

Hormonal contraception and venous thrombosis. An update.

Øjvind Lidegaard

Hindsgavl, September 14, 2012

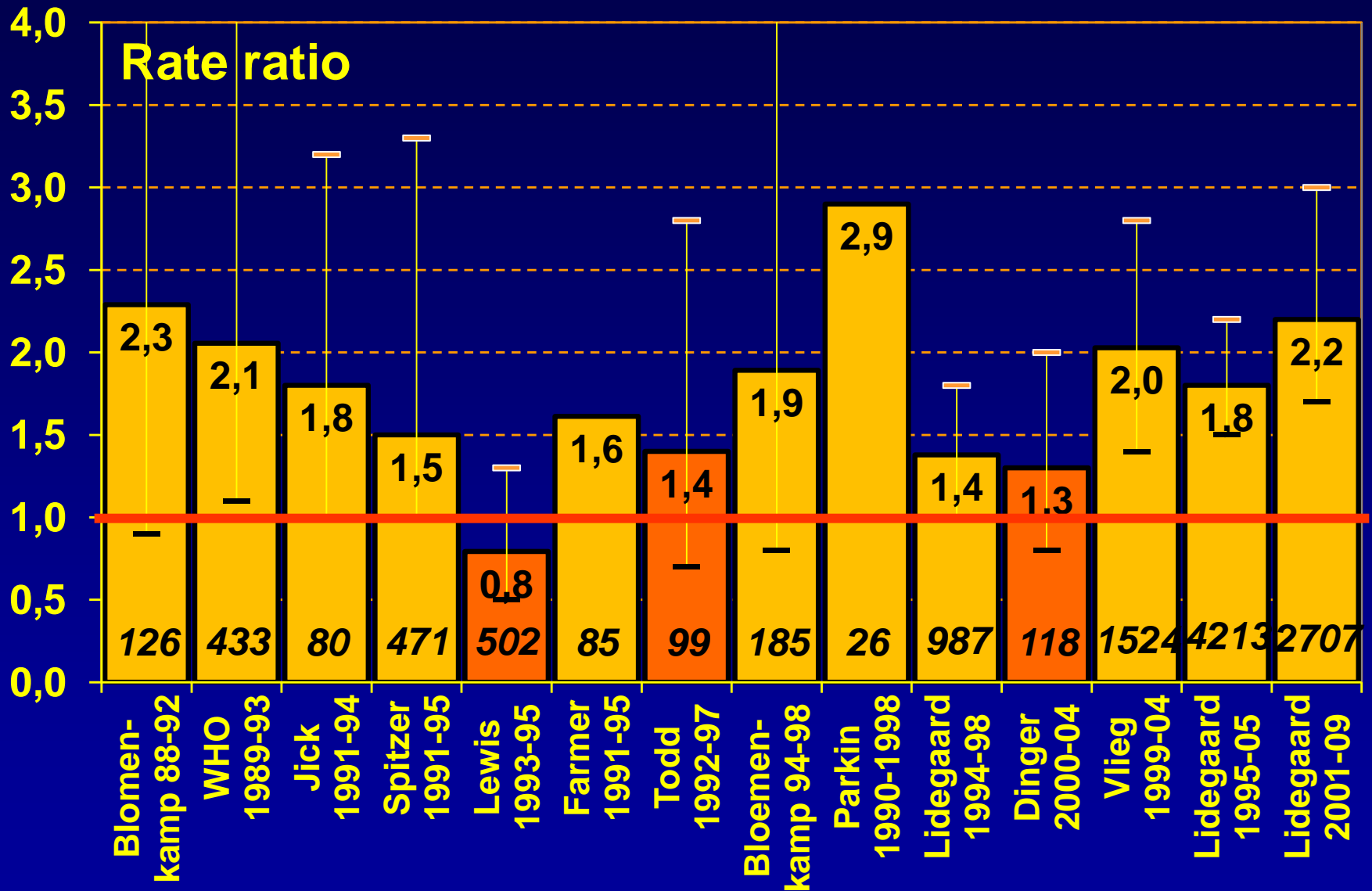
**Gynaecological Clinic, Rigshospitalet
University of Copenhagen**

OC generations according to oestrogen dose and progestogen type

Progestogen generation

| | 1 | 2 | "2" | 3 | 3 | 4 |
|----------------------|-----------------|---------------------|-------------------|------------------|----------------|-------------------|
| | Estrans NETA | Levonor- gestrel | Norges- timate | Deso- gestrel | Gesto- dene | 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

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 manager⁴


ABSTRACT

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

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

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}

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

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.

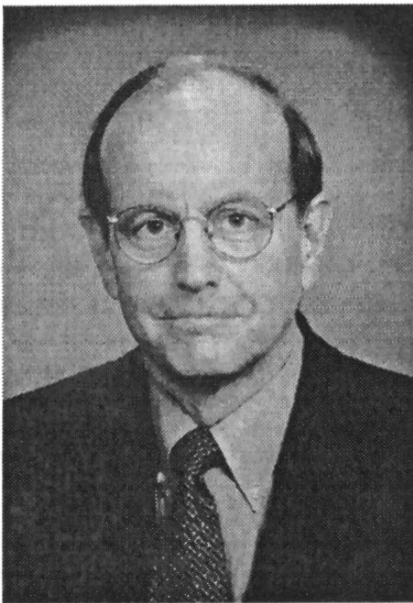
Keywords combined oral contraceptives, progestogen, risk assessment, venous thromboembolism

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

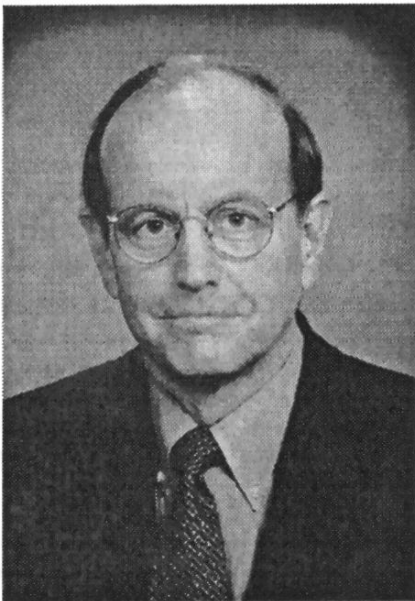
Research using vital records should be limited to simple descriptive reports with caveats about data accuracy. Using birth certificate information for epidemiologic analyses is inappropriate because of well documented deficiencies in information quality³. Similarly, epidemiologic research using administrative databases, such as the Danish National Patient Registry, must at a minimum validate each reported outcome by chart review⁹ 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 ignored.

An Editor

Epidemiologic Research Using Administrative Databases

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David A. Grimes, MD

Administrative databases stem from claims made for services by health

Financial Disclosure

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

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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

1.3 million women

2005

2009

Cause of Deaths Registry (>1977)


Lethal VT

Statistics Denmark

PIN-codes, education
vital status, emigration

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

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

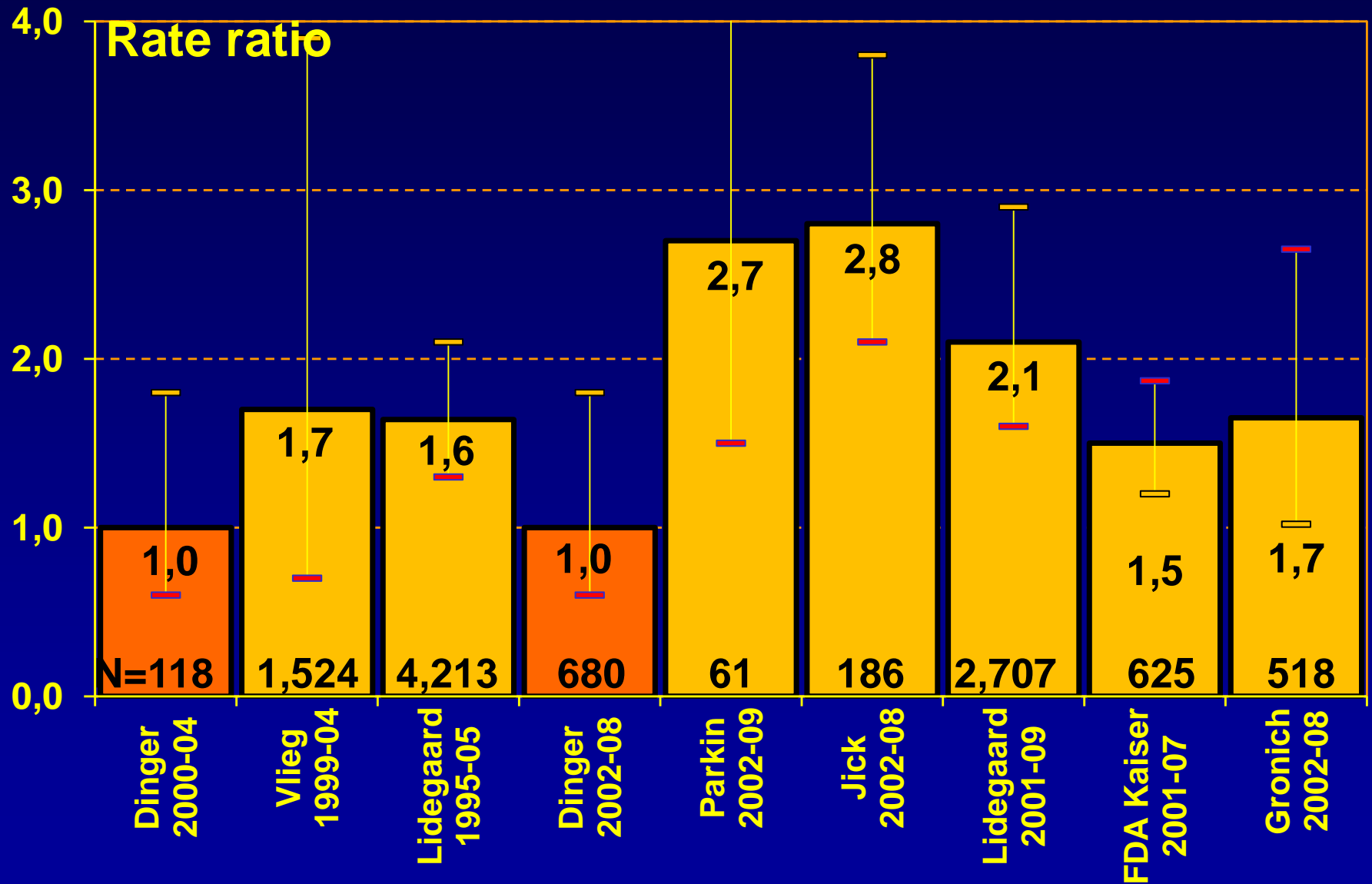
IR = incidence per 10,000 women years

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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 Editorial Nov 2011

This new study has tackled many of the concerns expressed about the earlier investigation. Although unpalatable to some, it is difficult not to conclude that combined oral contraceptives with desogestrel, gestodene, or drospirenone confer a higher risk of venous thromboembolism than those with levonorgestrel.

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

¹Gynaecological Clinic 4232, Blegdamsvej 9, DK-2100 Copenhagen Ø, Juliane Marie Centre, Rigshospitalet, University of Copenhagen, Denmark;

²Department of Obstetrics and Gynaecology, Hillerød Hospital, University of Copenhagen, Denmark

OC and VT: Progestogen type

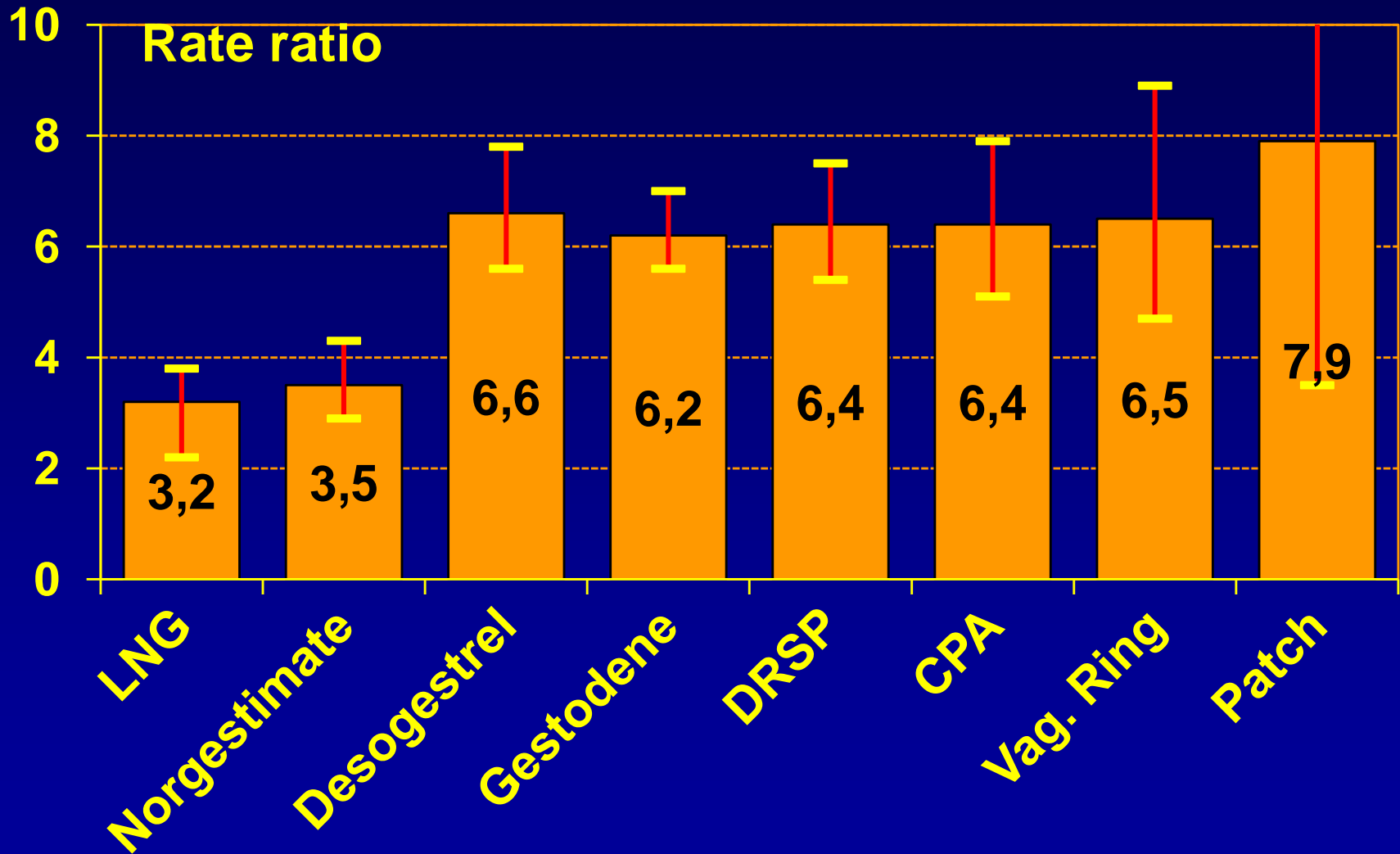
Confirmed versus non-use

| ug EE | Neta | Lng | NGM | Deso | Gest | Drsp | Cypr |
|---------|-----------------|----------------|-------------------------|------------------|----------------|-----------------|----------------|
| 50 | 6.2 3.0-13.2 | 4.5 2.9-6.9 | 7.9 ← Patch 3.5-17.7 | na | 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



.....on the road again

Publication in BMJ on May 10, 2012

- Anne Szarewski (14.5.2012)

“...biologically nonsensical results”



.....on the road again

Publication in BMJ on May 10, 2012

- Anne Szarewski (14.5.2012)
- Samuel Shapiro (16.5.2012)

“..the Danish registry is an unsuitable resource for the evaluation of VTE risk”

.....on the road again

Publication in BMJ on May 10, 2012

- Anne Szarewski (14.5.2012)
- Samuel Shapiro (16.5.2012)
- Mary E. Gaffield (16.5.2012)

“These new data .. may lead to a new (unfounded) scare”

.....on the road again

Publication in BMJ on May 10, 2012

- Anne Szarewski (14.5.2012)
- Samuel Shapiro (16.5.2012)
- Mary E. Gaffield (16.5.2012)
- Julie M Chandler (17.5.2012)

*“Higher abortion rate in areas where
....prescribing restrictions are in place”*

.....on the road again

Publication in BMJ on May 10, 2012

- Anne Szarewski (14.5.2012)
- Samuel Shapiro (16.5.2012)
- Mary E. Gaffield (16.5.2012)
- Julie M Chandler (17.5.2012)
- Anne L Connolly (18.5.2012)

“...poor studies such as this one...”

.....on the road again

Publication in BMJ on May 10, 2012

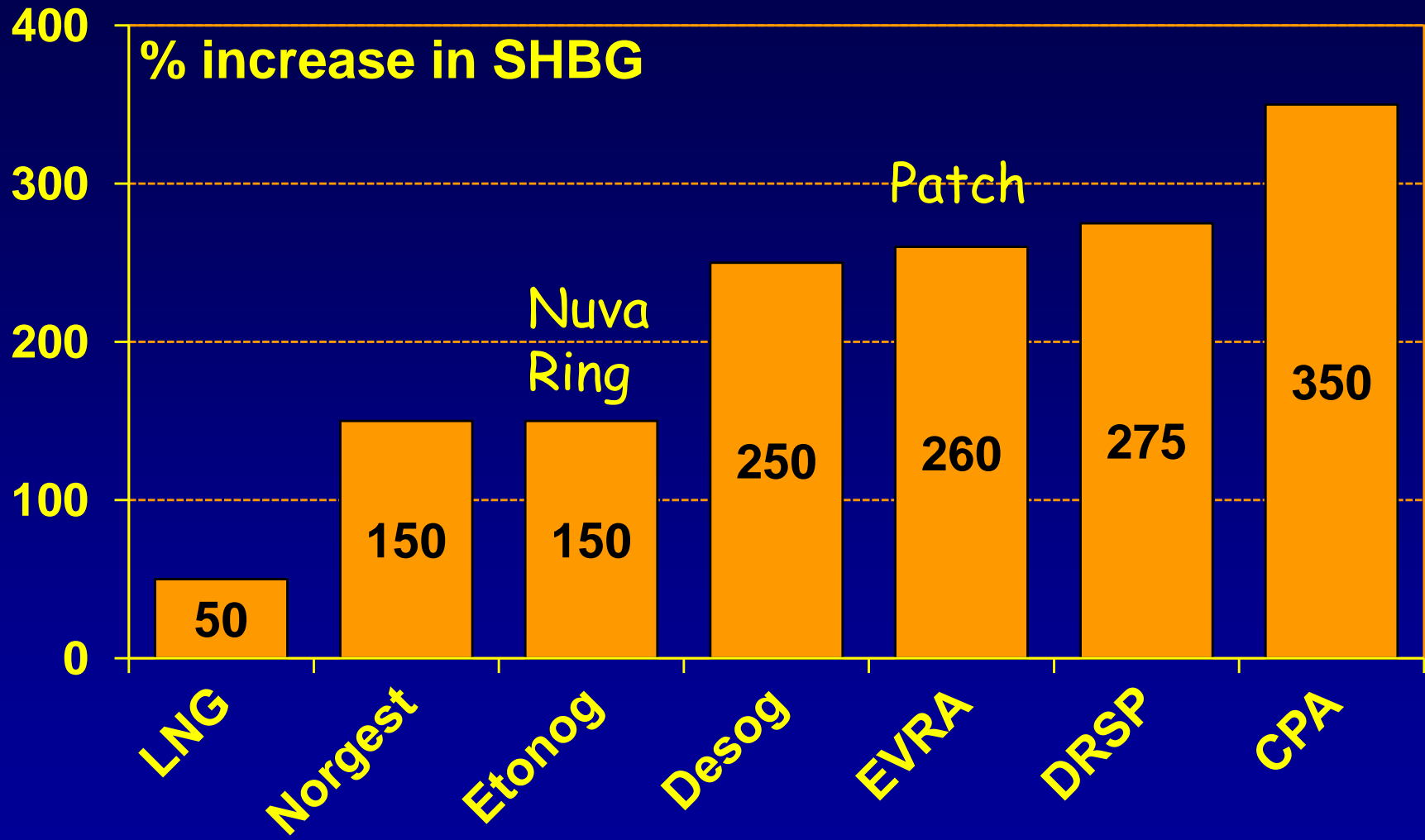
- Anne Szarewski (14.5.2012)
- Samuel Shapiro (16.5.2012)
- Mary E. Gaffield (16.5.2012)
- Julie M Chandler (17.5.2012)
- Anne L Connolly (18.5.2012)
- Jørgen Jespersen (19.5.2012)

“We find no reason to repeat the clear and concise arguments by Anne Szarewski”

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 | | |

OCs and SHBG changes



HC and venous thrombosis

Current status September 2012

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

ORIGINAL ARTICLE

Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception

Øyvind 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

HC and thrombotic diseases

Current status September 2012

| | Venous | Arterial |
|--------------------|--------|----------|
| 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 |

AOGS REVIEW ARTICLE

Hormonal contraception and venous thromboembolism

ØJVIND LIDEGAARD¹, IAN MILSOM², REYNIR TOMAS GEIRSSON³ & FINN EGIL SKJELDESTAD⁴

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Key words

Oral contraceptives, hormonal contraception, venous thromboembolism, drospirenone, levonorgestrel, deep venous thrombosis

Correspondence

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Conflict of interests

Abstract

Background. New studies about the influence of hormonal contraception on the risk of venous thromboembolism (VTE) have been published. **Aim.** To evaluate new epidemiological data and to propose clinical consequences. **Design.** A literature survey. **Methods.** Studies assessing the risk of specific types of hormonal contraception were evaluated, compared and set into a clinical perspective. **Results.** The majority of newer studies have demonstrated a threefold increased risk of VTE in current users of medium- and low-dose combined oral contraceptives (COCs) with norethisterone, levonorgestrel (LNG) or norgestimate compared with non-users. The same studies have demonstrated a sixfold increased risk of VTE in users of com-

Hormonal contraception and thrombotic risk

Thanks for your attention

www.lidegaard.dk/slides
