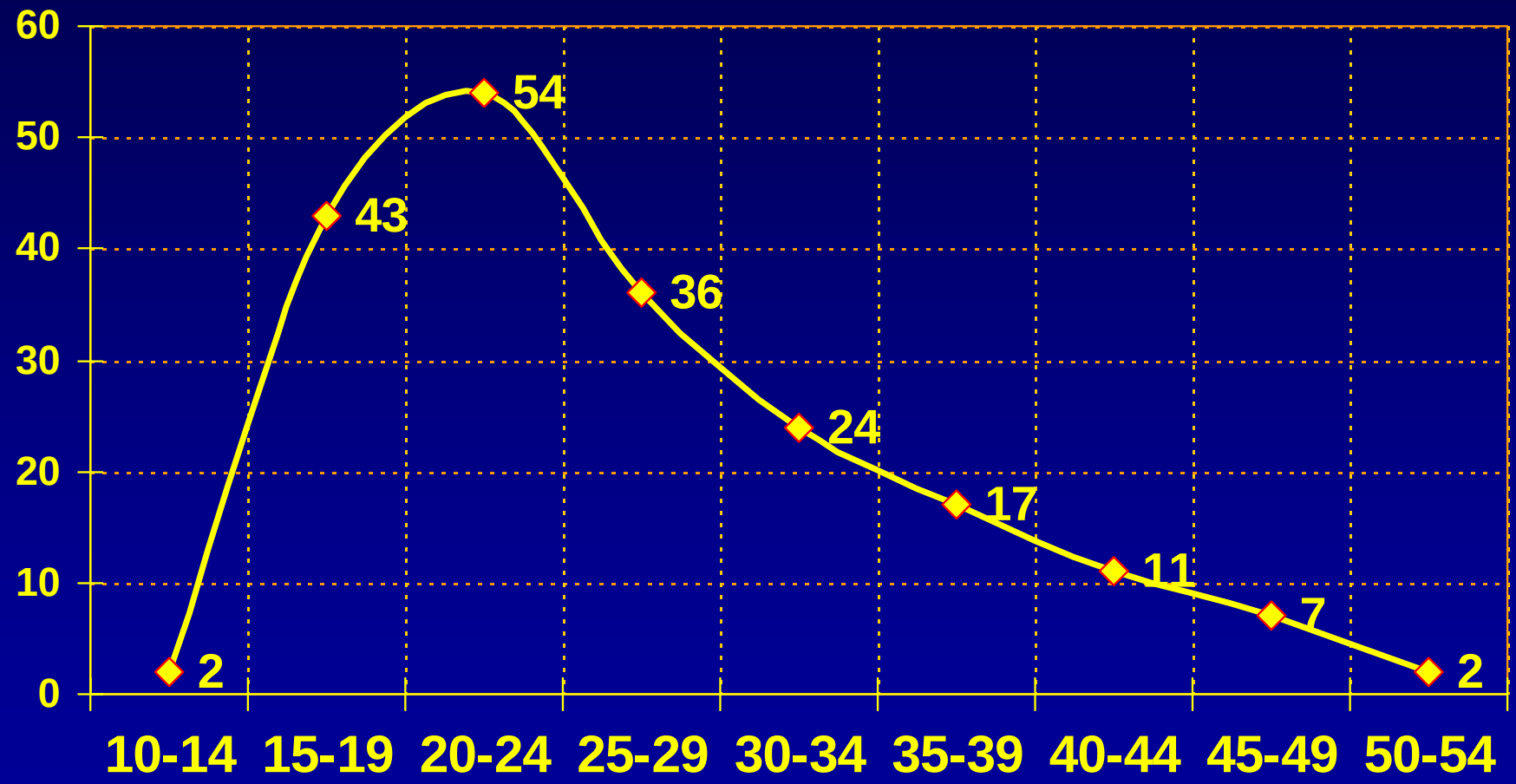


Sale statistics. Dansk Lægemiddelstatistik

Li/08

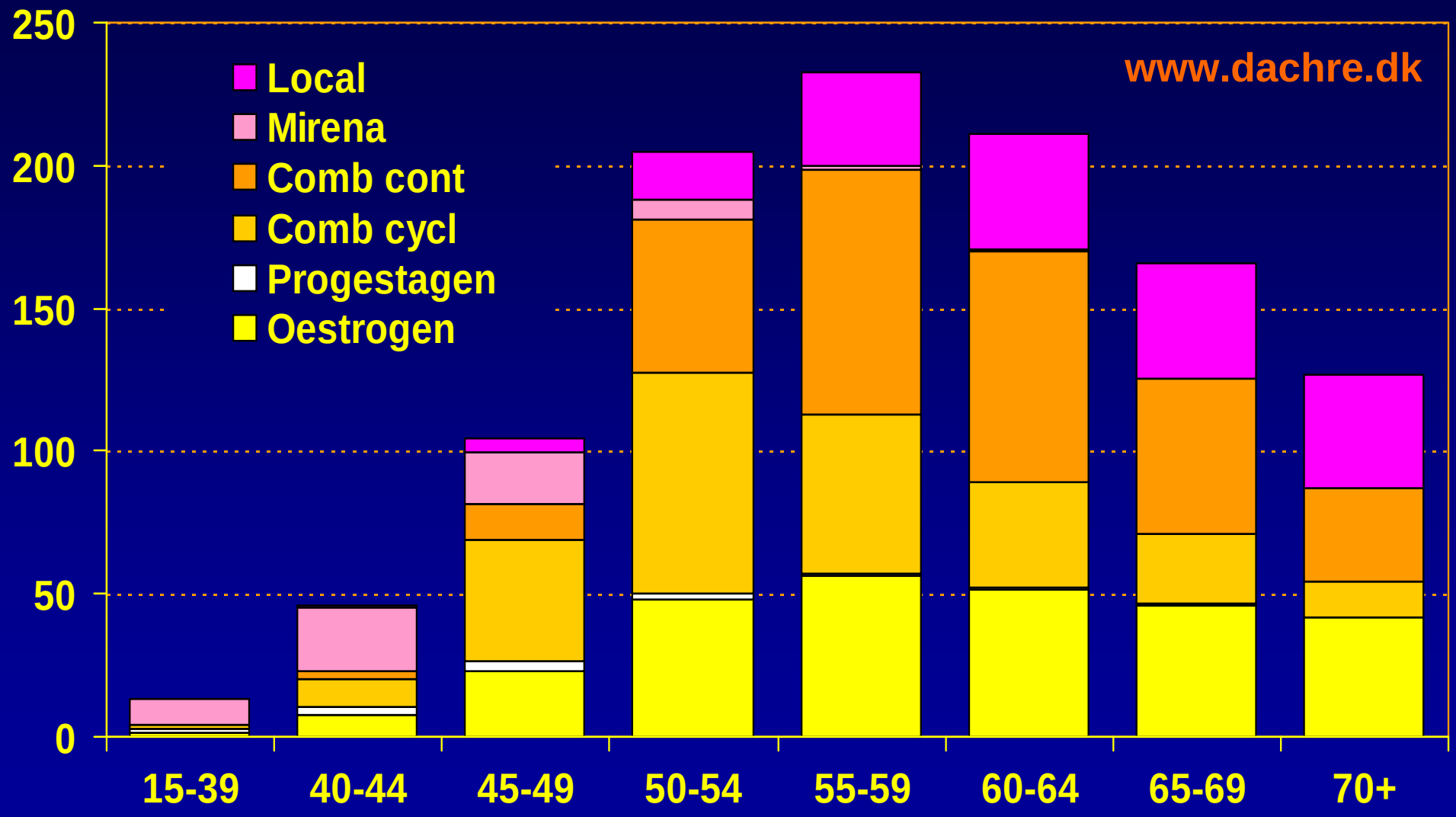
Use of OC according to age

DDD/100 women/day



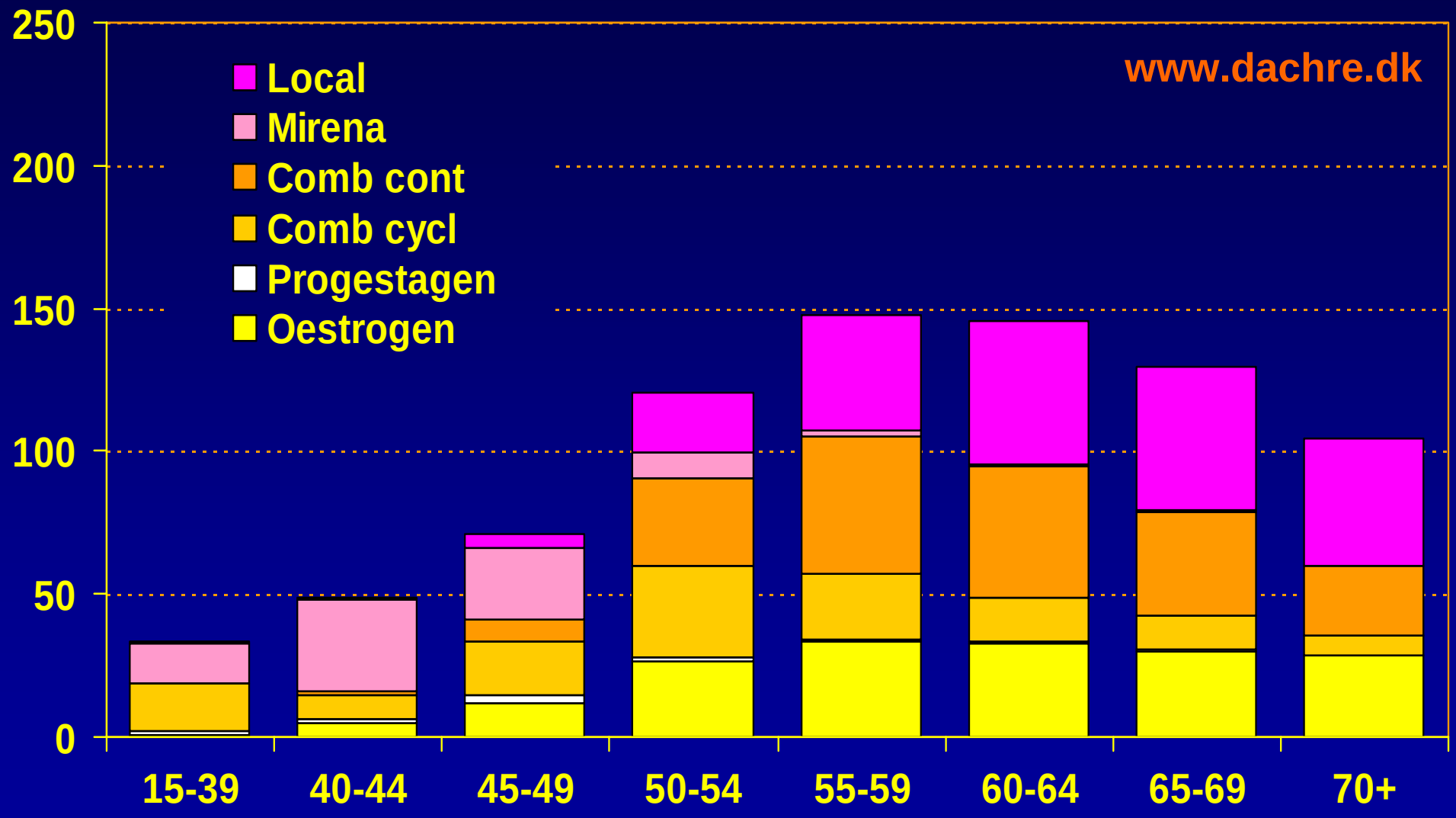
www.laegemiddelstyrelsen.dk

HT sale DK 2002. DDD/1,000 per day



Danish Sex Hormone Register Study (DaHORS).

HT sale DK 2004. DDD/1,000 per day



Danish Sex Hormone Register Study (DaHORS).

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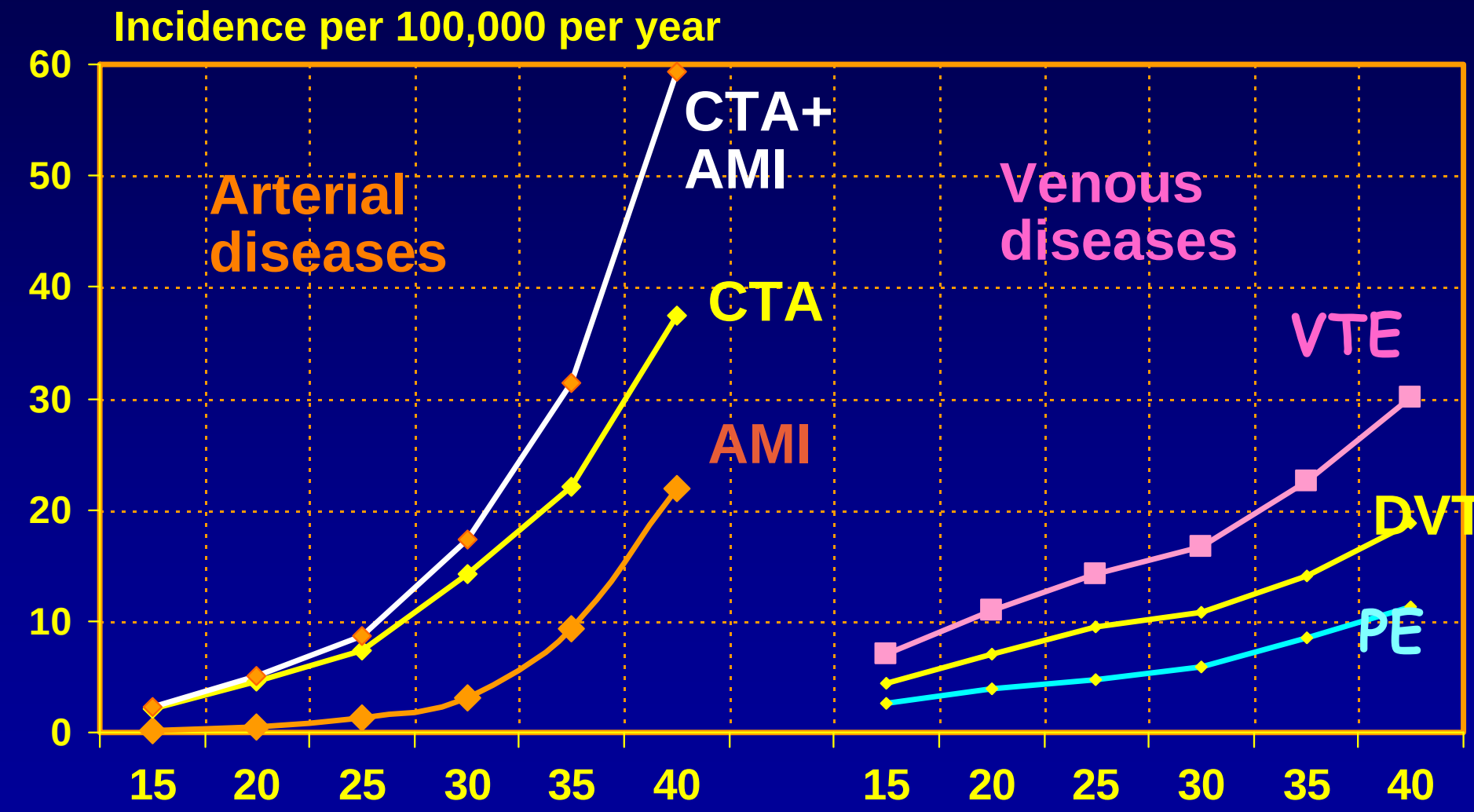
CTA, AMI and VTE in DK 1980-93

Pregnant and puerperal women excluded



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

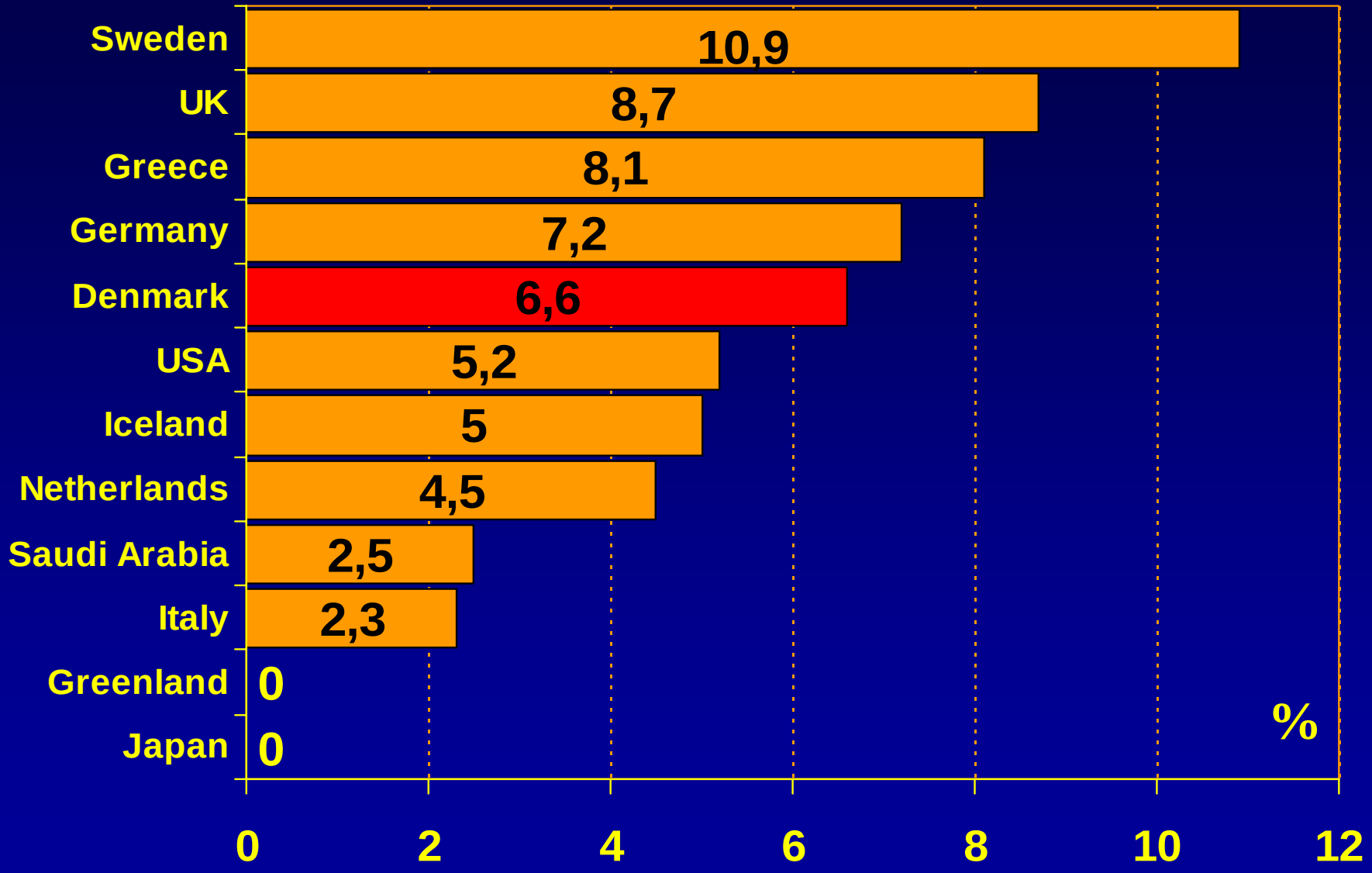
Li/04

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

Leiden V mutations, prevalence



Larsen et al. Thrombosis Res 1998; 89: 211-15

VTE: Genetic risk factors

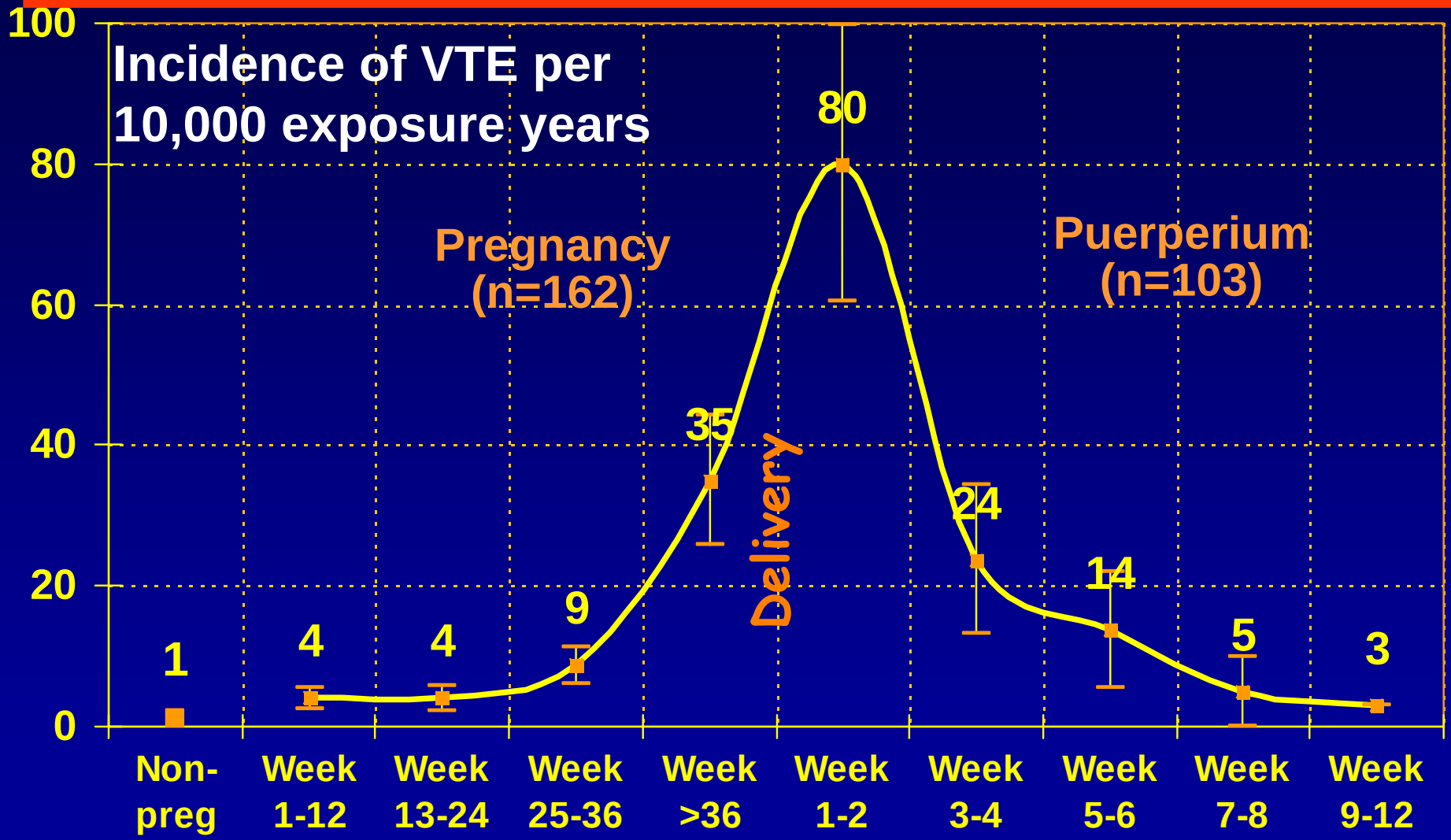
Risk factor	Prevalence	RR
Leiden fact V hetero	6.6%	8
Leiden fact V homoz	0.2%	64
Protein C insufficiency	0.2%	15
Protein S insufficiency	<0.1%	>10
Antithrombin III insuff.	0.02%	50
Prothrombin 20210A	2%	3
Hyperhomocysteinaemia	3%	3

Høibraaten E. HRT and risk of VTE. Diss. Oslo 2001

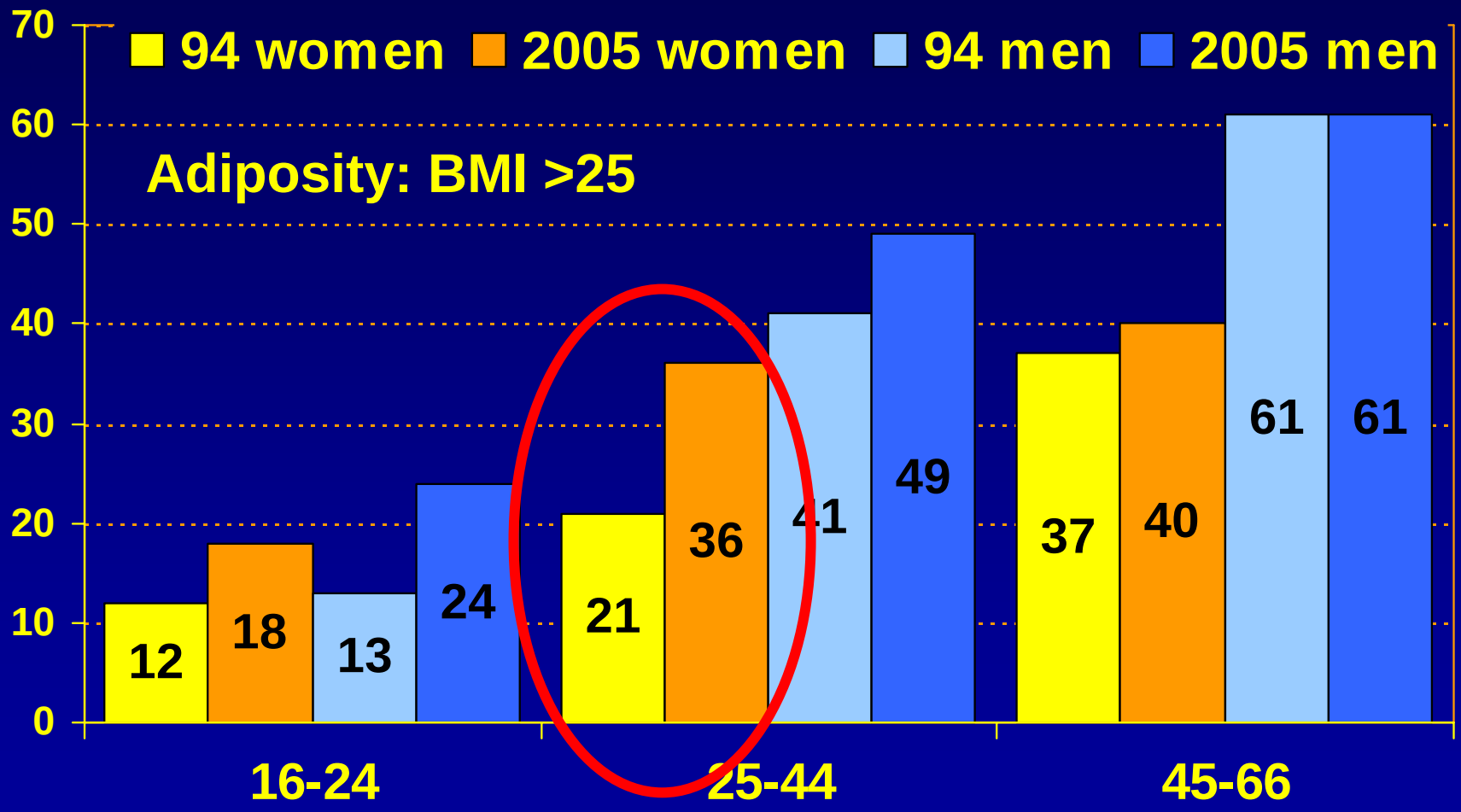
VTE: Acquired risk factors

	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

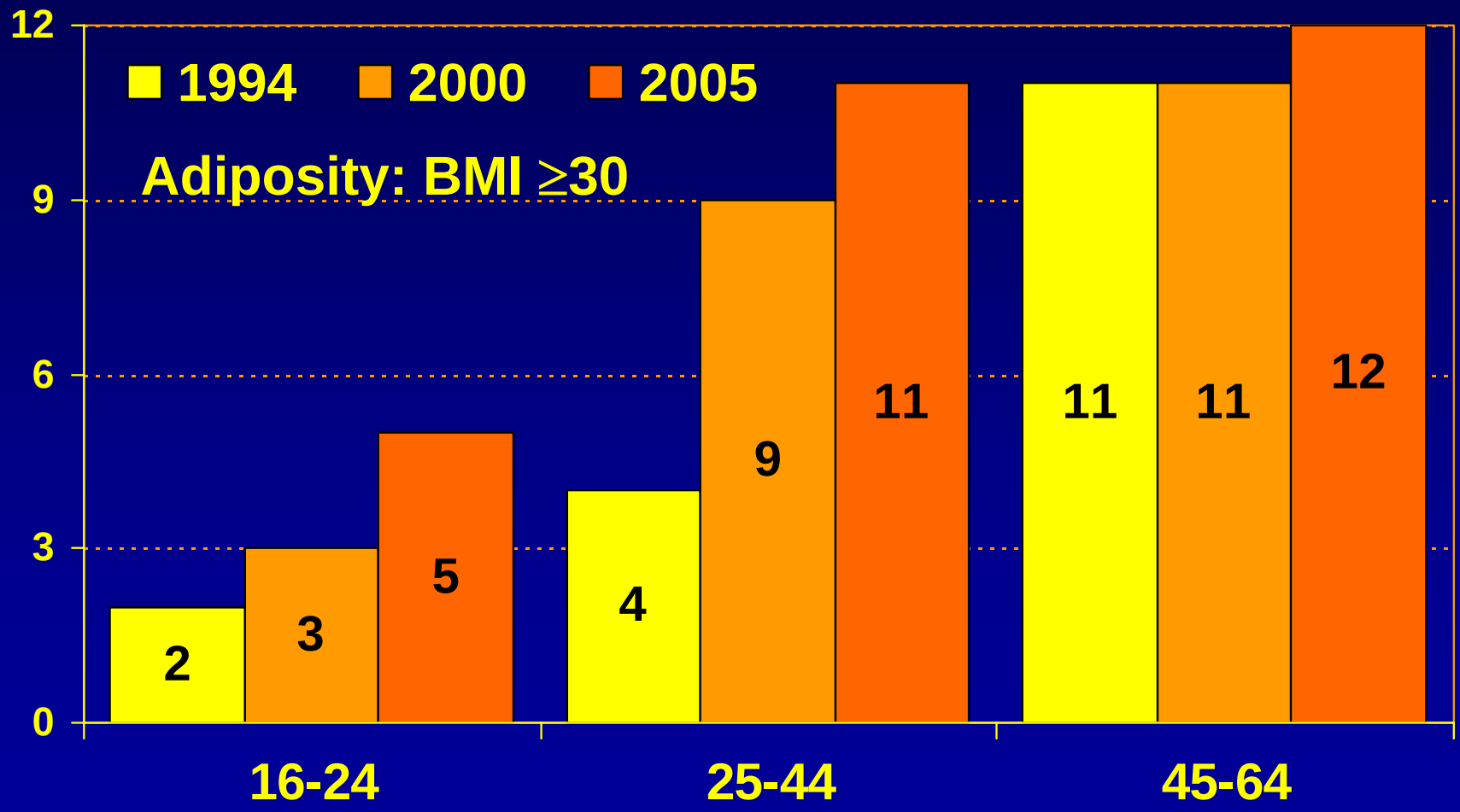
Incidence rate of VTE among pregnant and puerperal women, DK 1994-96. N=265



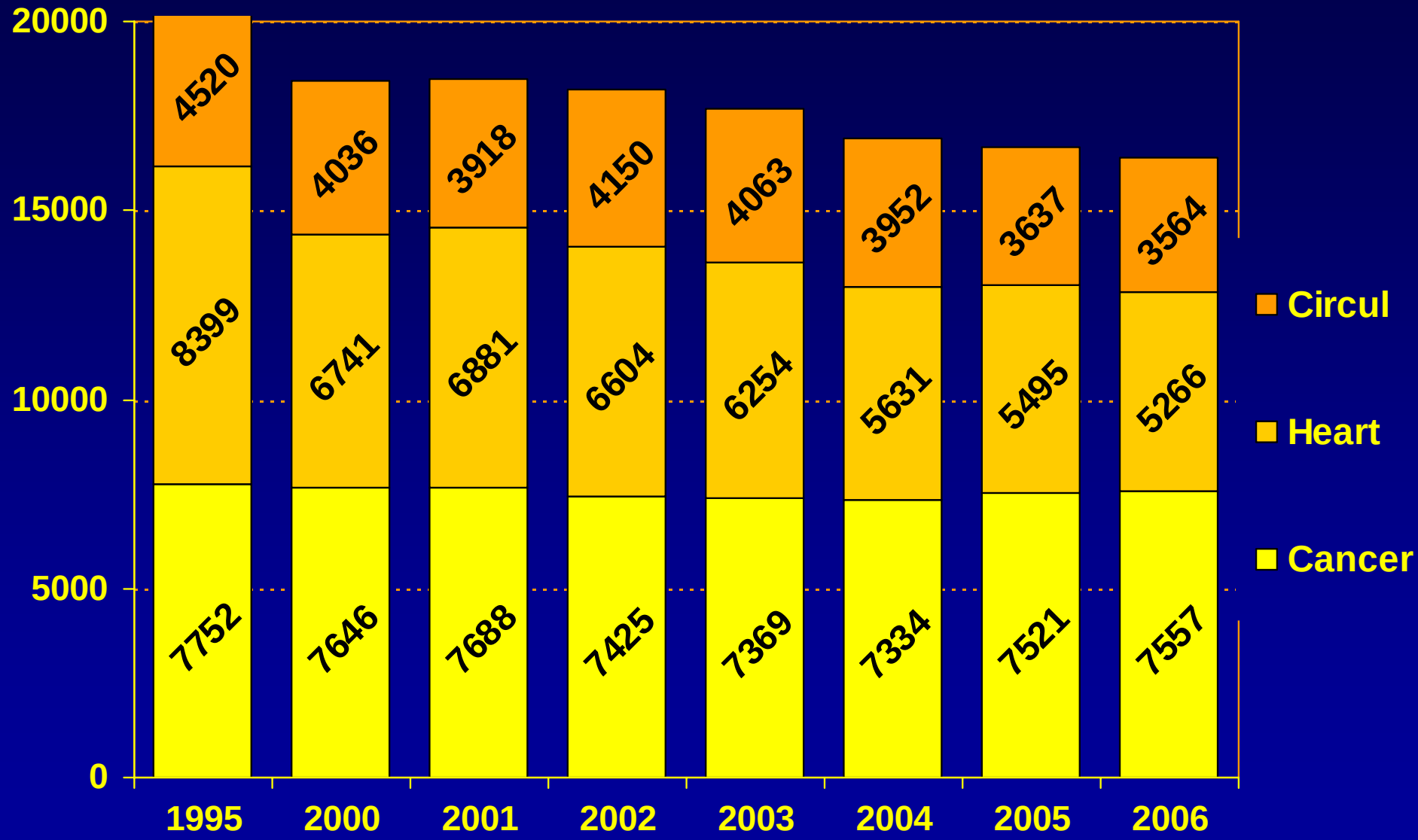
Adiposity in Danish women and men in 1994 and 2005



Severe adiposity in Danish women in 1994, 2000 and 2005



Deaths, women 1995-2006



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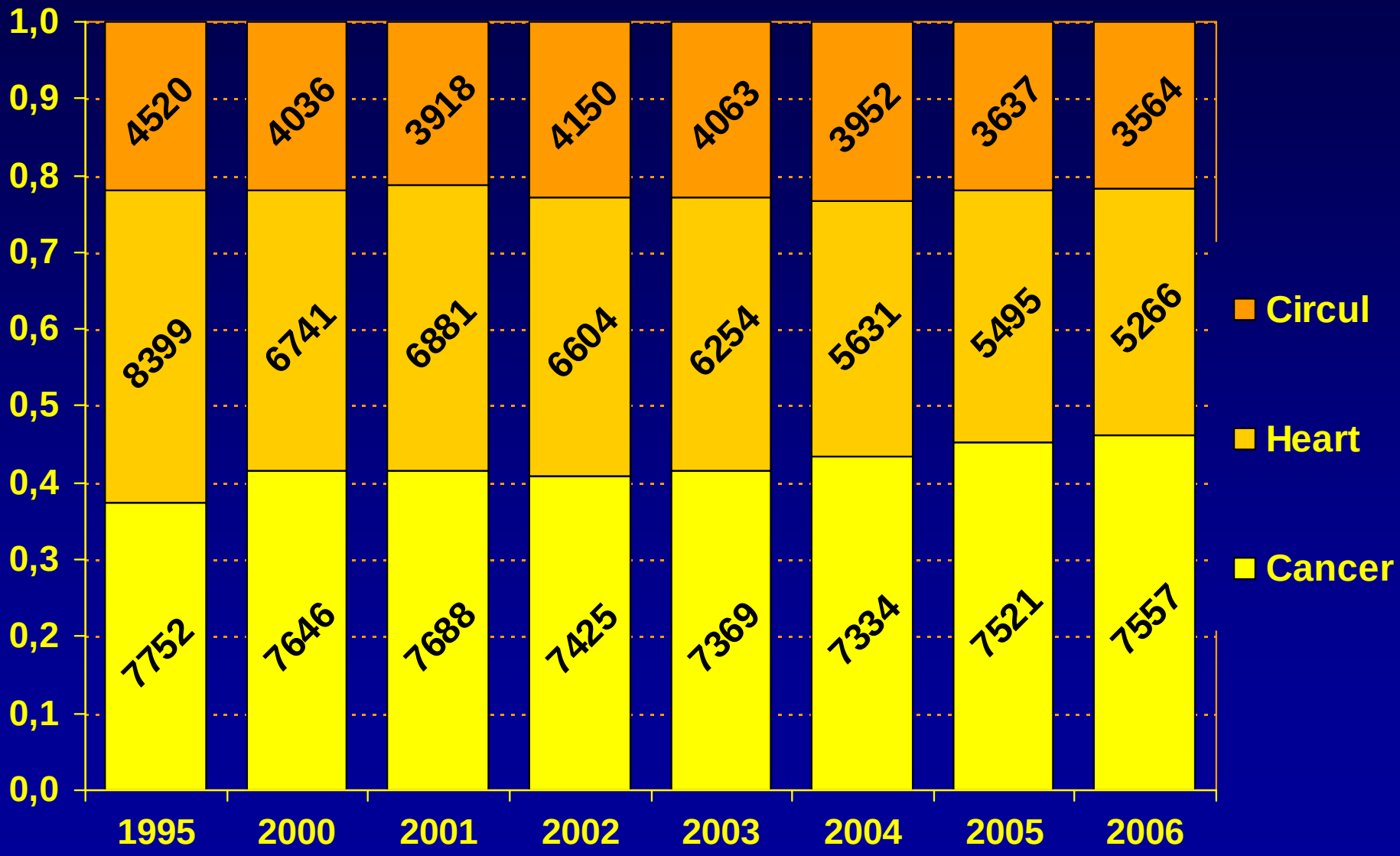
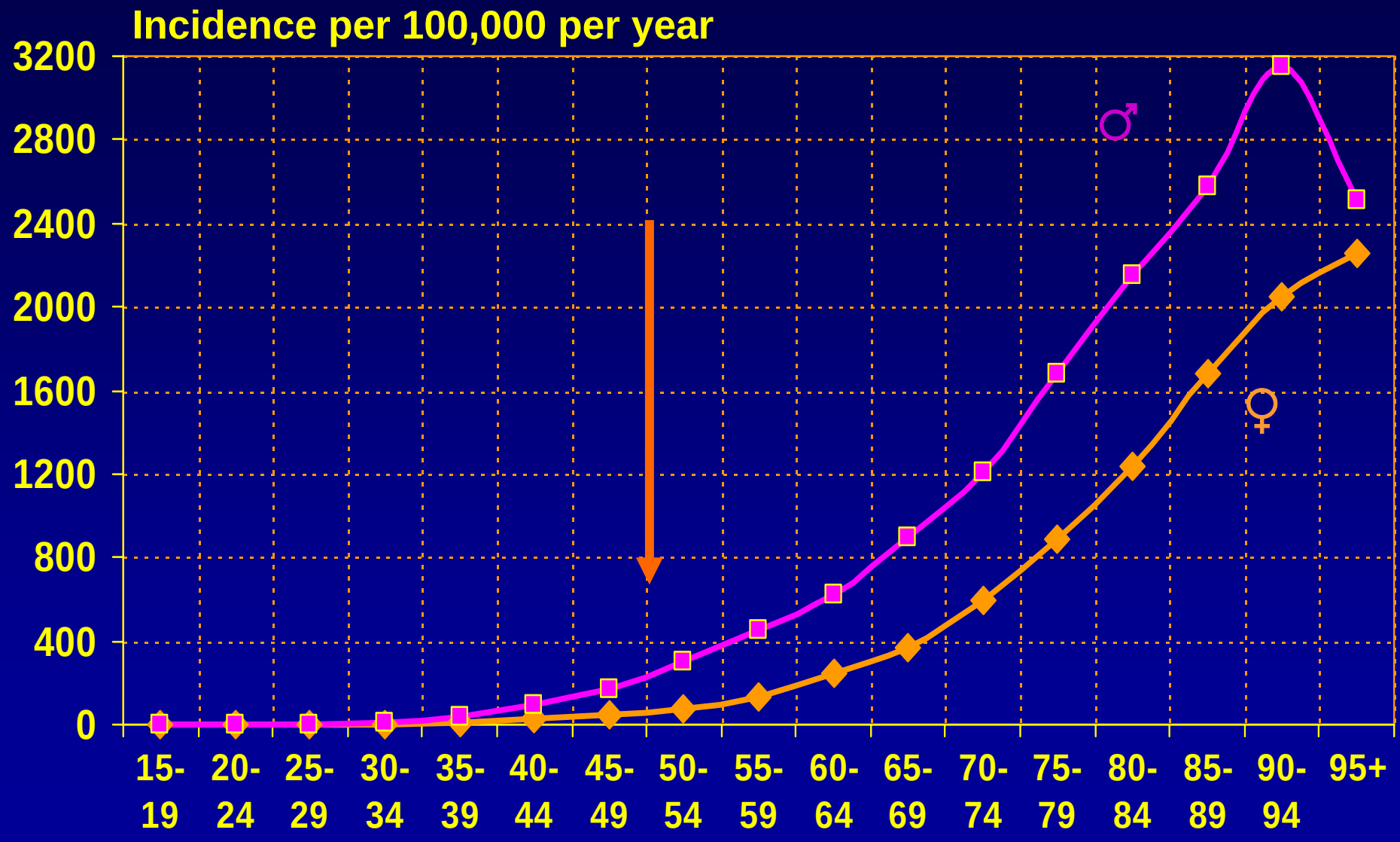
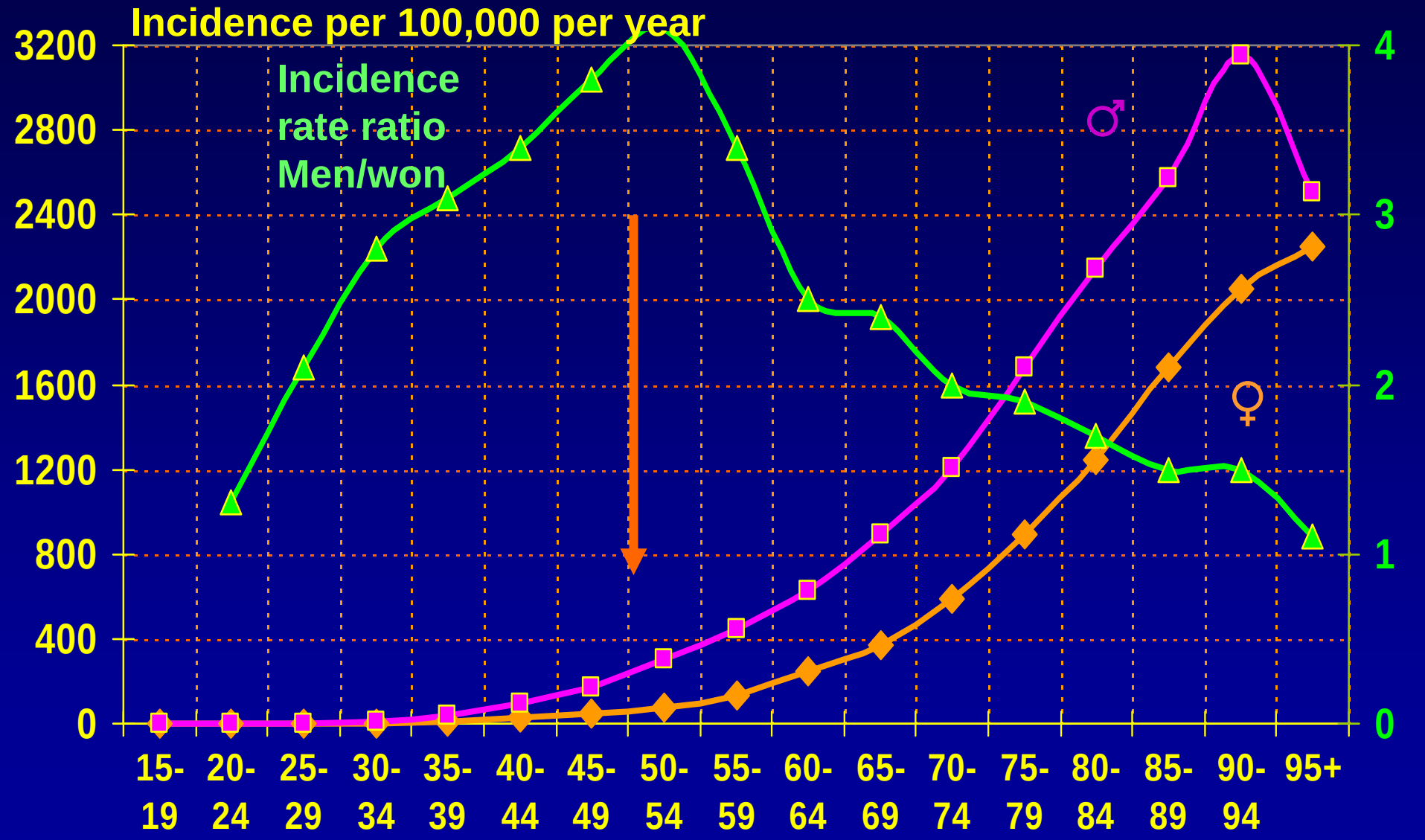


AMI in women and men in DK



Videbæk J, Madsen M. 2004 Hjertestatistik

AMI in women and men in DK



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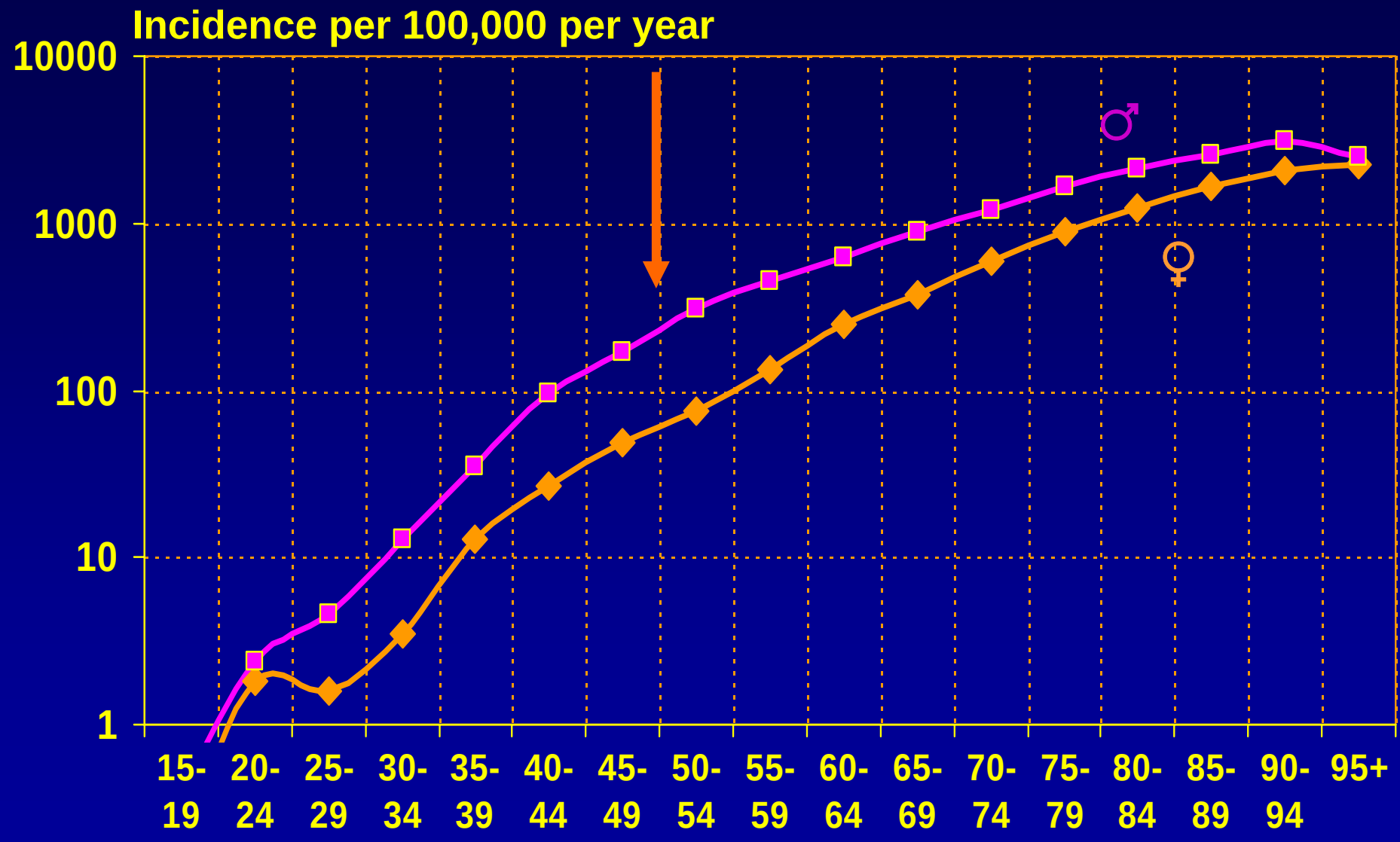

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Hormonal contraception and VTE Denmark 1995-2005

Danish Sex Hormone Register Study DaHoRS

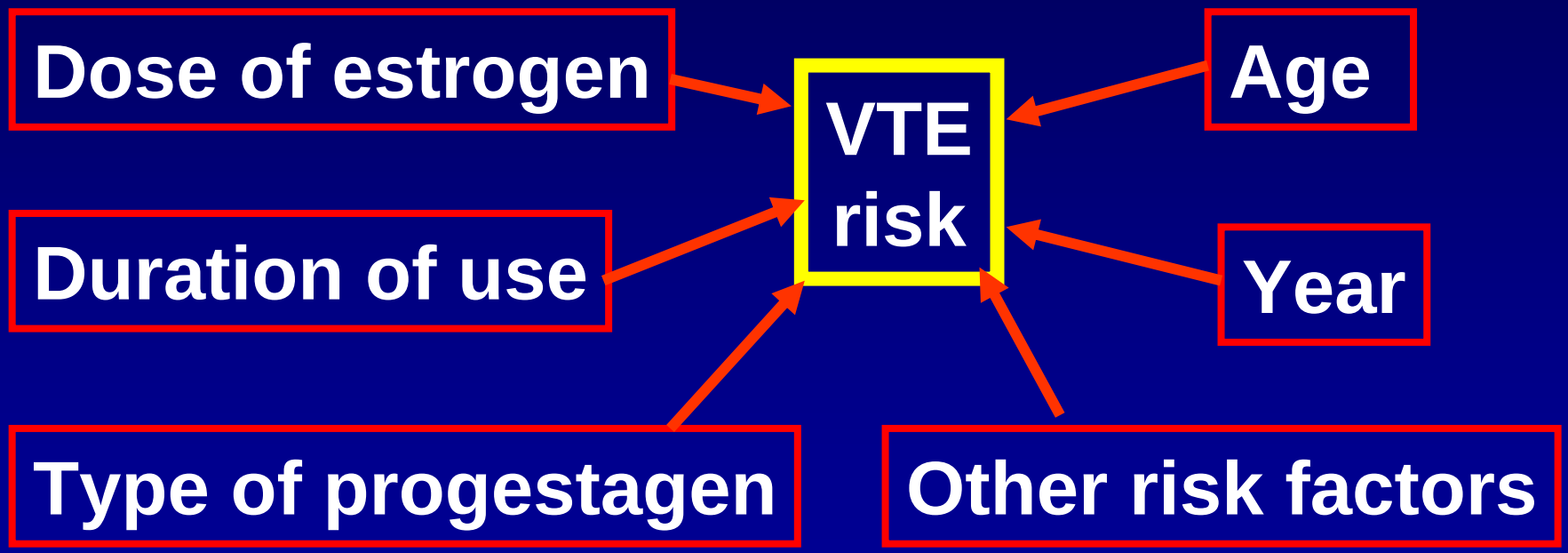
Øjvind Lidegaard, Rigshospitalet
Ellen Løkkegaard, Glostrup Hospital
Anne Louise Svendsen, Copenhagen University
Carsten Agger,
Research Centre for Prevention and Health

BMJ 2009; in press

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, 1977)

VTE diagnoses,

Previous CaVD/canc.

Pregnancies

National Registry of Medicinal products (NRM,1994): OC use

Medication against

BP↕, DM, Hyperchol.

1995 → 2005

Statistics of Denmark, 1960

Education, PIN-codes,

address, vital status

OC and VTE: Results

- Number of observation years: 10.4 million
- Number of current user years: 3.3 million
- Number of former user years: 2.3 million
- Number of 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: 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)

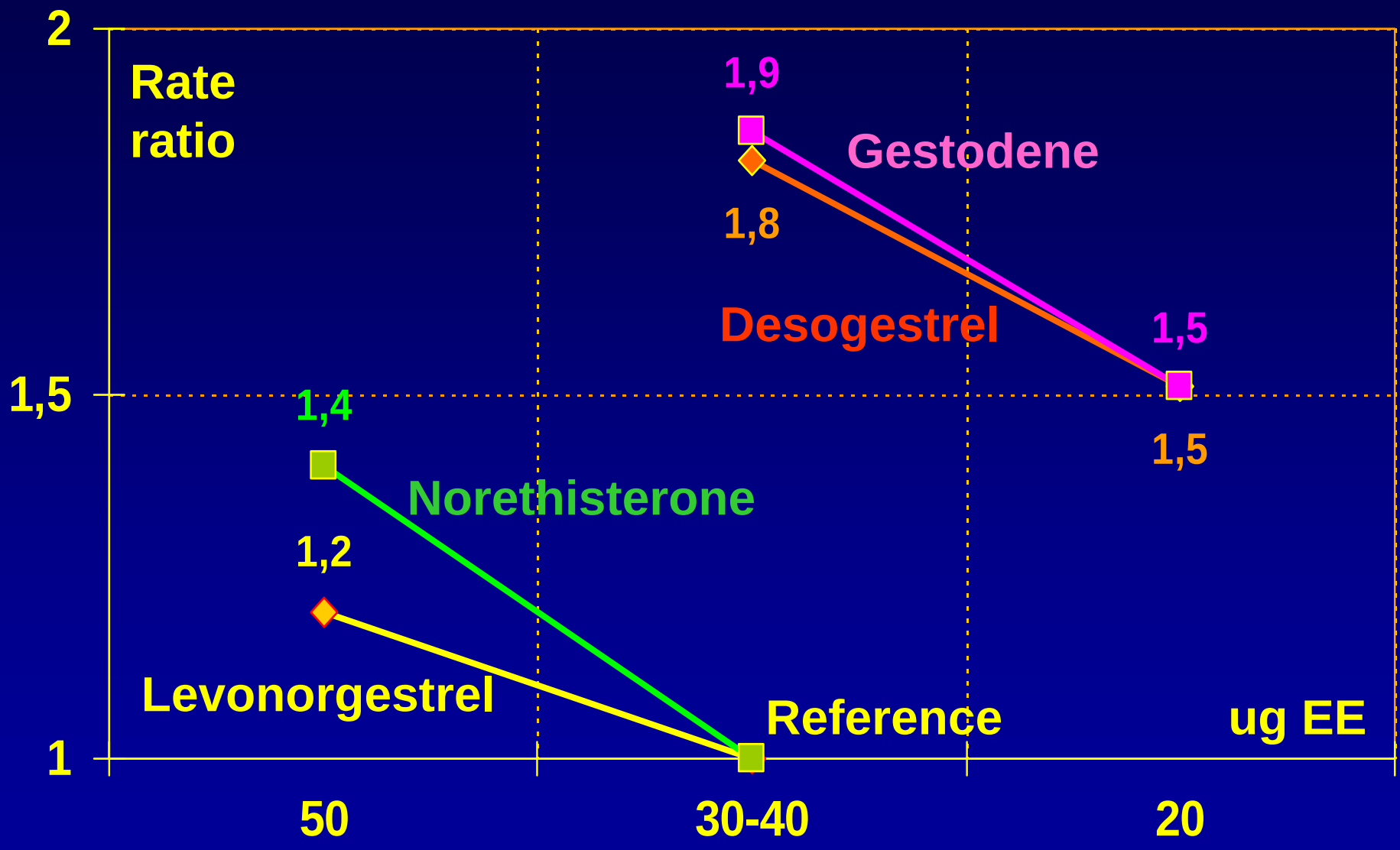
***) Adjusted for age, year, education**

Li/08

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

Li/08

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 November 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
Average:	2	1.5	3.5

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**
OC influence (RR)	**2**	**1.5**	**3.5**
Number of OC deaths	**+0.5**	**+2**	**+1.2**

OC induced: 3.8/20.3 = 19%

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

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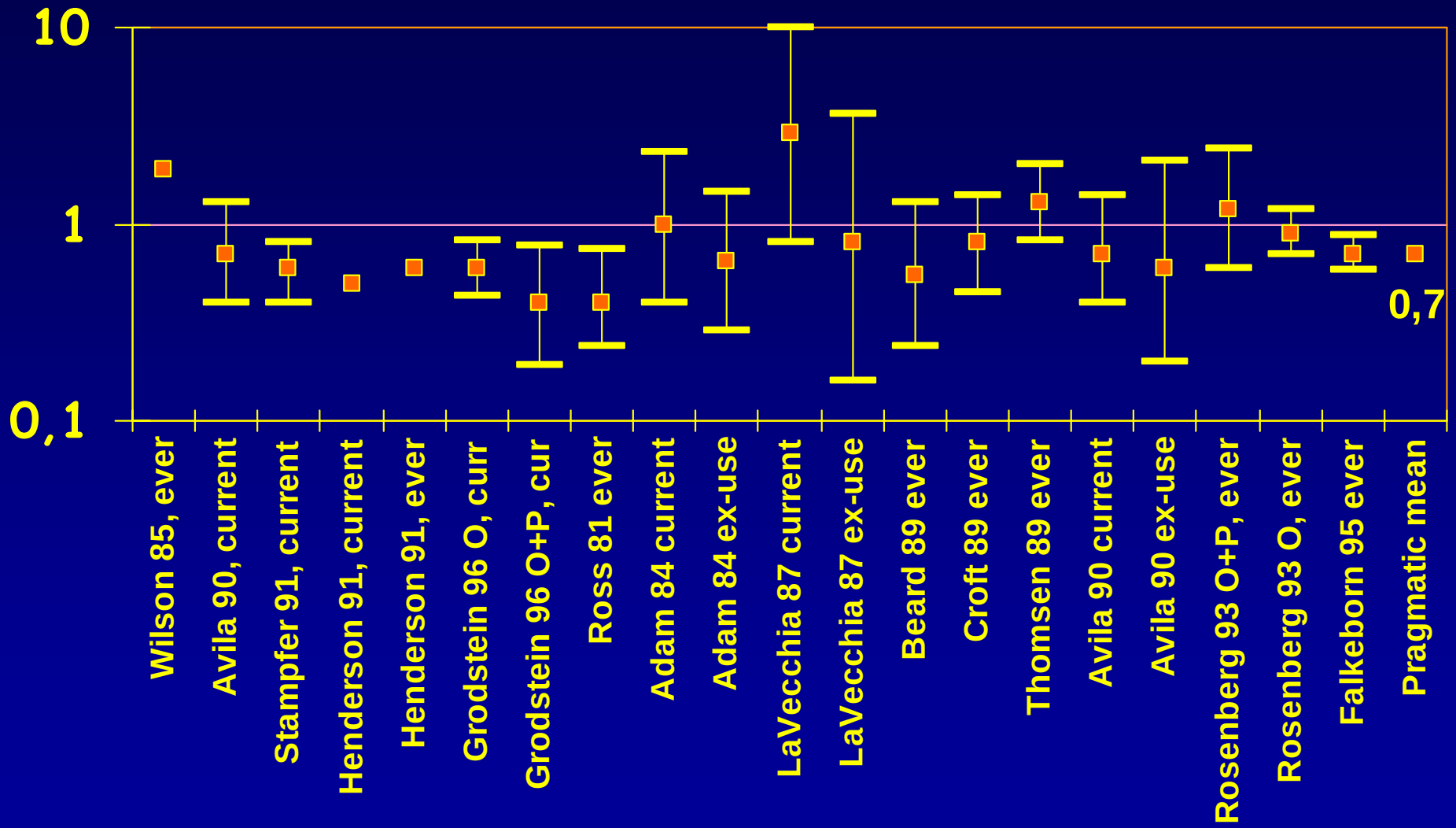
HT and acute myocardial infarction



Heart and oestrogen/progestin replacement study (HERS)

Design: Randomiseret blindet placebo-kontrolleret sekundært preventions studie

Materiale: 2,763 kvinder med koronar sygdom, yngre end 80 år. Gennemsnitsalder: 67y

Metode: Randomisering mellem placebo og 0.625mg østrogen + 2.5mg MPA.

HERS I: Follow up 4.1 år (randomiseret)

HERS II: Follow up 6.8 år (ikke randomiseret)

Outcome: Nye AMI tilfælde.

Hulley et al. JAMA 1998; 280: 605-13
Grady et al. JAMA 2002; 288: 49-57

HERS: results

	Estr-prog[1]	Placebo	RR	95% CI
n	1380	1383		
CHD[2] I	179	182	1.0	0.8-1.2
CHD I+II	290	293	1.0	0.8-1.2
Fatal I+II	132	122	1.1	0.9-1.4
Nonfatal AMI	183	196	0.9	0.8-1.2

Conclusion: Comb. HT has no influence on the risk of further AMI

1) Oestr-prog = conjugated estrogen 0.625mg + medroxyprogesterone acetate 2.5mg

2) CHD: coronary heart disease (=AMI)

WHI results

	EPT	ET	50-59
Coronary heart disease	**1.3**	**0.9**	**0.6**
Stroke	1.4	1.4	1.1
Venous thromboembolism	**2.1**	**1.3**	**1.2**
Breast cancer	1.3	0.8	0.7
Endometrial cancer	0.8	hysterect.	
Colorectal cancer	0.6	1.1	0.6
Hip fracture	0.7	0.6	NA
Vertebral fracture	0.7	0.6	NA
All cause mortality	**1.0**	**1.0**	**0.7**

Rossouw et al. JAMA 2002; 288: 321-33 & 2004: 291: 1701

Womens health initiative (WHI)

	EPT vs placebo	ET vs placebo
Age:	50-79	50-79, -uterus
Number:	16,608	10,739
Regimen:	0.6mg CEE/MPA	0.6mg CEE
Follow up:	5.2 yrs,	6.8 yrs
Average age:	63 years	
>60 years	66%	70%
Hypertension	36%	48%
BMI ≥25:	70%,	80%
BMI ≥30:	34%	45%

Rossouw et al. JAMA 2002; 288: 321-33
& JAMA 2004: 291: 1701

Danish sex Hormone Register Study
DaHoRS (1.8 mio women study)

Hormone therapy and AMI

Ellen Løkkegaard

Anne Helms Andreasen

Rikke Kart Jacobsen

Lars Hougaard Nielsen

Carsten Agger

Øjvind Lidegaard

Løkkegaard et al. Eur Heart J 2008; 29: 2660-8

Pharmacoepidemiology
Principal data sources

National Regisity of Ptt

Cases
Previous diseases
Deliveries, abortions

Statistics Denmark

Education
Deaths
Control women

1995 → 2001

National Registry of Medicine from 1994

Specific daily prescription of medicine

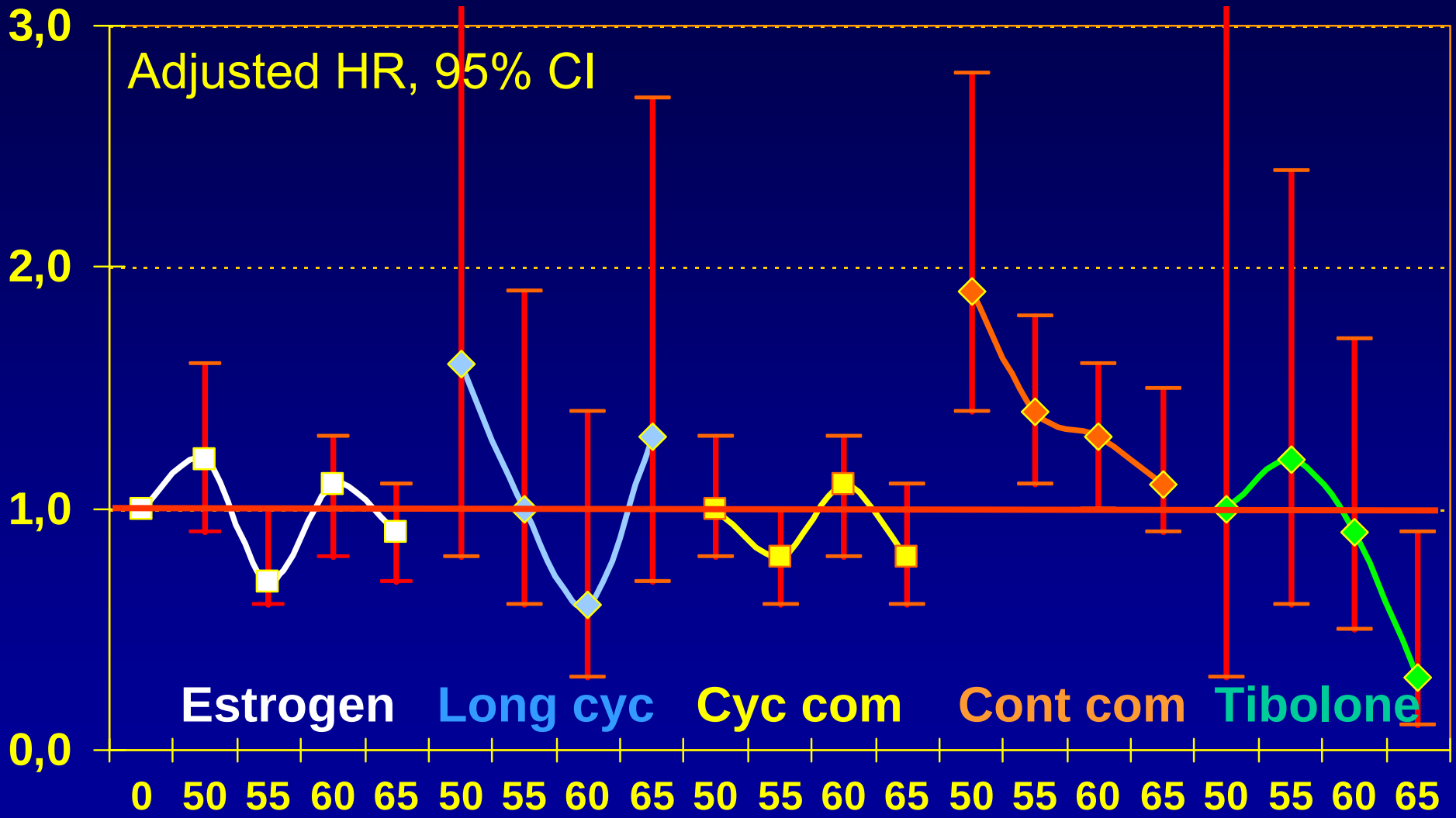
Identification of hypertensive, depressive, women with diabetes etc

Hormone therapy and AMI

- Cohort: Included women 51-69: 698,098
- Observation years: 2,952,635
- Women on HT 19%
- Previous HT 7%
- Never HT 74%
- Women with AMI: 4,947

Løkkegaard et al. Eur Heart J 2008; 29: 2660-8

AMI risk according to HT regimen



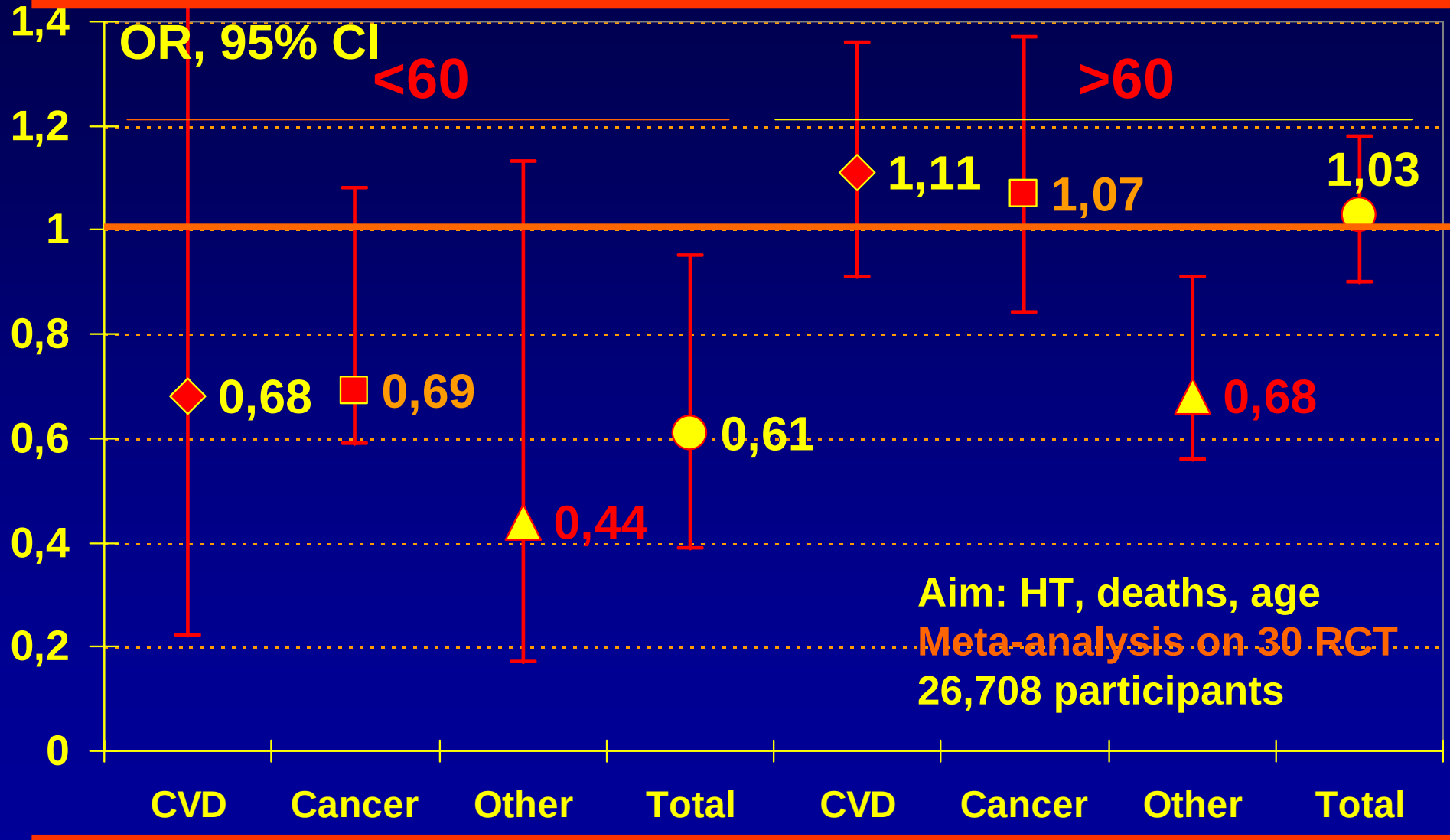
Løkkegaard et al. Eur Heart J 2008; 29: 2660-8

HT-AMI: Conclusion

- Overall no risk of AMI with HT
- No risk with estrogen only, vaginal, and cyclic combined therapy
- No risk with tibolone
- Increased risk in women on cont. combined
- This risk decreases with time
- Lower risk with cyclic combined therapy than with continuous combined therapy

Løkkegaard et al. Eur Heart J 2008; 29: 2660-8

Metaanalysis on HT and death



Salpeter et al. J Gen Intern Med 2004; 19: 791-804

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HT and AMI: Conclusion

- Observational studies: RR: 0.7-1

  Randomised studies: RR: 0.6-1.3
- Previous AMI is not an indication for HT
- Estrogen only protects more than EPT
- Protection is detectable only after several years of HT
- Protection more pronounced in women <60 years than in women >60 år
- HT has little influence on AMI in women

HT and AMI: Mechanism

- Estrogen exerts an anti-arteriosclerotic effect in all ages.
- Estrogen-progestagen does the same, to a lesser extent.
- HT exerts also a trombotic effect by an incluence on the coagulation system.
- In women at an already increased thrombotic risk, HT may increase this risk further, and thereby counteract its positive influence on the vessel wall.


24 HOUR
FITNESS

Thank you

www.Lidegaard.dk/slides

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