2017-11-09:

Reported adverse reactions from contraception in Norway – what are the learning points?

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Benefit-risk ratio

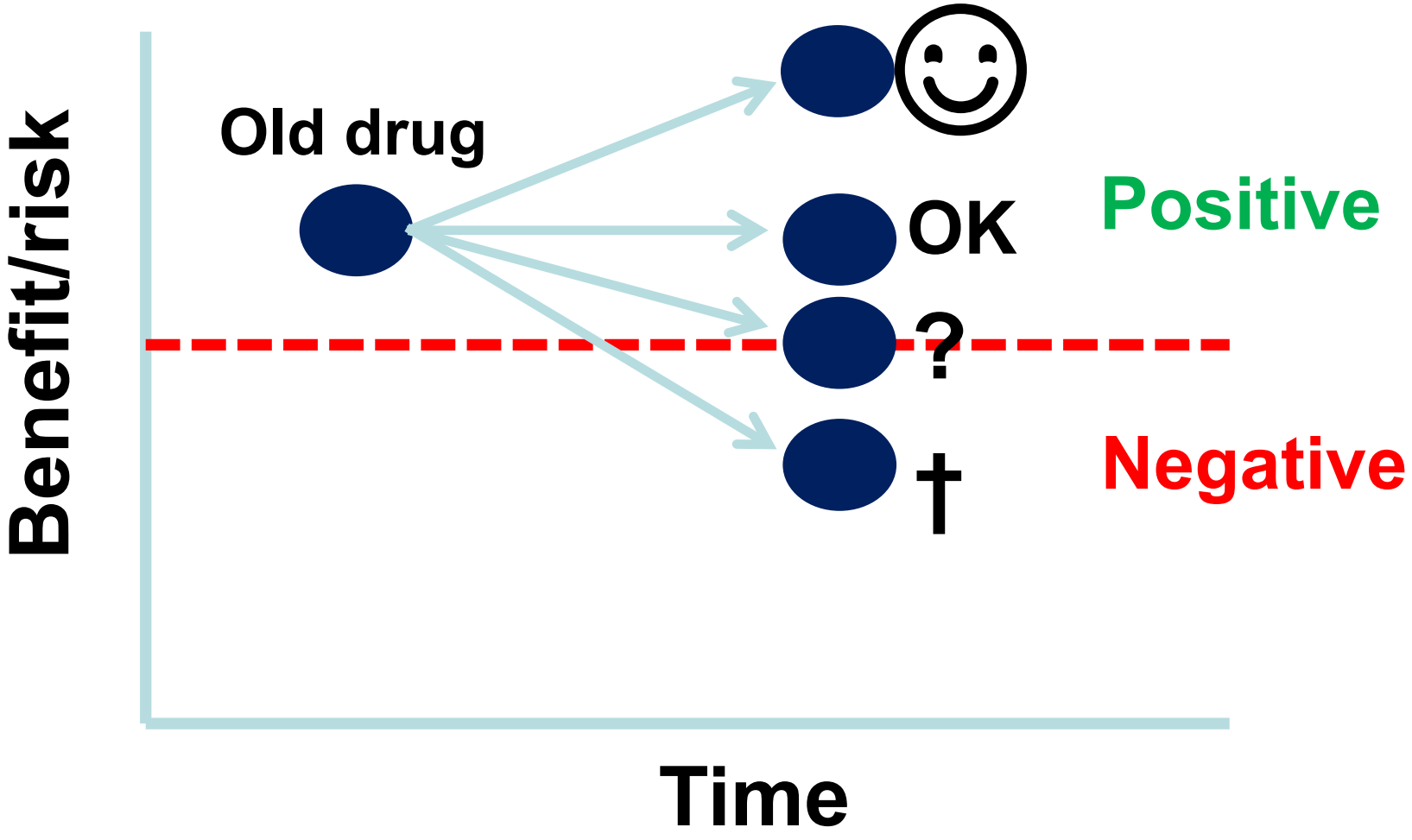
$$\text{Benefit/risk:} \quad \frac{\text{Postive effects}}{\text{Adverse reactions}}$$

Fundamental for all drugs from approval to clinical practice

Where can vi go wrong?

- Risk blindness or denial in people closely linked to the drug
  - Industry
  - Drug authorities
- It's not my fault – but whom to blame?
  - Health care professionals?
  - Patients?
  - Drug industry?
  - Drug authorities?
- Hard to detect adverse reactions
  - Infrequent reactions
  - Reactions also a (common) disease
- Not learning from previous experiences
  - Drug safety versus aviation safety

Lifespan of a drug



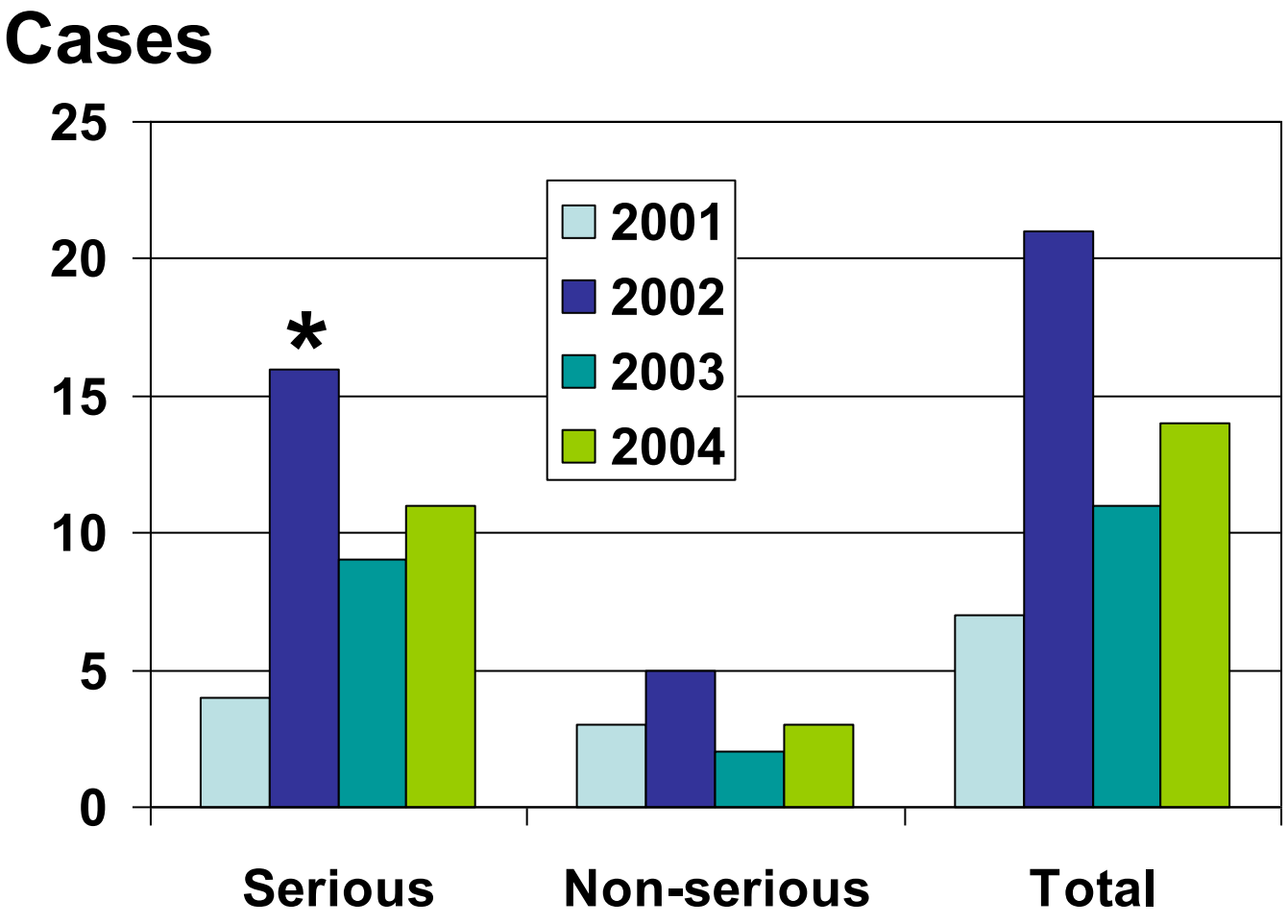
Drospirenone

- **Drospirenone based combination contraception pills (COC) was launced in Norway in November 2000.**

Marketing and adverse reactions

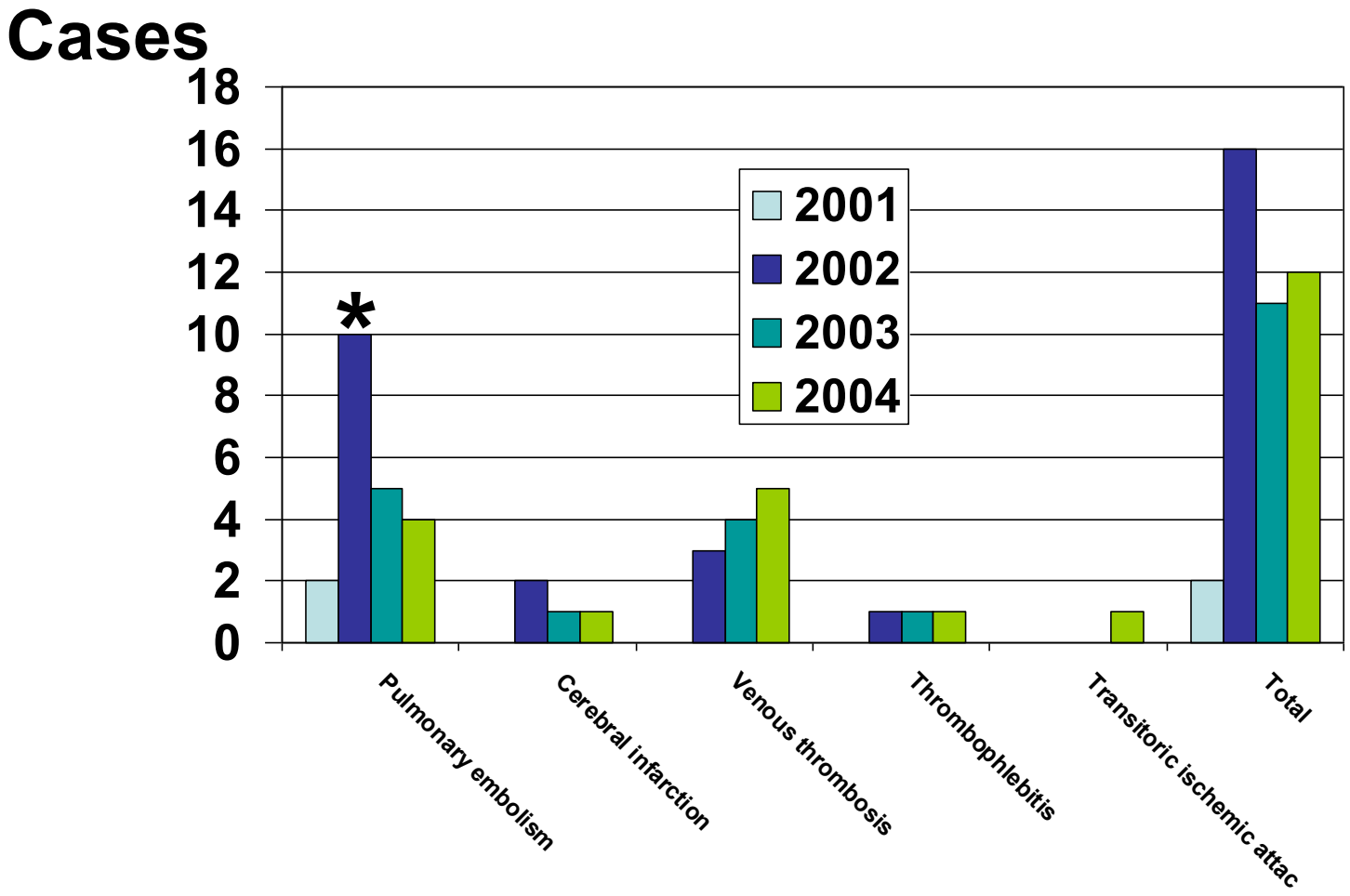
- **Agressive marketing**
  - **”The pill of wellbeeing”, weight loss, active against acne, ”uniqe properties”**
- **No focus on the uncertainties of a new COC**
- **An unexpected high number of reported adverse events (> 50% of all COC adverse reactions in Norway) from 2001-2004**
  - **Added to the national surveillance list in April 2002**

Adverse reactions - a signal?



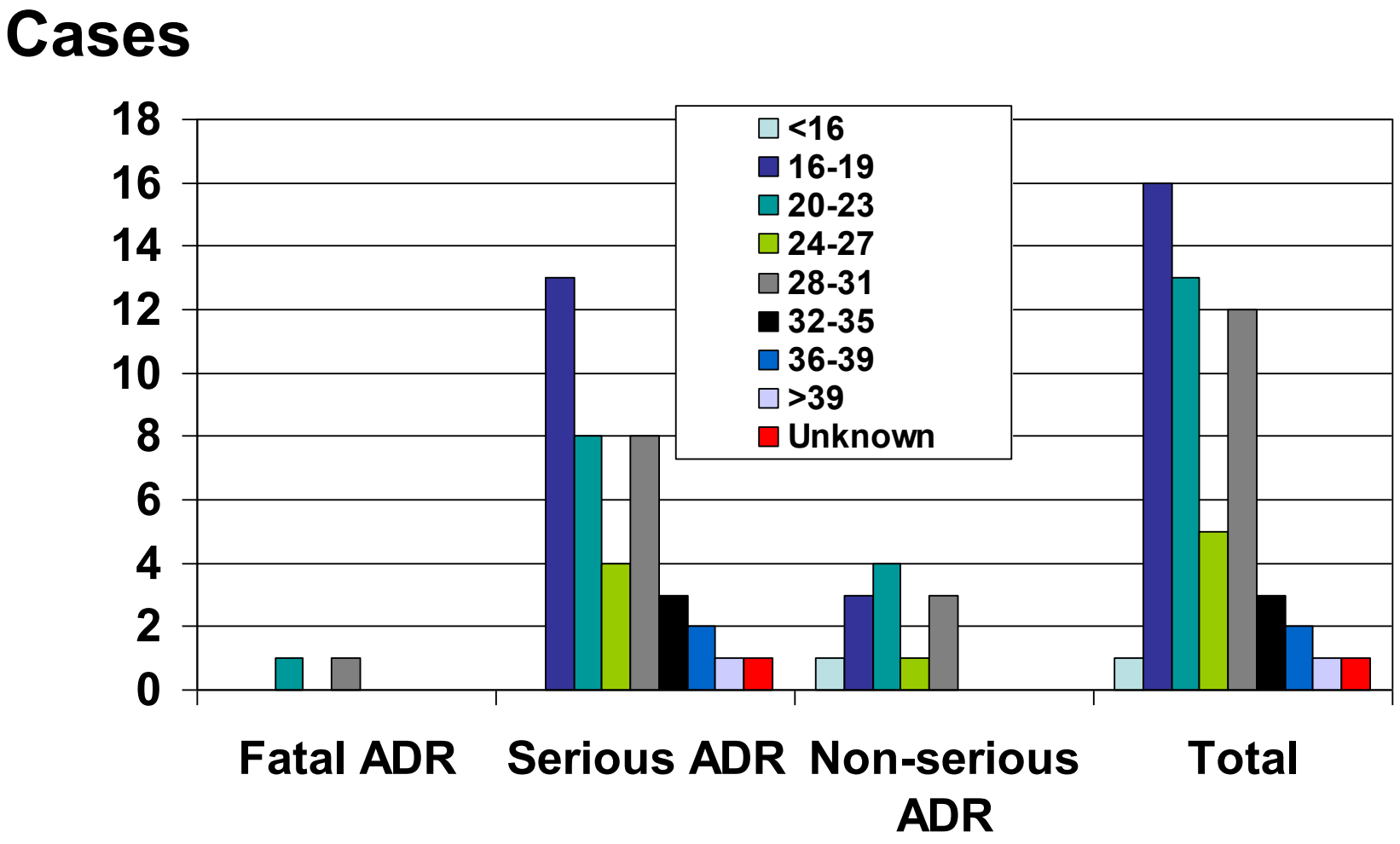
* Fatal case

Diagnoses



*Fatal case

Age



Adverse reactions 2001-2004

Epidemiology – ADR reports Norway

- **Reported serious adverse reactions**
  - **VTE events**
    - **August 2002:** **Approx. 4.6/10 000 woman-years**
    - **January 2005:** **Approx. 3.1/10 000 woman-years**
  - **Fatal events**
    - **August 2002:** **Approx. 3.5/1 000 000 woman-years**
    - **January 2005** **Approx. 2.9/1 000 000 woman-years**

Clinical trial 2007

- **The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation.**
  - **Dinger JC, Heinemann LA, Kühl-Habich D. Contraception. 2007; 75: 344-54. Epub 2007 Feb 23.**

- **CONCLUSIONS: Risks of adverse cardiovascular and other serious events in users of a DRSP-containing OC are similar to those associated with the use of other OCs.**

My biggest «mistake»

- **In 2007 I said publicly – after the publication of EURAS-study - that the risk for all COC were about similar and that there was no cause for concern**
- **Yasmin was removed from the surveillance list**

Cochrane 2014

- **Combined oral contraceptives: venous thrombosis.**
  - **Marcos de Bastos et al. Published Online: 3 March 2014**
- **The relative risk of venous thrombosis for combined oral contraceptives with 30-35 µg ethinylestradiol and gestodene, desogestrel, cyproterone acetate, or drospirenone were similar and about 50-80% higher than for combined oral contraceptives with levonorgestrel.**

Emerging evidence

- **Prescription of 3. generation COCs have decreased in France**
- **Cases of pulmonary embolism have probably decreased**

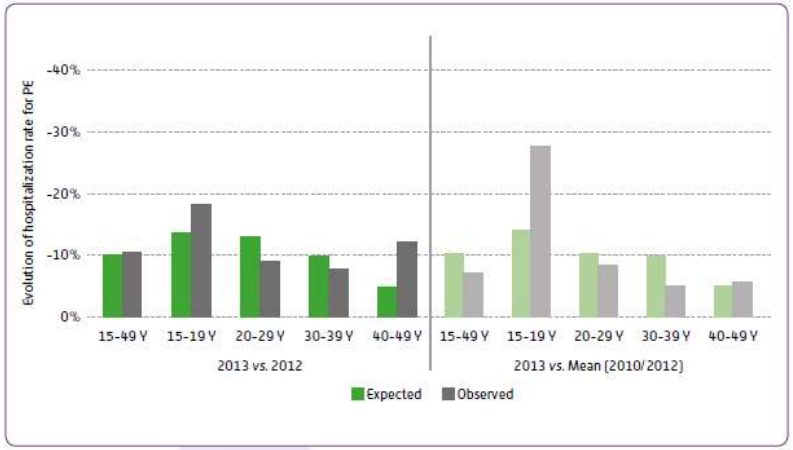
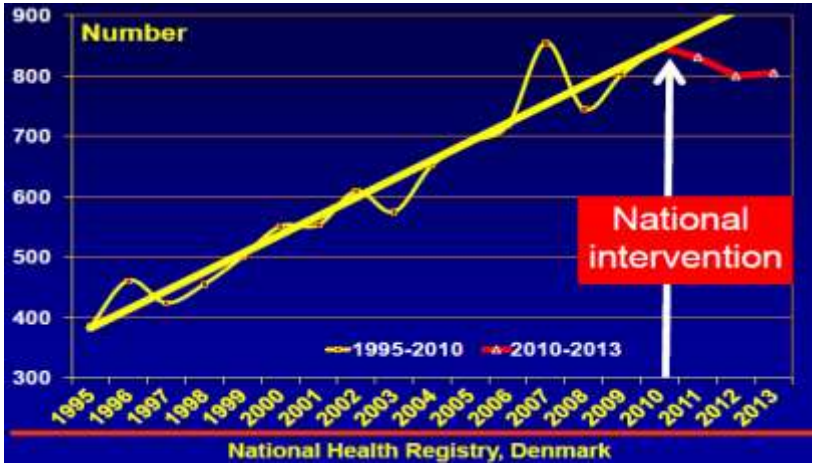


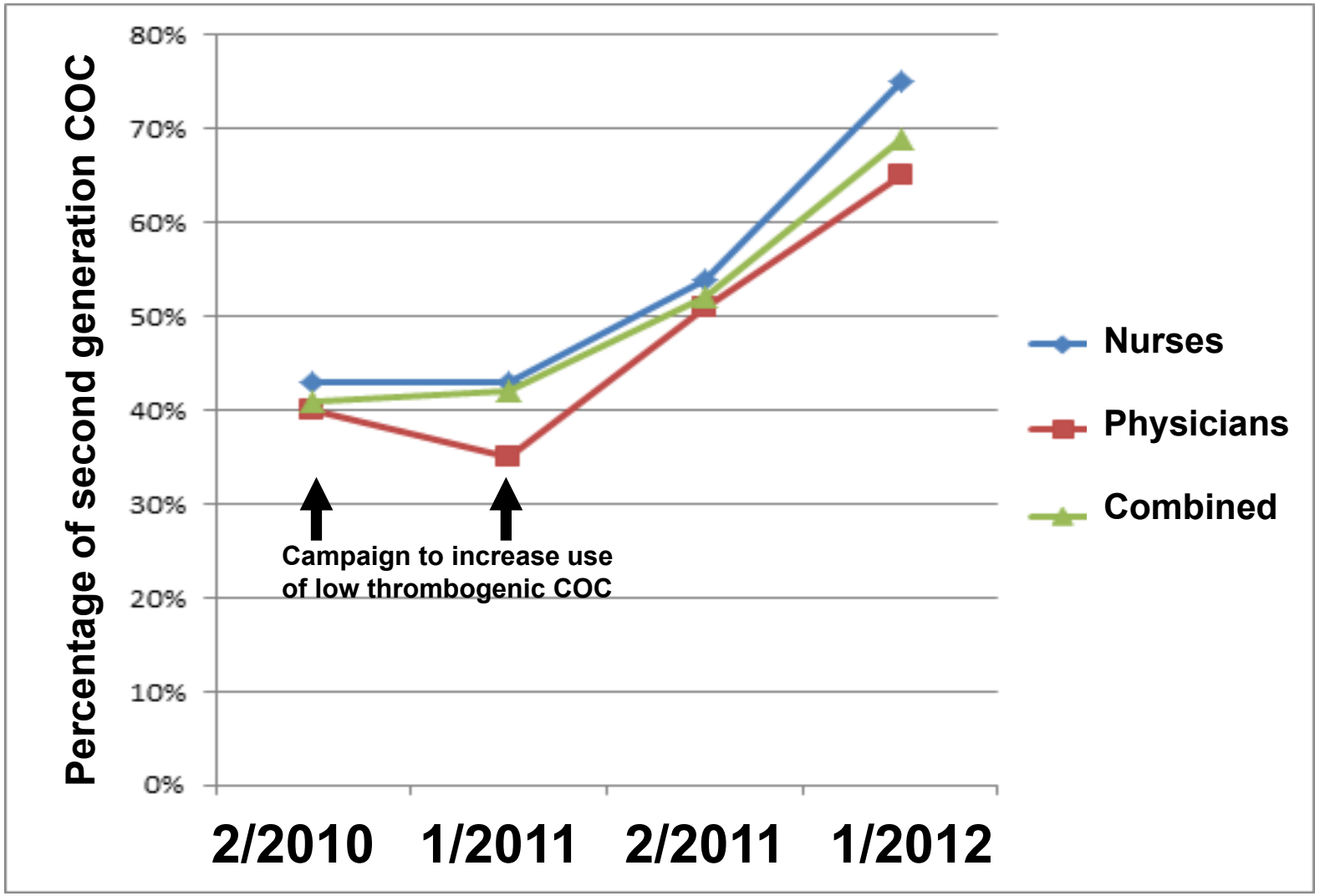
Figure 1. *Observed and expected evolution of hospitalization rates for PE in women aged 15-49 years in France in 2013 compared to 2012 and to 2010-2012* **Ticotin et al. 2016, ANSM**

- **Advice to switch treatment in Denmark**
- **A new trend for VTE?**

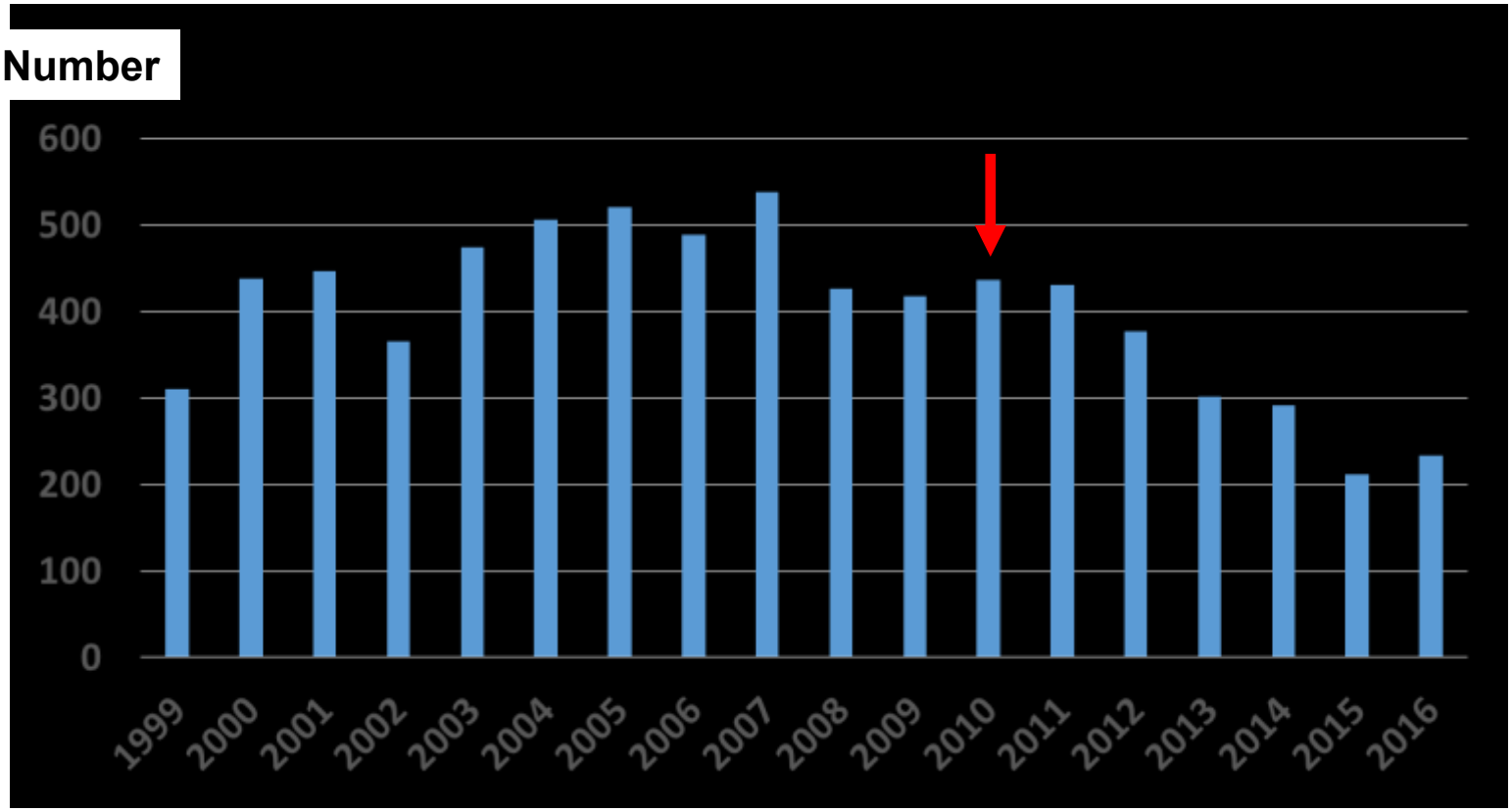


Personal communication, Ø. Lidegaard

New prescriptions in Norway

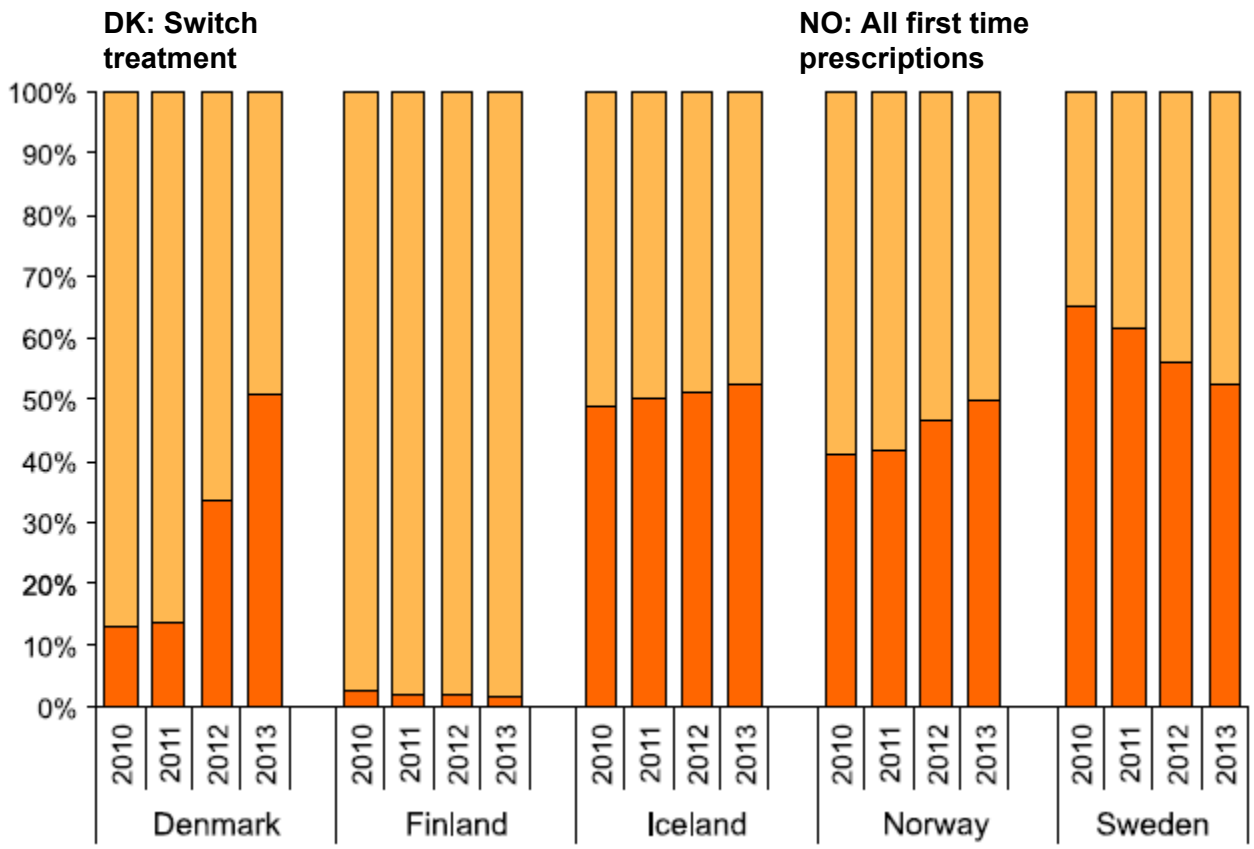


VTE in Norwegian women 1999-2016*



*Women 15-40 years, data from NPR

What to do?



High thrombogenic (EMA)

Low thrombogenic (EMA)

Acta Obstet Gynecol Scand 2017; 96:19–28.

Are postmarketing studies useful?

- Are post-mareting studies (including PASS, post authorisation safety study) designed to give correct and reliable answers?
  - Some studies are clearly not optimal
- Little is known, few published studies and reviews

WHAT IS ALREADY KNOWN ON THIS TOPIC

Systematic evaluations of post-marketing industry funded trials are sparse

The few studies available have criticised post-marketing studies for their low scientific value and lack of scientific integrity and for being seeding trials masking marketing interests of the sponsors as research

Current legislation relies on post-marketing studies for drug safety surveillance

WHAT THIS STUDY ADDS

Post-marketing studies are not serving as a key tool for drug safety surveillance, at least among those registered in Germany

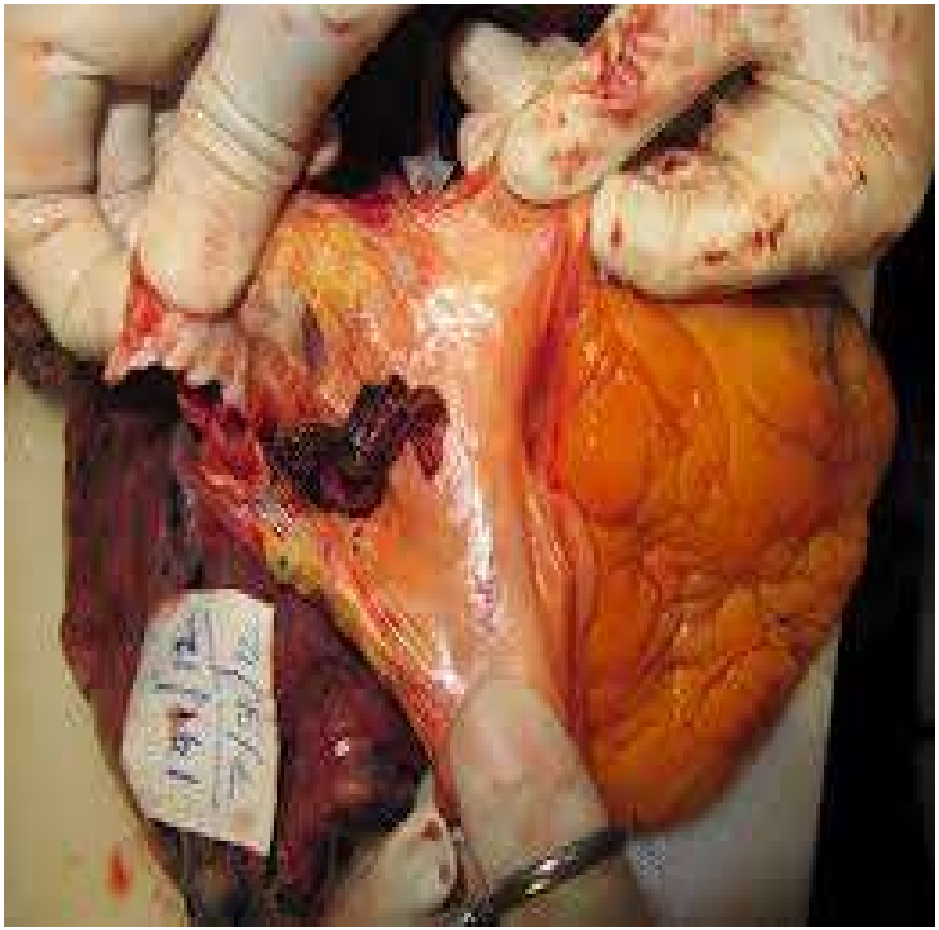
Sample sizes are generally too small to allow for the detection of rare adverse drug reactions, and many participating physicians are strictly obliged to maintain confidentiality towards the sponsor about all data, including adverse drug reactions

The post-marketing studies analysed are doing no measurable good to patients and could be taking resources away from more effective pharmacovigilance systems

the bmj | *BMJ* 2017;356:j337 | doi: 10.1136/bmj.j337

If we had persisted in our warnings……

- In Norway approx.
  - 2-4 less deaths
  - 100-200 less VTE cases



With a view to a pill!
Thank you!

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