Parenteral hormonal contraception and venous thrombosis

Øjvind Lidegaard

Bergen, June 19, 2012

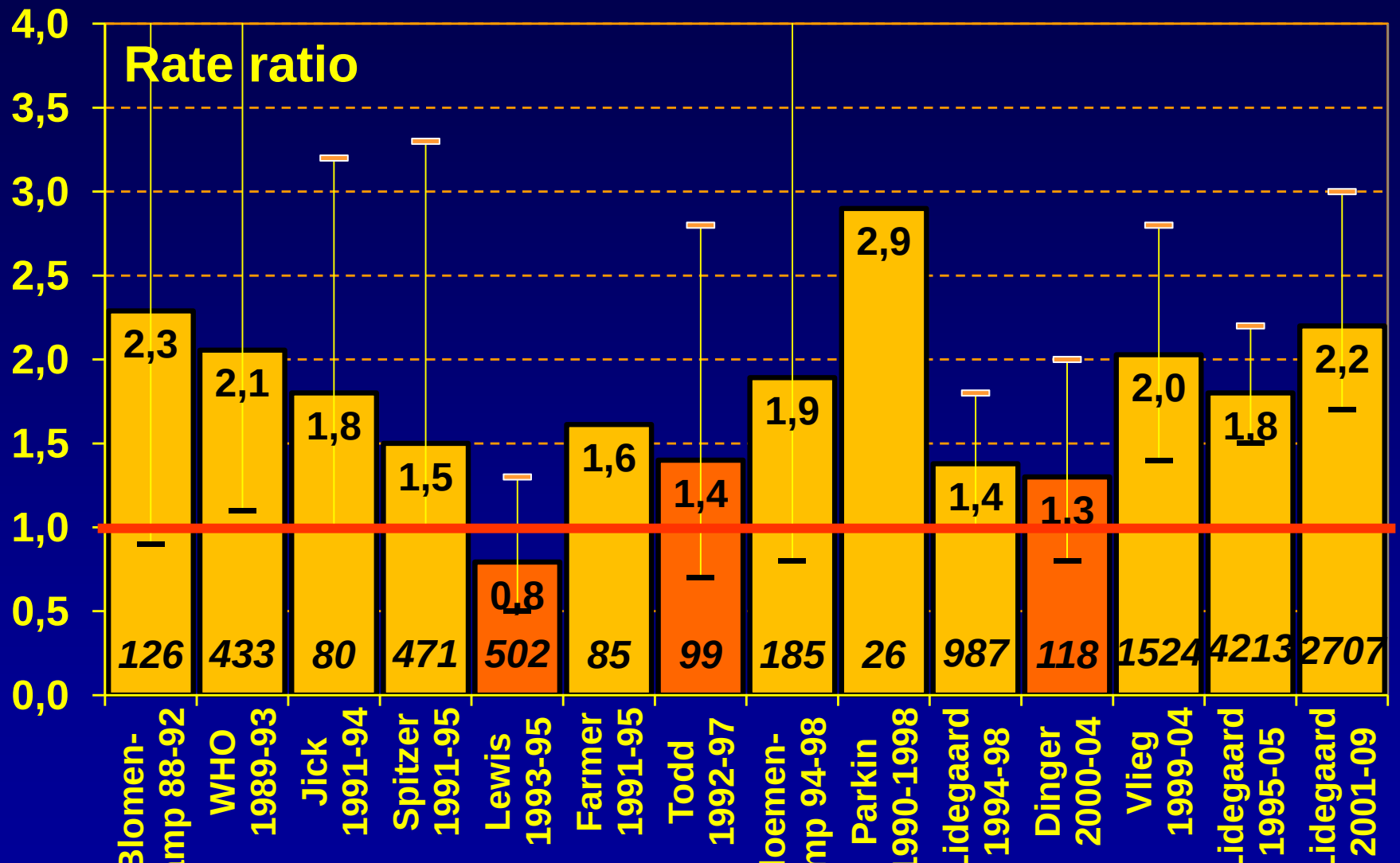
Gynaecological Clinic, Rigshospitalet
Copenhagen University

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	-	-	-
30-40^{mid}	1st	+ 2nd +		NuvaRing	+	+ 4th
20^{low}	-	-	-	3rd	+	+
E2/DNG	+	-	-	-	-	
POP	+	+		+		
Other		Lng-IUS		Implant		

3rd versus 2nd generation COC



VT and drospirenone

	VT	IR	Rate ratio
Dinger[07]	118	9.1	1.0 (0.6-1.8) 4th/2nd

IR = incidence per 10,000 women years

BMJ

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, Rigshospitalet, Copenhagen University, DK-2100 Copenhagen, Denmark

ABSTRACT

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

BMJ

RESEARCH

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,[1] Helmerhorst, professor of clinical epidemiology of fertility,[1,2] J P Vandenbroucke, professor of clinical epidemiology,[1] C J M Doggen, research fellow,[1] F R Rosendaal, professor of clinical epidemiology, head of department[1,3,4]

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

VT and drospirenone

	VT	IR	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

IR = incidence per 10,000 women years

Critique

REVIEW

Risk of venous thromboembolism among users of oral contraceptives: a review of two recently published studies

Samuel Shapiro, Jürgen Dinger

Abstract

Background Two recent studies, a cohort study from Denmark, and a case-control study from The Netherlands, have reported increased risks of venous thromboembolism (VTE) among users of oral contraceptives (OCs) containing desogestrel, gestodene, drospirenone and cyproterone, relative to the use of levonorgestrel.

Critique In the Danish study the comparisons were not valid. (1) VTE risk is highest soon after commencement of OC use, and duration of use was underestimated for levonorgestrel users, but not for drospirenone users; for the remaining compounds duration was only slightly underestimated. The underestimation for levonorgestrel resulted in systematic overestimation of the relative risks for the compared OCs. (2) Duration was also incorrectly estimated: only the duration of current use, *not duration of all episodes of use* was relevant to VTE risk. (3) Confounding was not adequately controlled.

In The Netherlands study the comparisons were not valid. (1) The relative risk for drospirenone versus levonorgestrel was not statistically significant. (2) Extensive publicity had been given to the risk of VTE among users of desogestrel, gestodene, drospirenone and cyproterone: information bias and detection bias were therefore likely. (3) Inadequate allowance was made for duration of use. (4) The combination of two different control groups, both of them likely to have been biased, into a single category was not valid.

Conclusion The best evidence continues to suggest that the increased risk of VTE in OC users is a class effect, dependent on the estrogen dose and duration of use, and independent of the progestogen used.

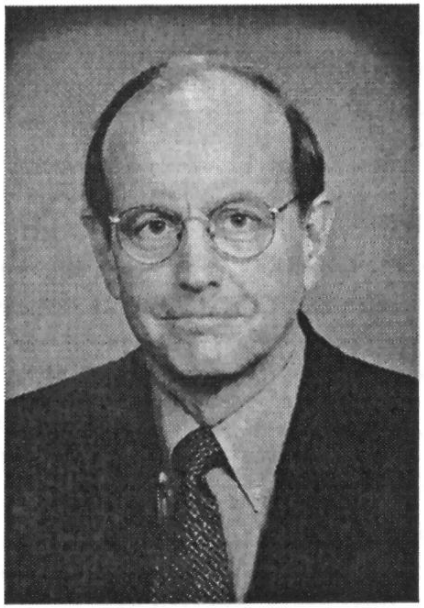
Keywords combined oral contraceptives, progestogen, risk assessment, venous thromboembolism

J Fam Plann Reprod Health Care 2010; **36**(1): 33–38
(Accepted 25 November 2009)

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 demographic information, drug dispensing, provider visits, and hospitalization. Examples of administrative databases often used by researchers include Medicare, Medicaid, and those of health maintenance organizations such as Kaiser Permanente.

Vital records, such as birth certificates, represent another administrative 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

Research using vital records should be limited to simple descriptive reports with caveats about data accuracy. Using birth certificate information for epidemiologic analyses is inappropriate because of well documented deficiencies in information quality[3]. Similarly, epidemiologic research using adminstrative databases, such as the Danish National Patient Registry, must at a minimum validate each reported outcome by chart review[9] or by patient interview.

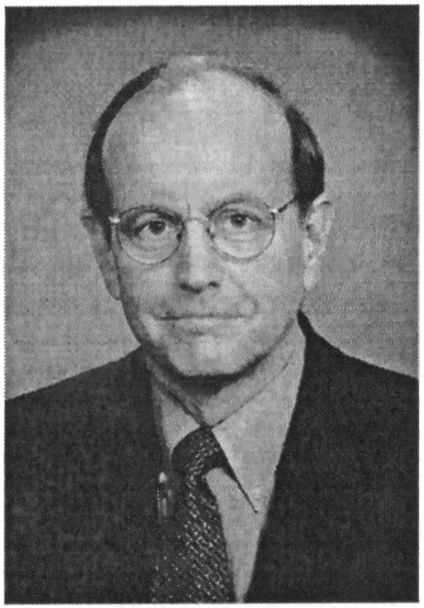
In recent decades, the computer science concept of "GIGO" ("garbage in, garbage out") has somehow come to mean "garbage in, gospel out[10]." When computer software tackles a large database, many accept the "computerized" output as trustworthy, regardless of the quality of the input. Sadly, no fancy statistical machinations can compensate for poor-quality data. Publications relying on unconfirmed database reports of venous thromboembolism should be ignord.

Grimes. Obstet Gynecol 2010; 116: 1018-19

An editor

Epidemiologic Research Using Administrative Databases

Garbage In, Garbage Out



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Financial Disclosure

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

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

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 → 2005 → 2009

1.3 million women

Cause of Deaths Registry (>1977)

Lethal VT

Statistics Denmark

PIN-codes, education

vital status, emigration

Lidegaard et al. BMJ 2011; 343: d6423

BMJ

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

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*[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]

[1]Gynaecological Clinic 4232, Rigshospitalet, University of Copenhagen, Denmark; [2]Department of Obstetrics and Gynaecology, Institute of Clinical Medicine, University of Tromsø, Norway; [3]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

VT and drospirenone

	VT	IR	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
Lidegaard[11]	4,246	9.3	2.1 (1.6-2.8)	4th/2nd

IR = incidence per 10,000 women years

VT and drospirenone

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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

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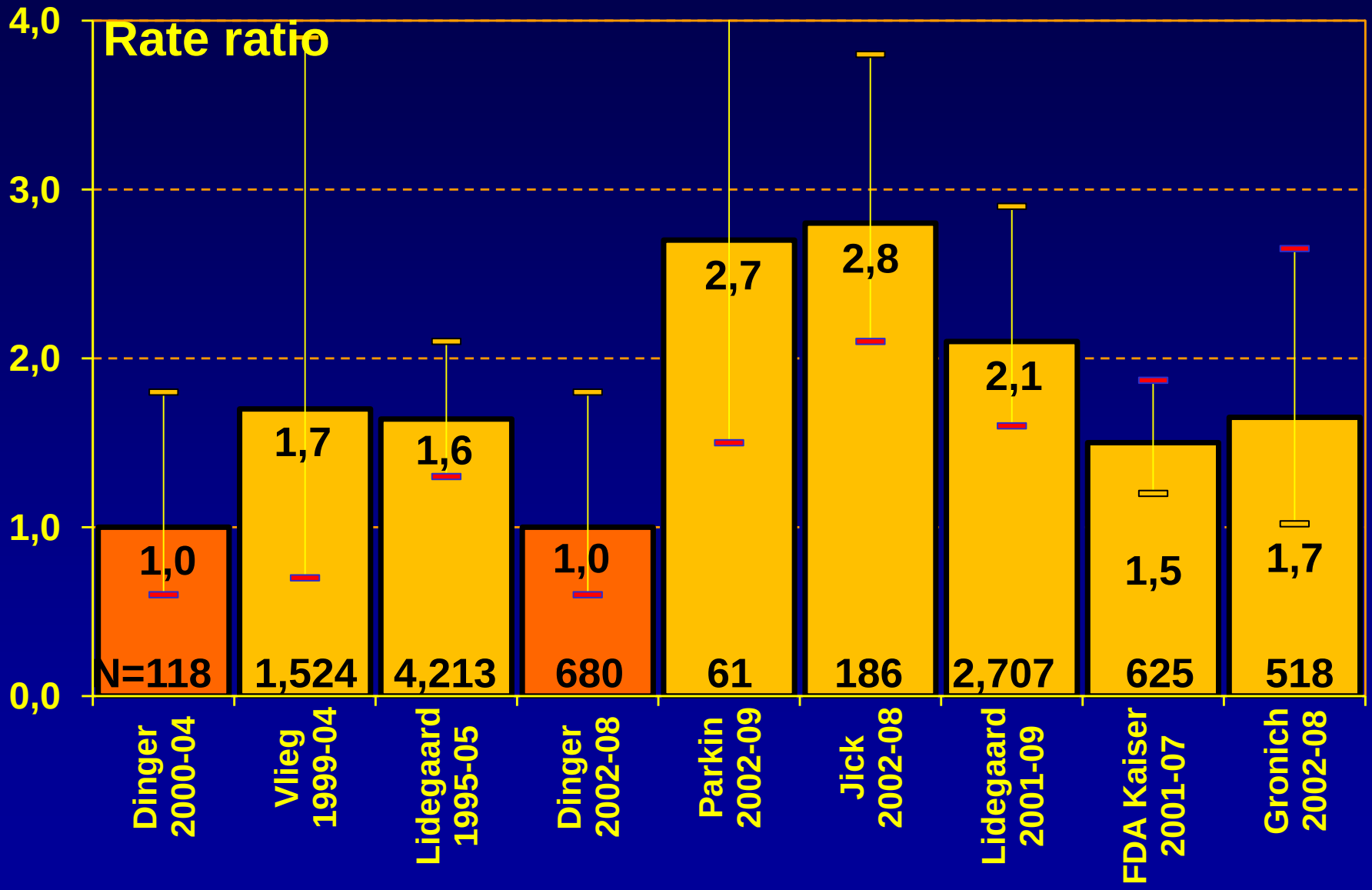
Lidegaard[11]	4,246	9.3	2.1 (1.6-2.8)	4th/2nd
FDA Kaiser[11]	625	7.6	1.5 (1.2-1.9)	4th/2nd
Gronich[11]	518	8.6	1.7 (1.0-2.7)	4th/2nd

IR = incidence per 10,000 women years

COC with DRSP vs LNG



We hear what we like to hear

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"

The Guardian, November 2011, about climate science

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
Lng-IUS		0.7 0.5-1.1	Implant

Lidegaard et al. BMJ 2011; 343: d6423

BMJ

BMJ 2012;344:e2990 doi: 10.1136/bmj.e2990 (Published 10 May 2012)

RESEARCH

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

OPEN ACCESS

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

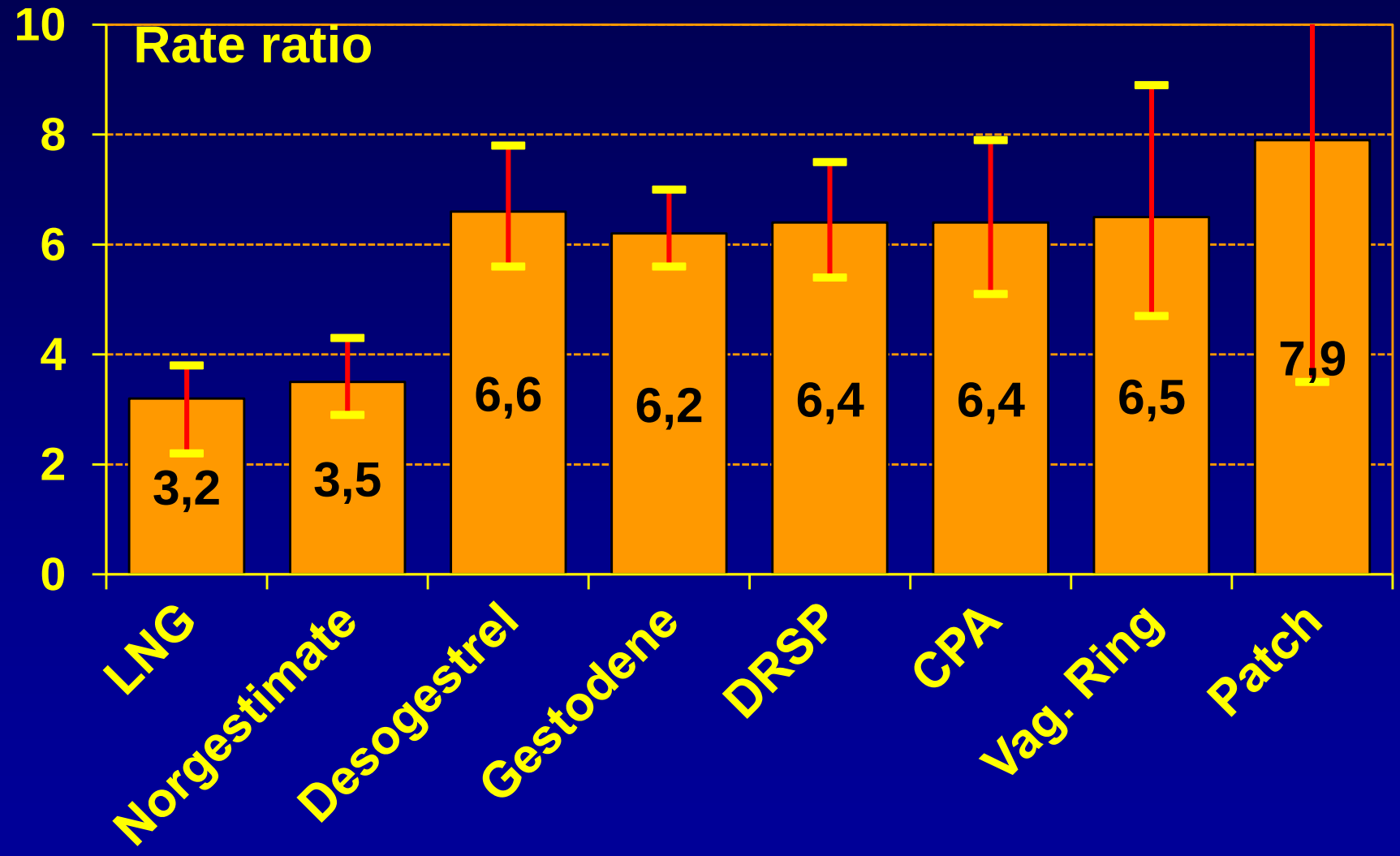
OC and VT: Progestogen type Confirmed versus non-use

ug EE	Neta	Lng	NGM	Deso	Gest	Drsp	Cypr
50	6.2 3.0-13.2	4.5 2.9-6.9	7.9 3.5-17.7 ← Patch	na	na	na	
30-40	2.2 1.1-4.5	3.2 2.7-3.8	3.6 3.0-4.3	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
				6.5 4.7-8.9 Vaginal Ring			
POP	0.7 0.3-1.5			0.6 0.2-1.9			
Lng-IUS		0.6 0.4-0.8		1.4 (0.6-3.4) Implant			

Lidegaard et al. BMJ 2012; 344: e2990

Relative risk versus non-use

Confirmed events only



Lidegaard et al. BMJ 2011; 343: d6423 + BMJ 2012; 344: e2990

Shapiro again

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

Samuel Shapiro, Visiting Professor of Epidemiology *University of Cape Town, Faculty of Health Sciences*

16 May 2012

In the Danish study the fundamental principle that exposure groups should be compared over the same time intervals is violated. The investigators state that follow-up was from 2001 to 2010. In fact, for women who were contraceptive users as of 2001, follow-up of COCs containing levonorgestrel (LNG) could actually have commenced as early as 1994, whereas for patch (EVRA) users follow-up could only have commenced in 2003, and for vaginal ring (NuvaRing) users in 2001 (the dates of introduction in Denmark). Only the occurrence of VTE was determined from 2001 to 2010.

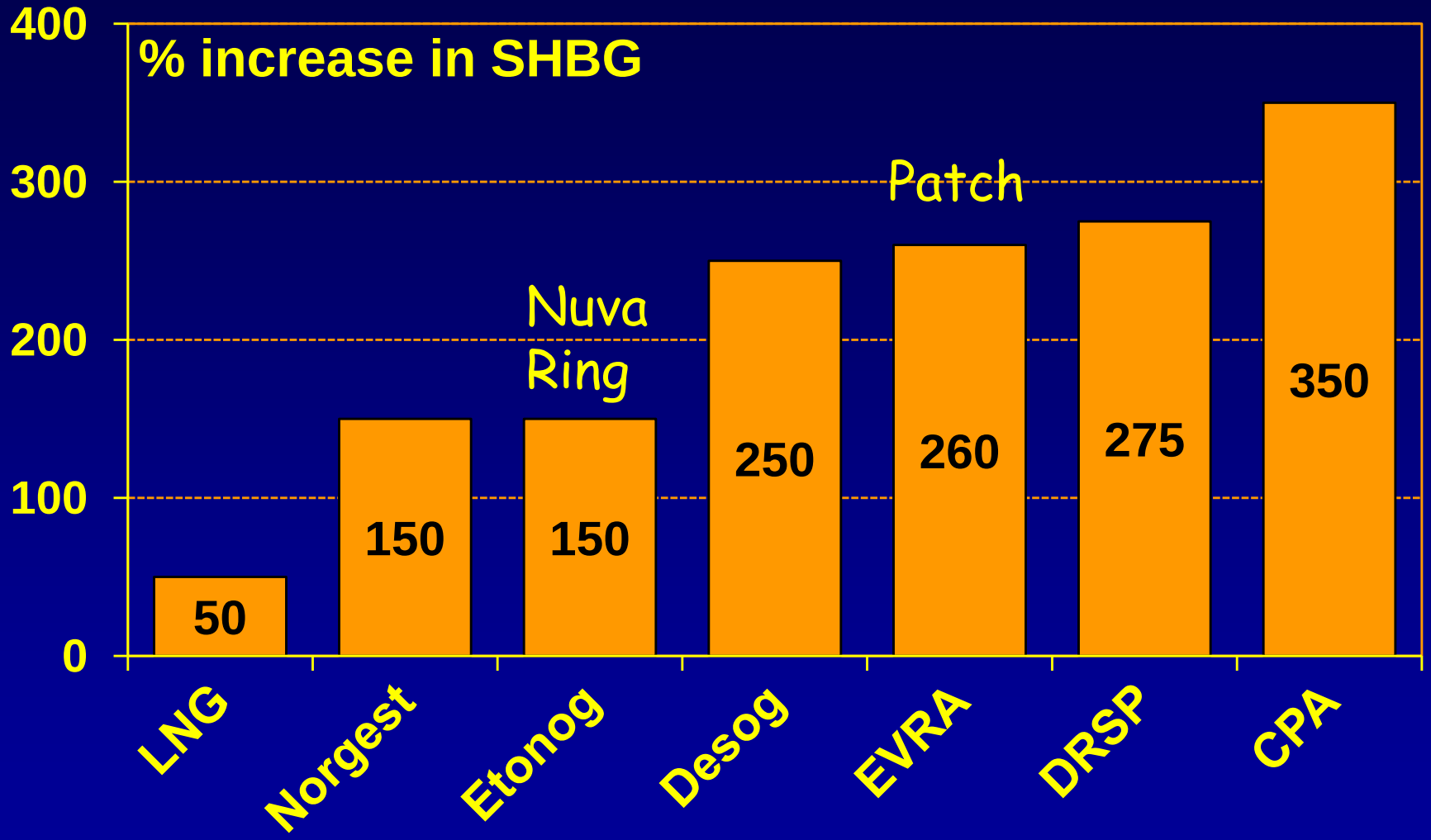
HC and VT according to oestrogen dose and progestogen type

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

FDA Kaiser, 2011. www.fda.gov

OCs and SHBG changes



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

OCs and venous thrombosis

Current status June 2012

Non use	1
POP & implants:	1
Hormone IUD:	<1
2nd gen:	3
3rd gen & vg ring:	6
4th gen:	6
Patch	7-8

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

ug EE	Neta	Lng	Norg	Deso	Gest	Drsp	CPA
50	1.2 0.6-2.4	2.2 1.5-3.1	3.2 0.8-12.7	2.5 1.4-4.4	na	na	na
30-40	2.2 1.5-3.2	1.6 1.4-1.9	1.5 1.2-1.9	2.2 1.8-2.7	1.8 1.6-2.0	1.7 **1.3-2.2**	1.4 1.0-2.0
20	na	na	na	1.6 1.3-1.9	1.7 1.4-2.2	0.9 0.2-3.6	na
POP	1.4 0.9-2.0			1.4 0.7-2.7			
Mirena		0.7 0.5-1.0		0.9 0.3-2.6	Implant		

N Engl J Med 2012; 366: 2257-66

OCs and venous thrombosis

Current status June 2012

	VTE	Tr Stroke
POP + implant:	1	1
Hormone IUD:	<1	1
2nd gen:	3	1.5
3rd gen / vg ring:	6	1.8/2.5
4th gen:	6	1.7
Patch	7-8	3

Hormonal contraception and thrombotic risk

Thanks for your attention

www.lidegaard.dk/slides

From Tuesday