Hormonal contraception (HC), thrombosis and cancer. An update

Øjvind Lidegaard
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DSOG's forårsmøde 8. april 2016

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Julie Lidegaard
Delivered 13
hours ago

HC, thrombosis and cancer

- Hormonal contraception
- Hormonal contraception and thrombosis
- Hormonal contraception and cancer
- Clinical recommendations

HC, thrombosis and cancer

- **Hormonal contraception**
- Hormonal contraception and thrombosis
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Hormonal contraception
How to get an overview?

<u>Combined products</u> (estrogen and progestogen)							
<u>Progestogen only products</u>							

Hormonal contraception
Combined - route

<u>Combined products</u> (estrogen and progestogen)							
Oral							
Non oral							
<u>Progestogen only products</u>							
Oral							
Non oral							

Hormonal contraception
Combined – route – e-dose – e-type

Combined products (estrogen and progestogen)							
Middle							
Low							
Nat e							
N-oral							
Progestogen only products							
Oral							
N-oral							

Hormonal contraception
Combined – route – e-dose – e/p-type

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospire-none	CPA Cyproterone-acetate
Combined products							
Middle							
Low							
Nat e							
N-oral							
Progestogen only products							
Oral							
N-Oral							

Hormonal contraception - generations
Combined – route – e-dose – e/p type

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospire-none	CPA Cyproterone-acetate
Combined products							
Middle	**1st**	**2nd gen**		**3rd gen**		**4th gen**	
Low		**2nd gen**					
Nat oe							
N-oral							
Progestogen only products							
Oral							
N-oral							

Hormonal contraception
Combined – route – e-dose – e/p type

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospire-none	CPA Cyproterone-acetate
Combined products							
Middle	**1st**	**2nd gen**		**3rd gen**		**4th gen**	
Low		**2nd gen'**					
Nat oe		E2V-DNG*			E2 NOMAC"		
N-oral			Patch	Vaginal ring¤			
Progestogen only products							
Oral	POP			Desogestrel#		DRSP	
N-oral	Depot	IUS§		Implant			

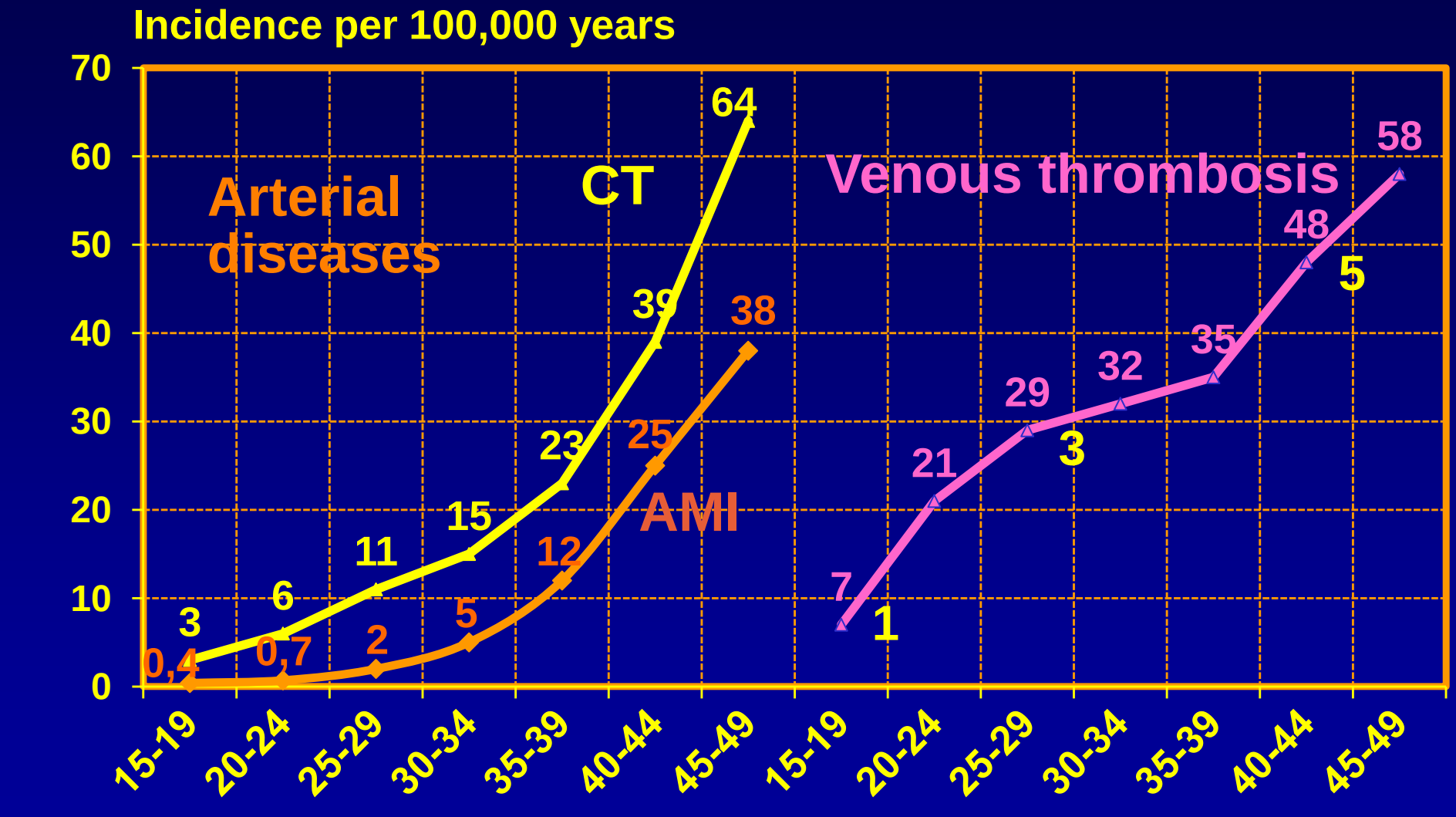
')Loette "')Zoely *)Qlaira ¤)NuvaRing #)Cerazette §) Mirena

HC, thrombosis and cancer

- Hormonal contraception
- **Hormonal contraception and thrombosis**
- Hormonal contraception and cancer
- Clinical recommendations

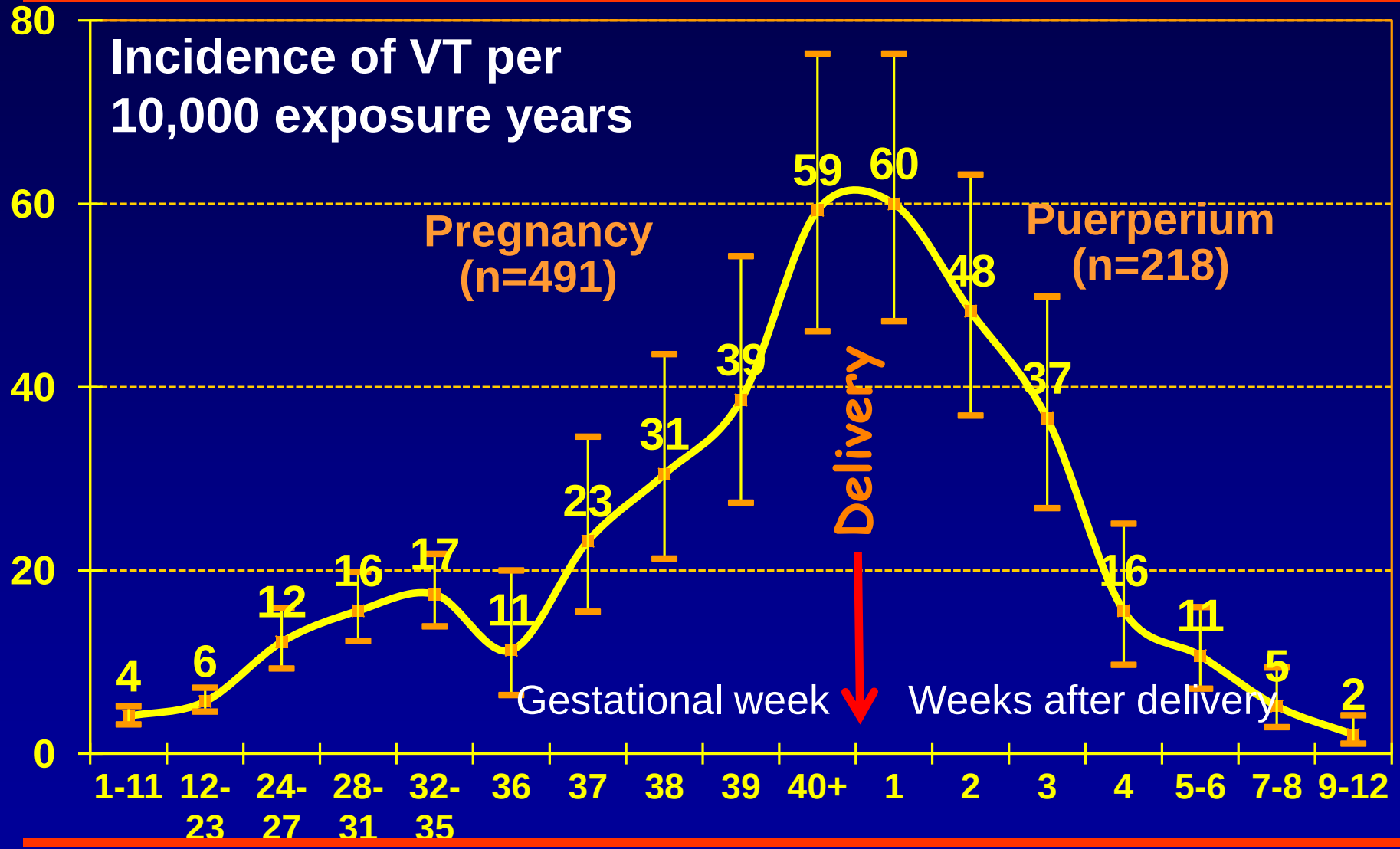
CT, AMI and VT in DK 2001-2009/10

Pregnant and puerperal women excluded



Lidegaard et al NEJM 2012 and BMJ 2011

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



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

Li/12

1st myth: HC vs pregnancy

Age	Exposure	VTE/10,000 years
30	pregnancy, 1st trim	3
30	pregnancy, 2nd trim	4
30	pregn, birth, puerp:	8
30	low risk pill	9
30	high risk pill	18

Conclusion: The risk of VTE is *higher* with HC than with pregnancy.

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
Hormonal contraception	35%	3-7
PCOS	10%	2
Medical diseases	5%?	2-5

OC and VT: Methods

National Health Registry (>1977)

VT diagnoses,

Previous CaVD/canc.

Pregnancies, surgery

Prescription Registry (>1995): HC use

Anticoagulation therapy

hypertension, DM,

Hyperlipidaemia

1995 → 2015

Cause of Deaths Registry (>1977)

Lethal VT

Statistics Denmark

PIN-codes, education

vital status, emigration

BMJ

RESEARCH

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,

BMJ

ABSTRACT

risk of venous thrombosis than oral contraceptives with

BMJ 2011;343:d6423 doi: 10.1136/bmj.d6423

Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9

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]

VT with drospirenone/LNG

	VT	IR[4]	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
Bird[13]	354	18.0	1.9 (1.5-2.4)	4th/2nd

Lidegaard, Expert Opinion Drug Safety 2014: 13: 1353-60

BMJ

BMJ 2012;344:e2990 doi: 10.1136/bmj.e2990

RESEARCH

Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10

Øjvind Lidegaard *professor*[1], Lars Hougaard Nielsen *statistician*[1], Charlotte Wessel Skovlund *data manager*[1], Ellen Løkkegaard *senior registrar*[2]

[1]Gynaecological Clinic 4232, Blegdamsvej 9, DK-2100 Copehagen Ø, Juliane Marie Centre, Rigshospitalet, University of Copenhagen, Denmark; [2]Department of Obstetrics and Gynaecology, Hillerød Hospital, University of Copenhagen, Denmark

Abstract

Objective To assess the risk of venous thrombosis in current users of

Conclusion Women who use transdermal patches or vaginal rings for contraception have a 7.9 and 6.5 times increased risk of confirmed

HC according to relative risk of VTE

Low risk <1.5	Middle risk 1.5-4	High risk >4	Few data	No data

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospi-renone	CPA Cyproterone-acetate
Combined products (significant results *)							
Middle	**2.2***	**3.0***	**3.5***	**6.6***	**6.2***	**6.4***	**6.4***
Low		Loette		**4.8***	**5.1***	**6.9***	
Nat oe	E2V-DNG **4.5***			E2 NOMAC			
N-oral			Patch **7.9***	Vaginal ring **6.5***			
Progestogen only products							
Oral	POP **0.7**			Cerazette **0.6**			
N-oral	Depot	IUS **0.6***		Implant **1.4**			

Lidegaard et al. BMJ 2009, 2011, and 2012

Statement on combined hormonal contraceptives containing third- or fourth-generation progestogens or cyproterone acetate, and the associated risk of thromboembolism

Johannes Bitzer

Cosignatories

Jean-Jacques Amy,[1] Rob Beerthuizen,[2] Martin Birkhäuser,[3] Teresa Bombas,[4] Mitchell Creinin,[5] Philip D Darney,[6] Lisa Ferreira Vicente,[7] Kristina Gemzell-Danielsson,[8] Bruno Imthurn,[9] Jeffrey T Jensen,[10] Andrew M Kaunitz,[11] Ali Kubba,[12] Medlard M Lech,[13] Diana Mansour,[14] Gabriele Merki,[15] Thomas Rabe,[16] Katarina Sedlecki,[17] David Serfaty,[18] Jacques Seydoux,[19] Lee P Shulman,[20] Regine Sitruk-Ware,[21] Sven O Skouby,[22] Anne Szarewski,[23] James Trussell,[24] Carolyn Westhoff[25]

Bitzer et al. Contraception 2013; J Fam Plann Reprod Health 2013

SUMMARY OF THE CURRENT EVIDENCE CONCERNING THE RISK OF VTE

The inherent inability of database studies to adequately control for baseline confounders render this design less suitable for providing further clarification.

Some epidemiologists question whether the RR increase of around 2 described in the aforementioned case-control studies reflects a clinically relevant difference.

Several studies have shown that the risk of VTE during pregnancy and the postpartum period is considerably higher (29–300 per 10 000 users) than during use of a CHC.[21]

Bitzer et al. Contraception 2013; J Fam Plann Reprod Health 2013

Dinger versus Lidegaard

Inclusion of potential confounders	Dinger	Lidegaard
Age	Yes	Yes
Education	No	Yes
Length of use	Yes	Yes
Oestrogen dose	No	Yes
Ovarian stimulation	No	Yes
Major surgery	No	Yes
BMI	Yes	No
Family disposition	No	No

1st myth: Confounders

- The Danish registry studies are not only the studies with the most detailed and most valid exposure data.
- The studies also include and control for more potential confounders than any other study conducted on HC and venous thrombosis.

SUMMARY OF THE CURRENT EVIDENCE CONCERNING THE RISK OF VTE

The inherent inability of database studies to adequately control for baseline confounders render this design less suitable for providing further clarification.

Some epidemiologists question whether the RR increase of around 2 described in the aforementioned case-control studies reflects a clinically relevant difference.

Several studies have shown that the risk of VTE during pregnancy and the postpartum period is considerably higher (29–300 per 10 000 users) than during use of a CHC.[21]

Bitzer et al. Contraception 2013; J Fam Plann Reprod Health 2013

2nd myth: HC vs pregnancy

Age	Exposure	VTE/10,000 years
30	pregnancy, 1st trim	3
30	pregnancy, 2nd trim	4
30	pregn, birth, puerp:	8
30	low risk pill	9
30	high risk pill	18

Conclusion: The risk of VTE is *higher* with HC than with pregnancy and delivery.

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

VT and drospirenone/LNG

	VT	IR[4]	Rate ratio	
Dinger[07]	118	9.1	1.0 (0.6-1.8)	4th/2nd
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Bird[13]	354	18.0	1.9 (1.5-2.4)	4th/2nd
Dinger[14]	123	7.2	0.8 (0.5-1.6)	4th/2nd
Vinogradova[15]	10,562	na	2.1 (1.6-2.7)	4th/2nd
Dinger[16]	306	10.7	1.1 (0.8-1.7)	4th/2nd

May 2015: New English study

Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases

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Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmj.h2135)

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doi: 10.1136/bmj.h2135

Accepted: 19 March 2015

ABSTRACT

OBJECTIVE

To investigate the association between use of combined oral contraceptives and risk of venous thromboembolism, taking the type of progestogen into account.

DESIGN

Two nested case-control studies.

SETTING

General practices in the United Kingdom contributing to the Clinical Practice Research Datalink (CPRD; 618 practices) and QResearch primary care database (722 practices).

PARTICIPANTS

Women aged 15-49 years with a first diagnosis of venous thromboembolism in 2001-13, each matched with up to five controls by age, practice, and calendar year.

MAIN OUTCOME MEASURES

Odds ratios for incident venous thromboembolism and

confidence interval 2.78 to 3.17) compared with no exposure in the previous year. Corresponding risks associated with current exposure to desogestrel (4.28, 3.66 to 5.01), gestodene (3.64, 3.00 to 4.43), drospirenone (4.12, 3.43 to 4.96), and cyproterone (4.27, 3.57 to 5.11) were significantly higher than those for second generation contraceptives levonorgestrel (2.38, 2.18 to 2.59) and norethisterone (2.56, 2.15 to 3.06), and for norgestimate (2.53, 2.17 to 2.96). The number of extra cases of venous thromboembolism per year per 10 000 treated women was lowest for levonorgestrel (6, 95% confidence interval 5 to 7) and norgestimate (6, 5 to 8), and highest for desogestrel (14, 11 to 17) and cyproterone (14, 11 to 17).

CONCLUSIONS

In these population based, case-control studies using two large primary care databases, risks of venous thromboembolism associated with combined oral contraceptives were, with the exception of norgestimate, higher for newer drug preparations than for second generation drugs.

Vinogradova 2015

VTE confirmed	Vinogradova
Non use	1 reference
COC levonorgestrel	3.0 (2.6-3.3)
COC norgestimate	3.5 (2.9-4.4)
COC desogestrel	6.2 (5.0-7.7)
COC gestodene	6.5 (5.0-8.4)
COC drospirenone	6.1 (4.7-7.8)
COC cyproterone	6.0 (4.7-7.7)

Vinogradova et al. BMJ 2015; 350: h2135

Vinogradova vs Lidegaard

VTE confirmed	Vinogradova	Lidegaard
Non use	1 reference	1 reference
COC levonorgestrel	3.0 (2.6-3.3)	3.0 (2.2-4.0)
COC norgestimate	3.5 (2.9-4.4)	3.5 (2.9-4.3)
COC desogestrel	6.2 (5.0-7.7)	6.6 (5.6-7.8)
COC gestodene	6.5 (5.0-8.4)	6.2 (5.6-7.0)
COC drospirenone	6.1 (4.7-7.8)	6.4 (5.4-7.5)
COC cyproterone	6.0 (4.7-7.7)	6.4 (5.1-7.9)

Vinogradova et al. BMJ 2015; 350: h2135
Lidegaard et al. BMJ 2011; 343: d6423

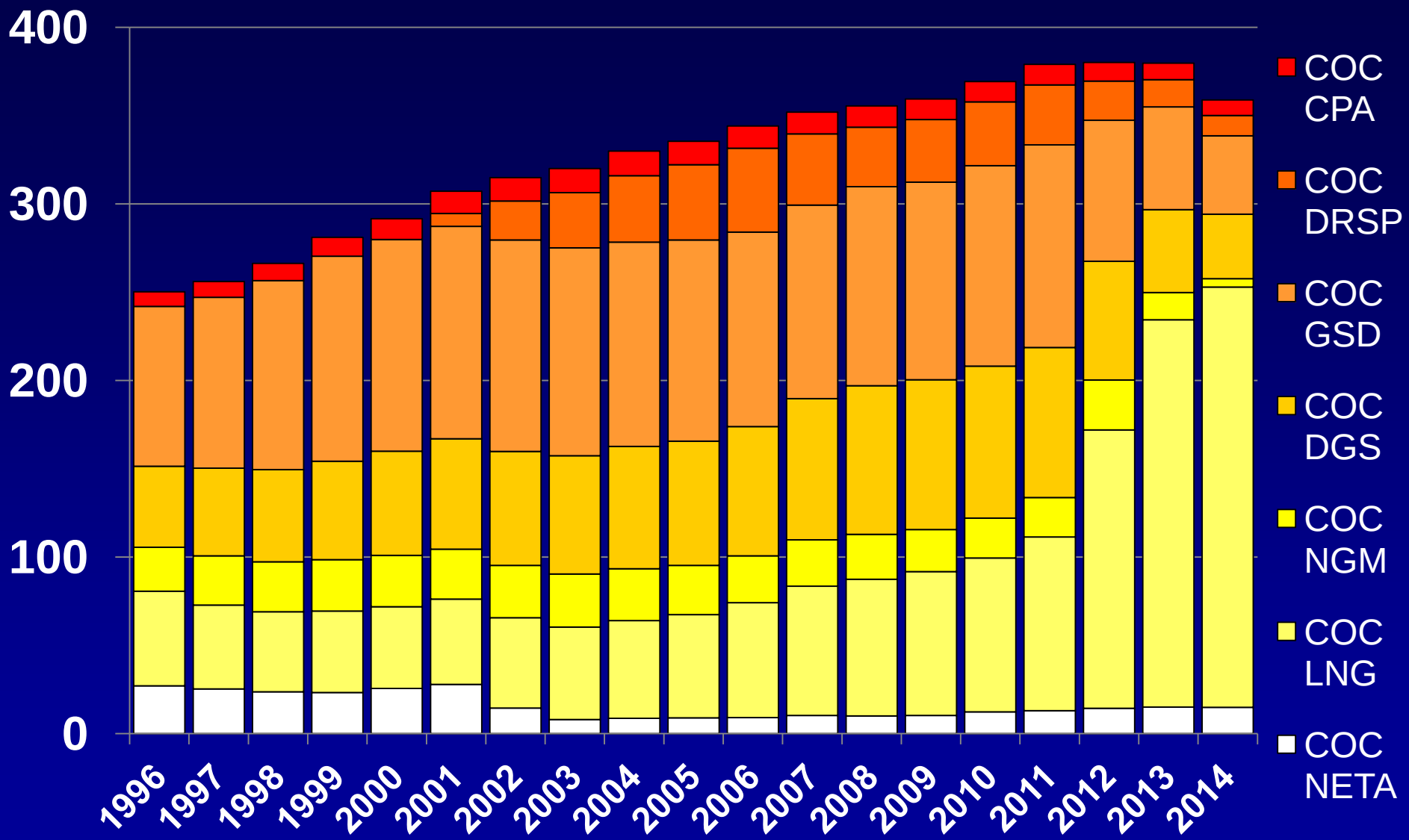
HC and RR of VTE: Conclusion

No/low risk <1.5	Middle risk 1.5-4	High risk >4	Few data	No data

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospire-none	CPA Cyproterone-acetate
Combined products							
Middle	**3**	**3**		**6**		**6**	**6**
Low		**2.5?'**		**5**			
Nat oe		E2V-DNG **4.5***			E2 NOMAC"		
N-oral			Patch **7**	Vaginal ring **6¤**			
Progestogen only products							
Oral	POP **1**			Cerazette **1**			
N-oral	Depot **1**	IUS **1§**		Implant **1.4**			

')Loette ")Zoely *)Qlaira ¤)NuvaRing #)Cerazette §) Mirena

Sale of COC in DK acc to progestogen 1996-2014

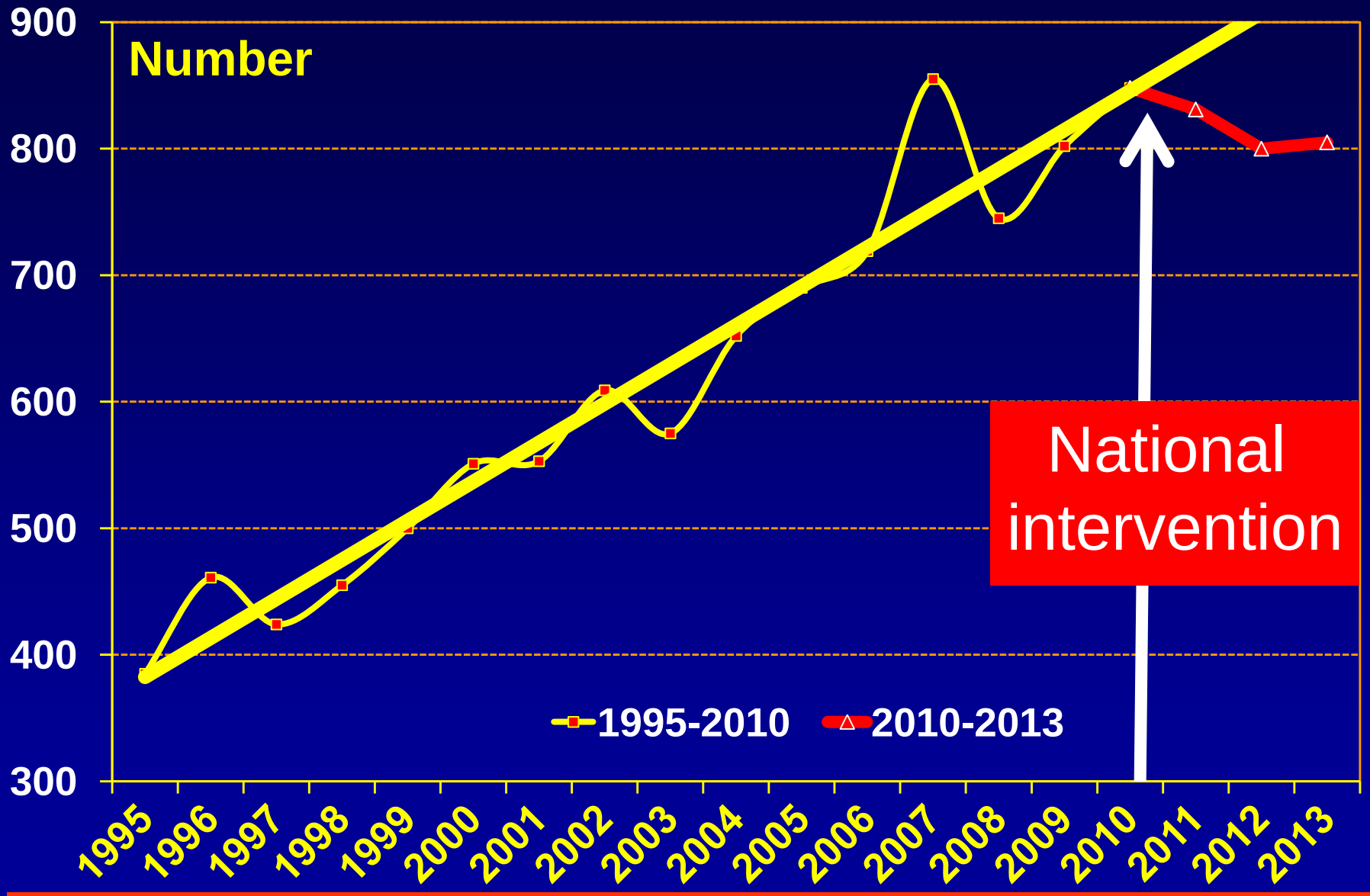


National Prescription Registry, Denmark 1996-2014

3rd myth: Pill scares

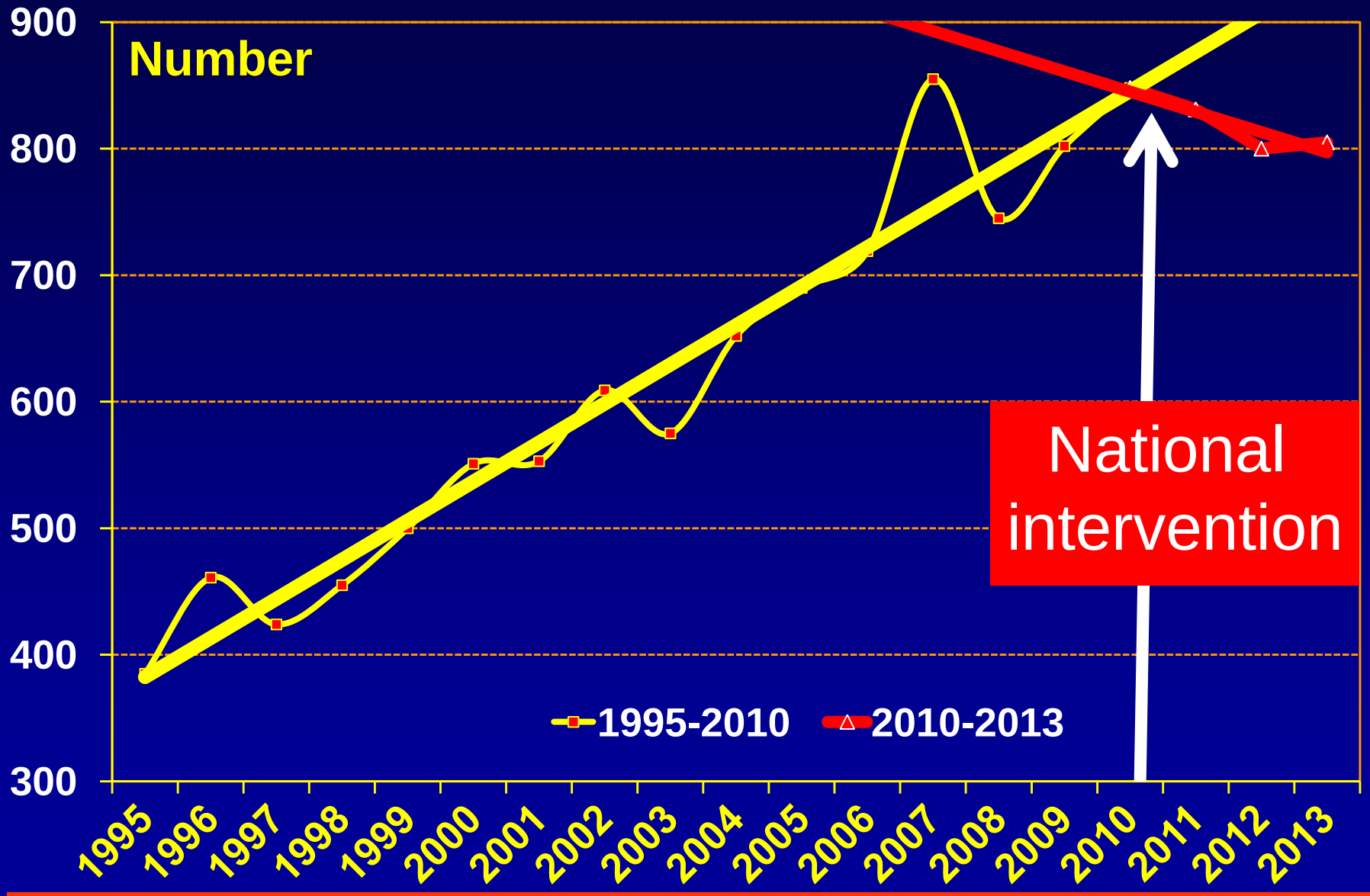
- An appropriate information about thrombotic risks with different product types is mandatory in order to
- Ensure the lowest possible risk of VTE
- Ensure immediate action in case of an event
- Such sober information does not cause a new pill scar, but contrary keeps people's confidence in advices from experts
- Hiding or manipulating scientific evidence has been responsible for all serious pill scares in the past.

First ever VTE, women 15-49



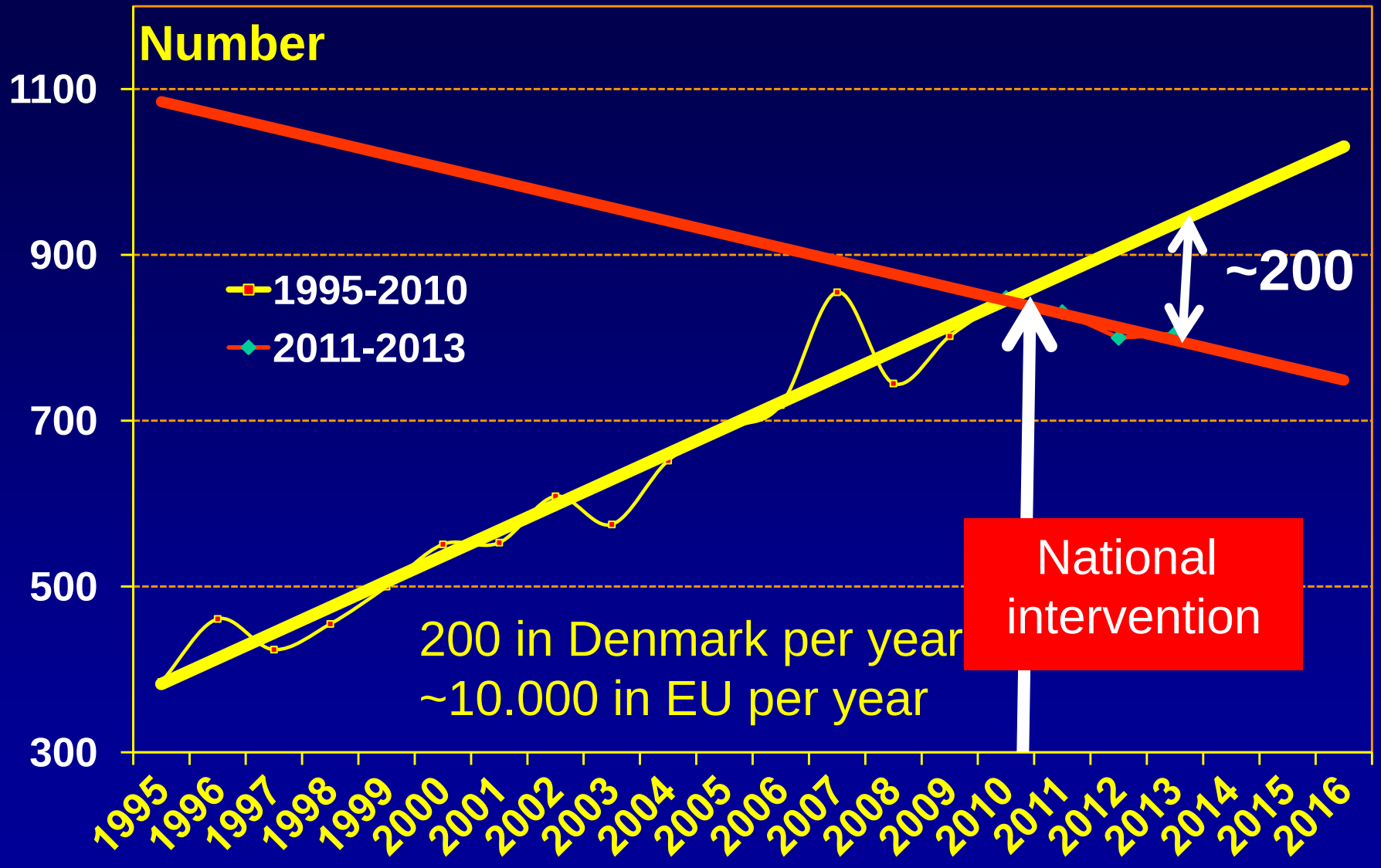
National Health Registry, Denmark

First ever VTE, women 15-49



National Health Registry, Denmark

First ever VTE, women 15-49



National Health Registry, Denmark

An appropriate practice

- Scientists have to reach consensus
- Health authorities should update their recommendations
- The press should inform the public without overdramatizing the scientific evidence
- The general practitioners should follow the updated recommendations.
- Women should be informed about the symptoms of VT to ensure immediate action

Lidegaard, Expert Opinion Drug Safety 2014: 13: 1353-60

Inconvenient research findings

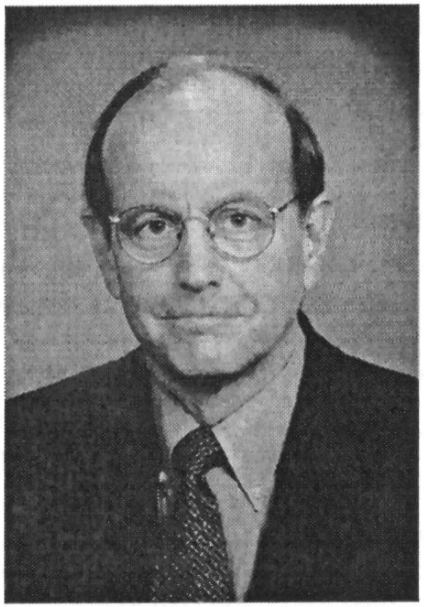
- When clinicians have had a practice for many years, and new scientific findings challenge this practice, typically three successive reactions are seen:
- Surprise
- Scepticism
- Powerlessness
- Anger (goes as far as decapitation)

Lidegaard, Expert Opinion Drug Safety 2014: 13: 1353-60

An editor

Epidemiologic Research Using Administrative Databases

Garbage In, Garbage Out



David A. Grimes, MD

Administrative databases stem from claims made for services by health care providers and institutions.[1] Simply put, they are billing systems. These databases were created for reasons other than epidemiologic research—a key limitation. Data fields commonly include only basic demo hospital- izatio earchers includ rganiza- tions

Financial Disclosure

Dr. Grimes serves as a consultant (DSMB member) for Bayer.

V ministra- tive database commonly used for epidemiologic research.[2,3] Again, these data are collected for civil and legal purposes, not for research.

Research using administrative databases has important strengths and weaknesses. Sample sizes are often large, which provide power to find differences. Those enrolled may be representative of the community of interest. Recording of drug prescriptions occurs contemporaneously, which

Grimes, Obstet Gynecol Nov 2010, 116: 1018-19

Grimes on the road again

Human Reproduction, Vol.0, No.0 pp. 1–4, 2015
doi:10.1093/humrep/dev151

human reproduction

INVITED COMMENTARY

Epidemiologic research with administrative databases: red herrings, false alarms and pseudo-epidemics

David A. Grimes*

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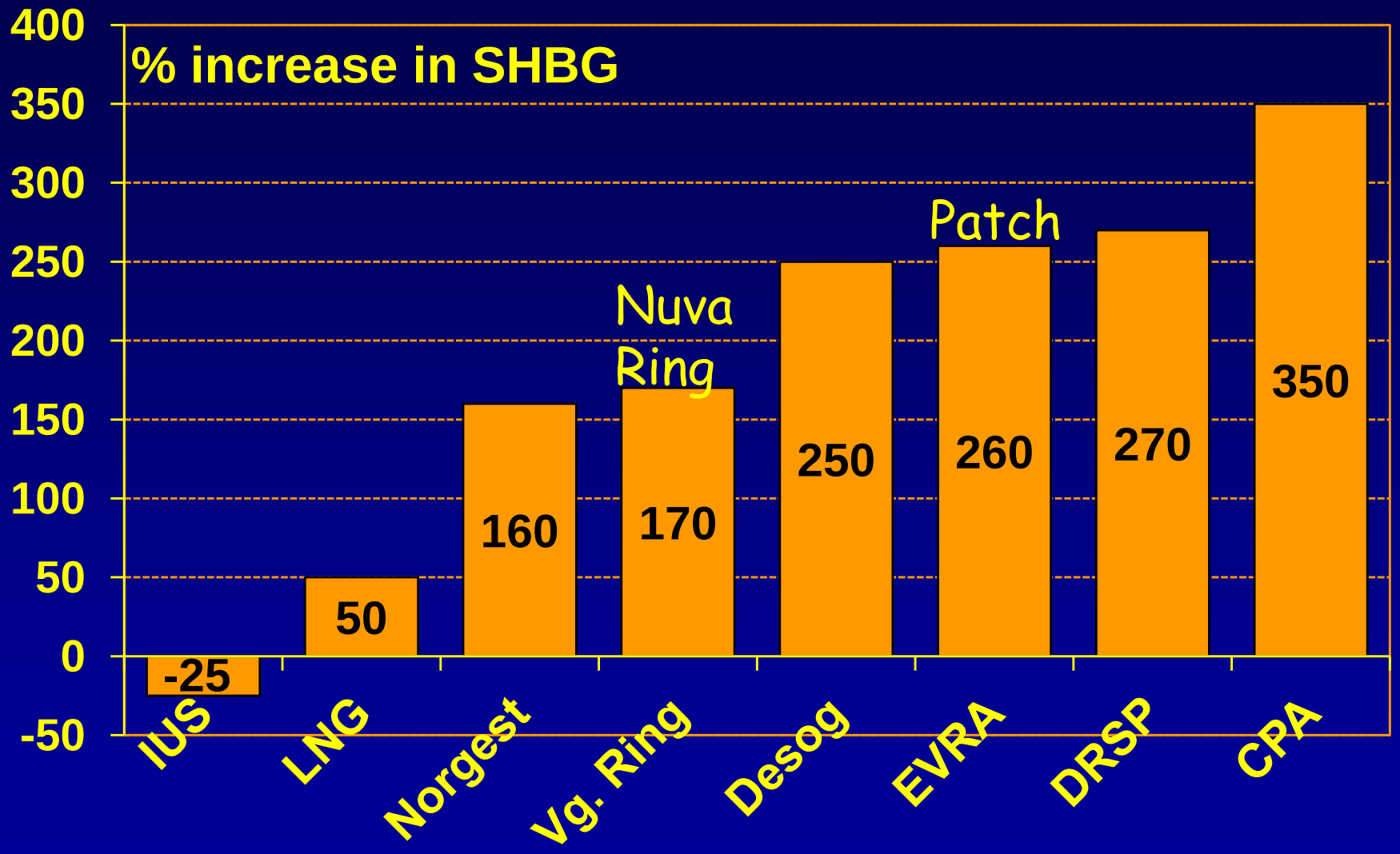
Grimes. Editorial. Hum Reprod 2015: doi:10.1093/humrep/dev151

In Denmark, studies of venous thromboembolism using the National Registry of Patients have produced red herrings as well (Grimes, 2010). For example, reports in high-profile general medical journals claimed that the levonorgestrel intrauterine system was associated with statistically significant protection against venous thrombosis (Lidegaard *et al.*, 2012b) and thrombotic stroke (Lidegaard *et al.*, 2012a). While this intra-uterine device (IUD) has several established non-contraceptive health benefits (Fraser, 2013), prevention of clots and prevention of stroke are not among them. Without validation of outcomes (Severinsen *et al.*, 2010; U.S. Food and Drug Administration) and adequate control

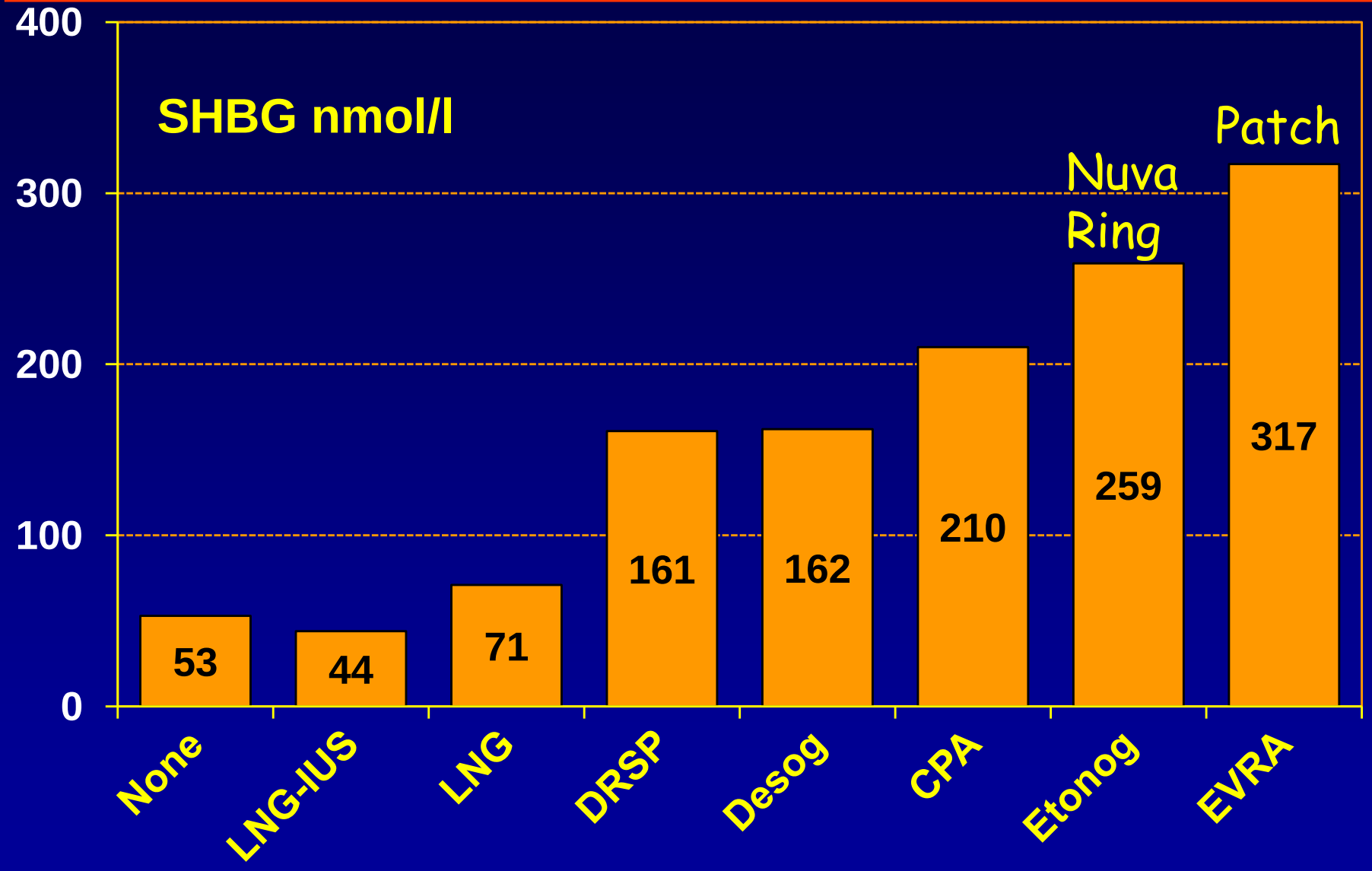
Facts: Three studies have demonstrated ***decreasing*** levels of SHBG among users of LNG-IUS. SHBG is a surrogate marker for the risk of venous thromboembolism.
Therefore, the decreased risk of venous thromboembolism among users of LNG-IUS is expected and in agreement with bio-medical findings.

Hormonal contraception and SHBG



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

Hormonal contraception & SHBG



Raps et al. Thrombosis Haemostasis 2012; doi: 10.1111

are not among them. Without validation of outcomes (Severinsen *et al.*, 2010; U.S. Food and Drug Administration) and adequate control for potential confounding (Dinger and Shapiro, 2012), these database studies (Lidegaard *et al.*, 2012a,b) are not credible.

Facts:

In contrast to the study by Dinger et al. all events of venous thromboembolism were in our study cross checked with succeeding anticoagulation therapy. Thus all our end points were objectively confirmed. In the study of Dinger et al. just an increased D-dimer was taken as evidence of a true venous thrombosis.

Facts:

Our study was controlled for more confounders than any other study done so far.

Dr. Grimes knows that fact but continuous nevertheless with these groundless claims. Why?

George Monbiot

One of the most widespread human weaknesses is our readiness to accept claims that fit our beliefs and reject those that clash with them. We demand impossible standards of proof when confronted with something we don't want to hear, but will believe any old cobblers if it confirms our prejudices:

Guardian, November 22, 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception

Øjvind Lidegaard, Dr. Med. Sci., Ellen Løkkegaard, Ph.D., Aksel Jensen, M.Sc., Charlotte Wessel Skovlund, M.Sc., and Niels Keiding, M.Sc.

ABSTRACT

BACKGROUND

Although several studies have assessed the risk of venous thromboembolism with newer hormonal contraception, few have examined thrombotic stroke and myocardial infarction, and results have been conflicting.

HC and thrombotic stroke Reference: Non-users

- All women in Denmark 15-49 years old during the period January 1995 through December 2009 (15 years)
- Data from four National registries
- Included: 1,626,158 women

  14,251,063 women years

  4,914,401 current use

  3,311 thrombotic strokes

Lidegaard et al. N Engl J Med 2012; 366: 2257-66

HC and thrombotic stroke

Low risk: <1.5	Middle risk: 1.5-4	High risk: >4	No data

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospi-renone	CPA Cyproterone-acetate
Combined products							
Middle	**2.2***	**1.7***	**1.5***	**2.2***	**1.8***	**1.6***	**1.4**
Low				**1.5***	**1.7***	**0.9**	
Nat oe	E2V-DNG			E2 NOMAC			
N-oral			Patch **3.2**	Vaginal ring **2.5***			
Progestogen only products							
Oral	POP **1.4**			Cerazette **1.4**			
N-oral	Depot	IUS **0.7**		Implant **0.9**			

HC, thrombosis and cancer

- Hormonal contraception
- **Hormonal contraception and thrombosis**
- Hormonal contraception and cancer
- Clinical recommendations

HC, thrombosis and cancer

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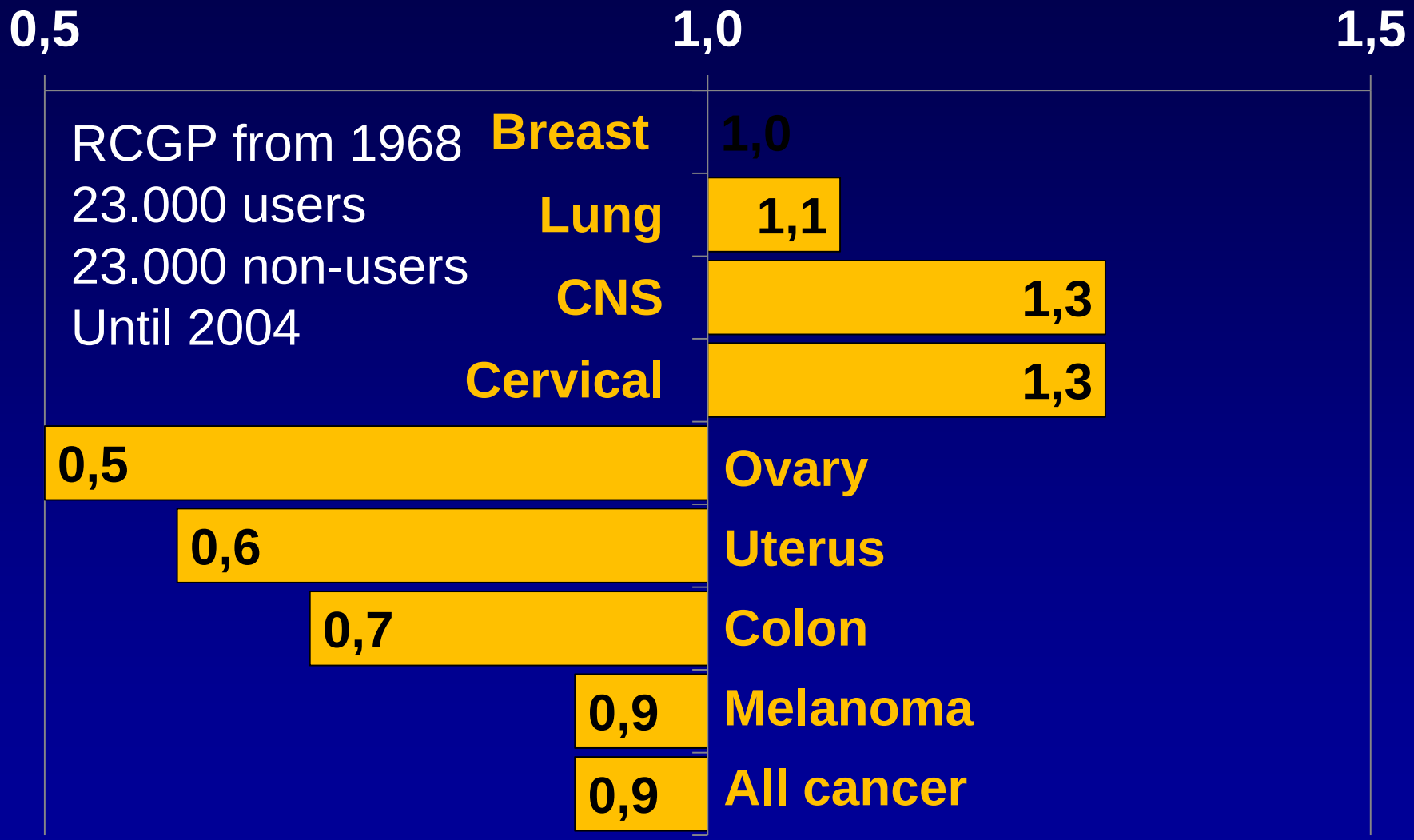
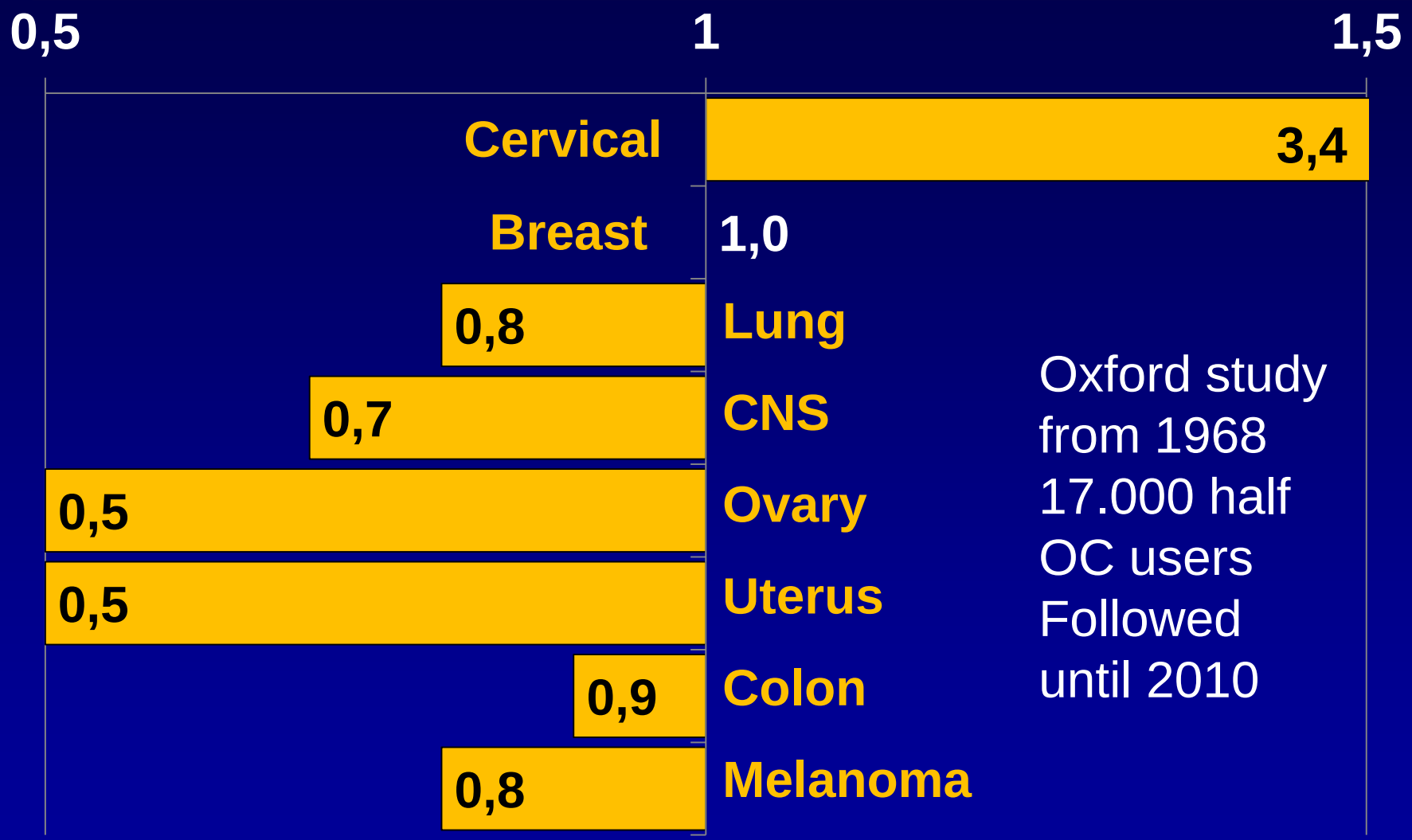
HC ever use and cancer



Hannaford et al. BMJ 2007

HC ever use and cancer



Vessey et al. Contraception 2013

Hormonal contraception and breast cancer

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Shona Fielding, statistician

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HC and breast cancer

- Design: Prospective cohort study 1995-2012
- Women 15-49 years in Denmark
- Exposure from prescription registry
- End points from cancer registry
- Confounders: Age, year, parity, age at first birth, education, PCOS, endometriose, BMI.
- 1.8 mio women, 20 mio women years
- 11,517 breast cancer events
- Current or recent use versus non-use

Mørch et al. 2016

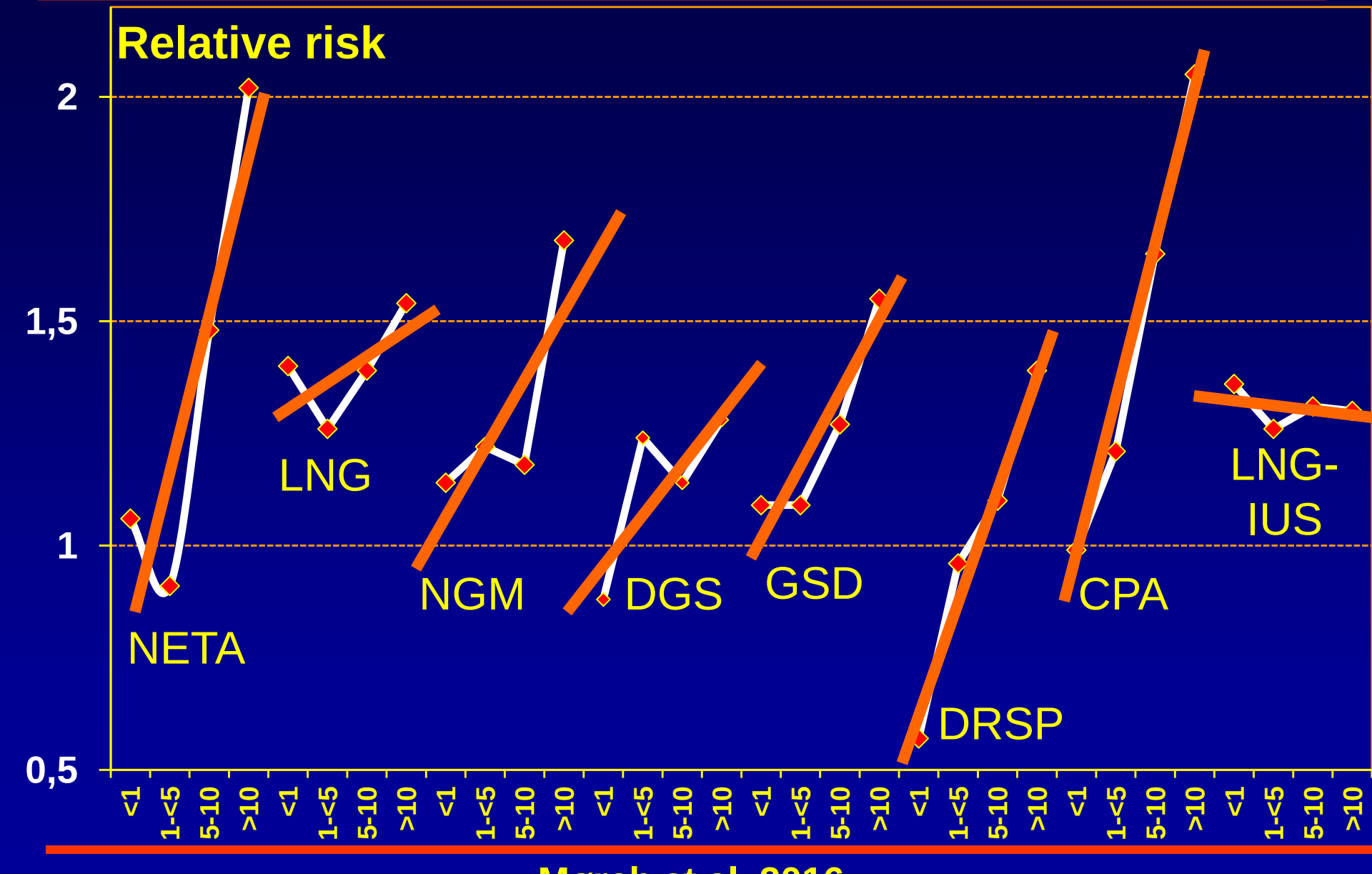
HC and breast cancer risk

Low risk: <1.5	Middle risk: 1.5-4	High risk: >4	No data

EE dose	NETA Norethis-terone	LNG Levonor-gestrel	NGM Norges-timate	DGS Deso-gestrel	GSD Gesto-dene	DRSP Drospi-renone	CPA Cyproterone-acetate
Combined products Significant results: *							
Middle	**1.2**	**1.4***	**1.3***	**1.2***	**1.3***	**1.1**	**1.6**
Low				**1.3***	**1.5***	**1.6***	
Nat oe		E2V-DNG			E2 NOMAC		
N-oral			Patch **1.0**	Vaginal ring **1.1**			
Progestogen only products							
Oral	POP **1.1**			Cerazette **1.3**			
N-oral	Depot **1.1**	IUS **1.3***		Implant **1.0**			

Mørch et al. 2016

BC risk according to length of HC use



Mørch et al. 2016

HC, thrombosis and cancer

- Use of hormonal contraception
- Hormonal contraception and thrombosis
- Hormonal contraception and cancer
- **Clinical recommendations**

Hormonal contraception – age Clinical recommendations

Young women (<35 years)

1st choice	Middle risk (2nd gen) COC
2nd choice	Low risk LNG-IUS (e.g Jaydess)
3rd choice	High risk 3rd or 4th gen COC

Women from 35 years or women at risk

1st choice	Low risk LNG-IUS
2nd choice	Middle risk 2nd gen. COC
3rd choice	Non hormonal contraception

Lidegaard, Expert Opinion Drug Safety 2014: 13: 1353-60

PCOS

- Fertile women with PCOS have a doubled risk of thrombotic stroke which is not explained by a higher BMI or use of hormonal contraception.
- Other studies have demonstrated also a doubled risk of venous thrombosis in women with PCOS.
- Therefore, also women with PCOS should have middle risk 2nd generation hormonal contraception as first choice

Hormonal contraception
That's where we are now.

Thanks for your attention

www.lidegaard.dk/slide