The risk for venous thromboembolism (VTE) during the use of the modern low dose combined oral contraceptives

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Global Medical Affairs, Women's Healthcare

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Weighing the Risks & Benefits: Patient Safety First

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Understanding Risk: Cardiovascular Adverse Events

Most common major adverse events associated with COC use

Farley TMM, Collins J, Schlesselman JJ. *Contraception*. 1998.

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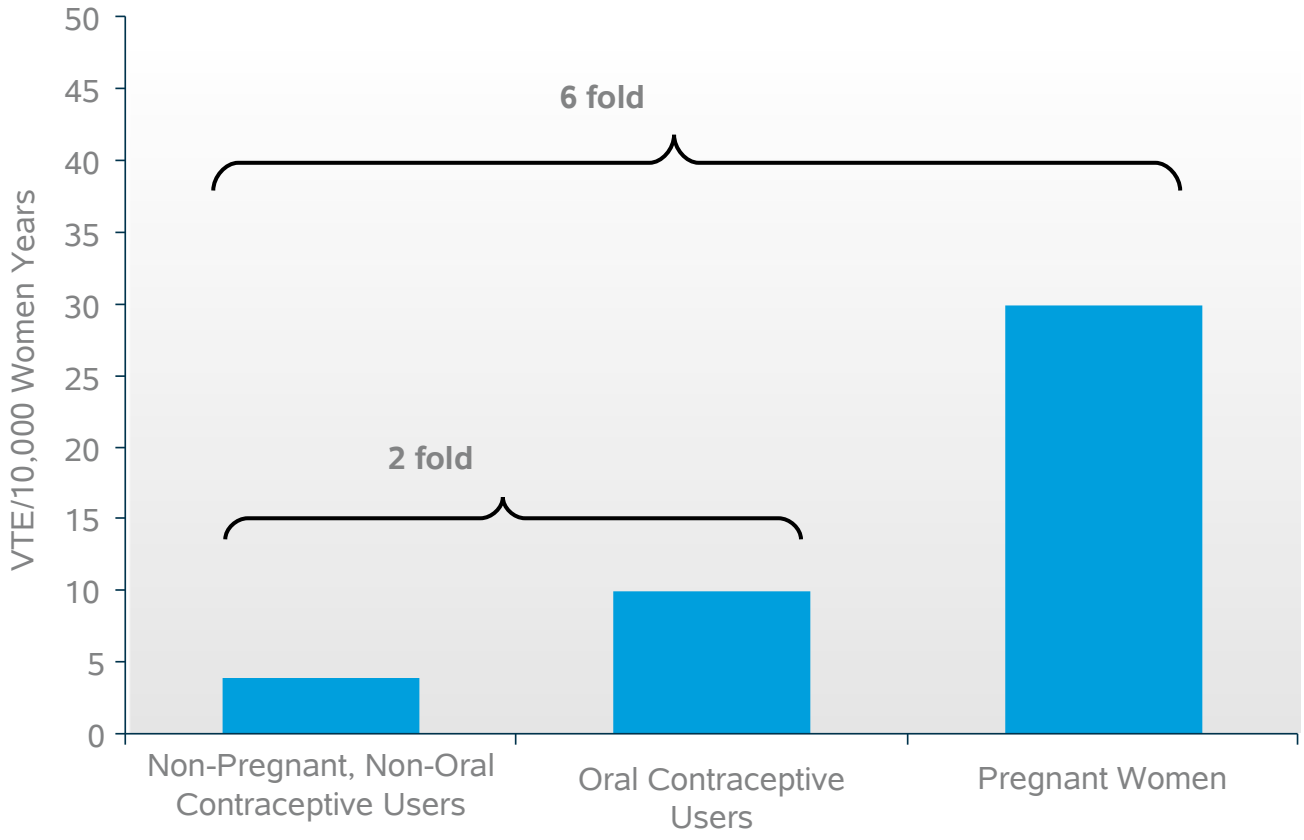
Risk of VTE in Non Users, OC Users & Pregnancy



Dinger Contraception 2007

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Background: The Risk of VTE during COC Use

- Use of COCs has been associated with an increased risk for VTE since 1960s
- The VTE risk has generally been associated with the level of the EE dose
- In the 1990s, a debate ensued that suggested that different progestins in COCs have different levels of VTE risk
- Most of the studies were hampered by methodological shortcomings such as failing to control for:
  - duration of COC use
  - difference in risk factors for VTE in users

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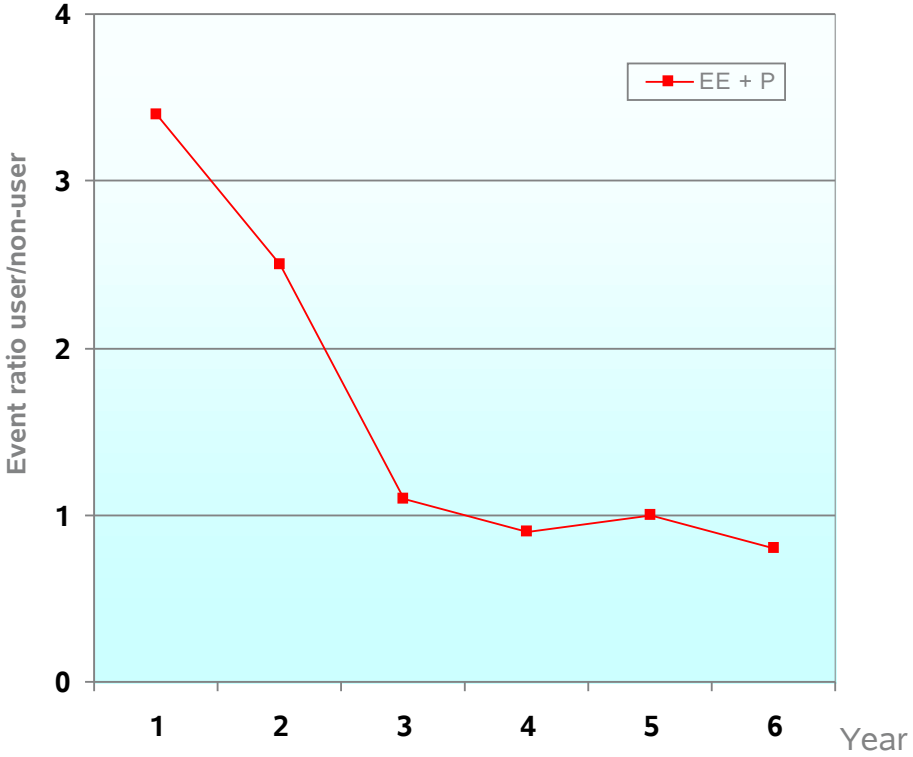
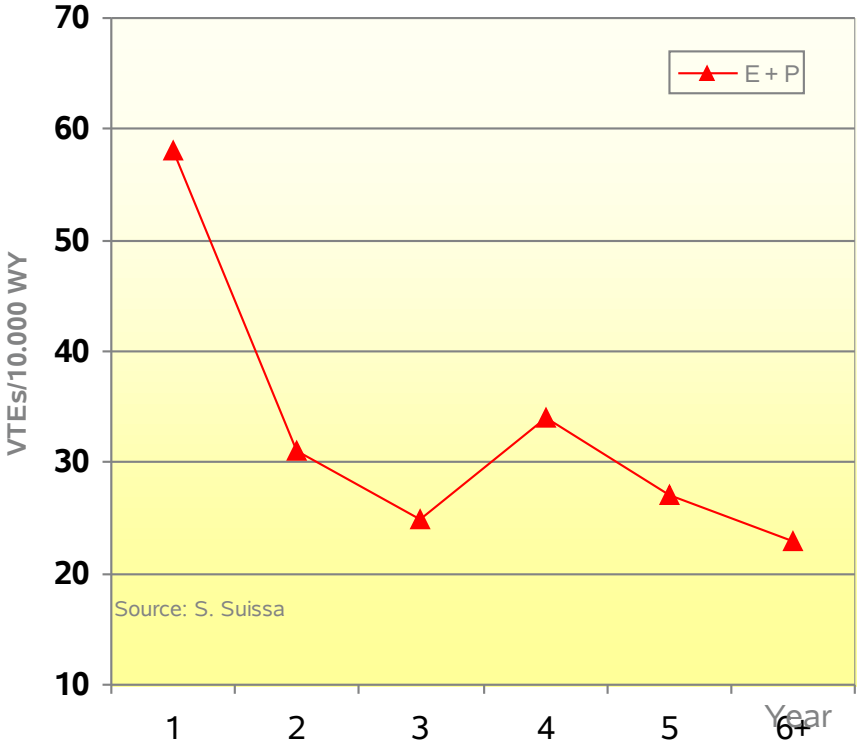
All estrogen/progestin combinations increase the risk of VTE in pre- and post-menopausal women: Impact of "Duration of Use“

OCs: Data from the Transnational Study



HRT: Data from the WHI Study



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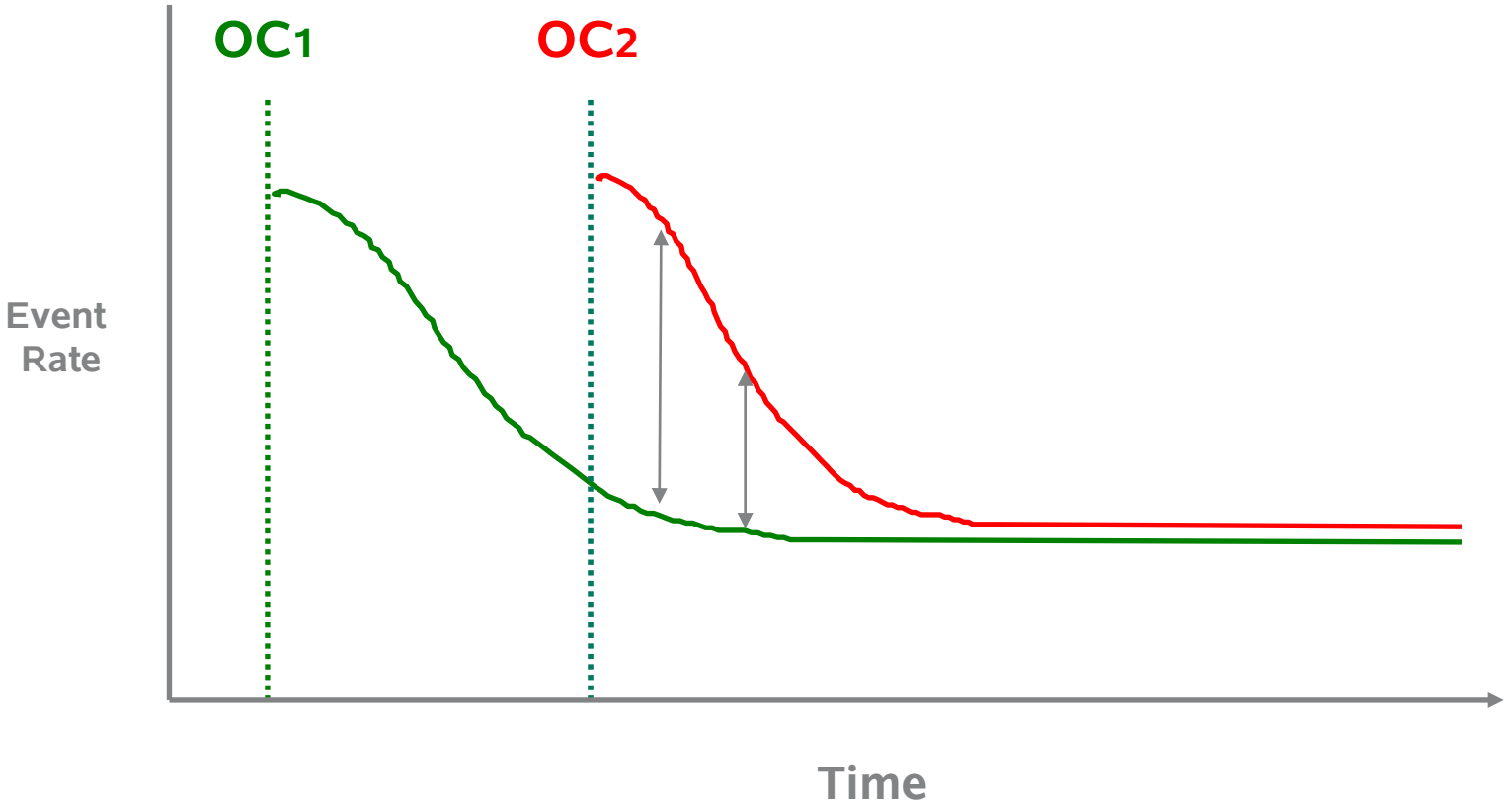
Failure to account for differences VTE prevalence in short term and long term users introduces bias



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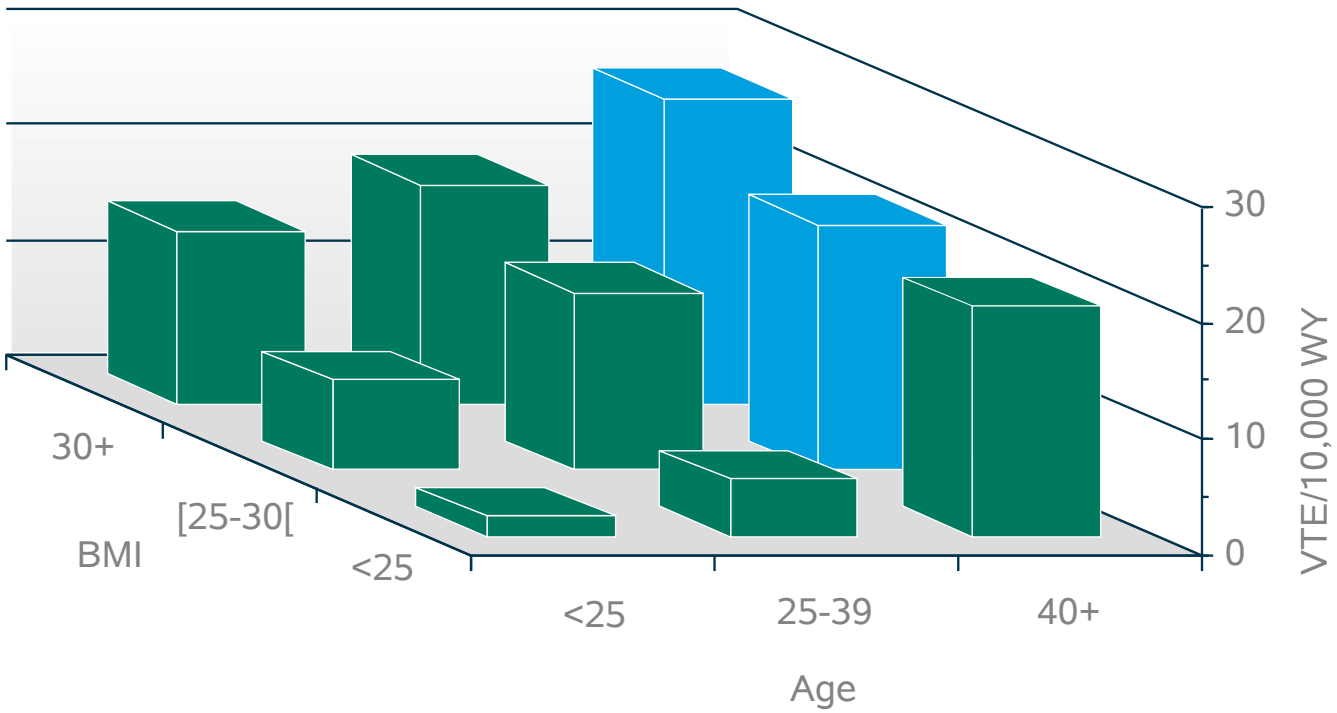
EURAS results: Impact of age and BMI on VTE incidence in OC users WITHOUT other known risk factors



Dinger, EURAS Study, Presentation EC Prague 2008

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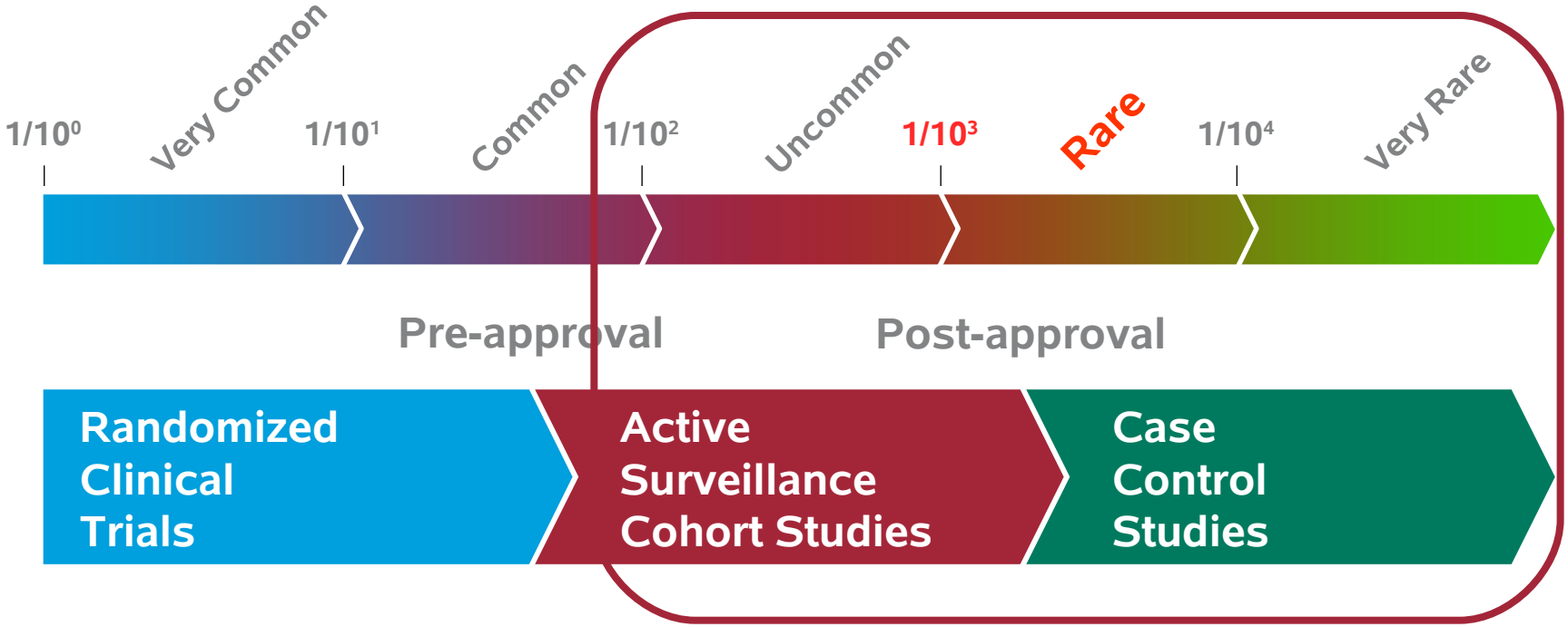
Rare events are typically studied in large post approval safety studies



CIOMS Classification: Frequency of Events

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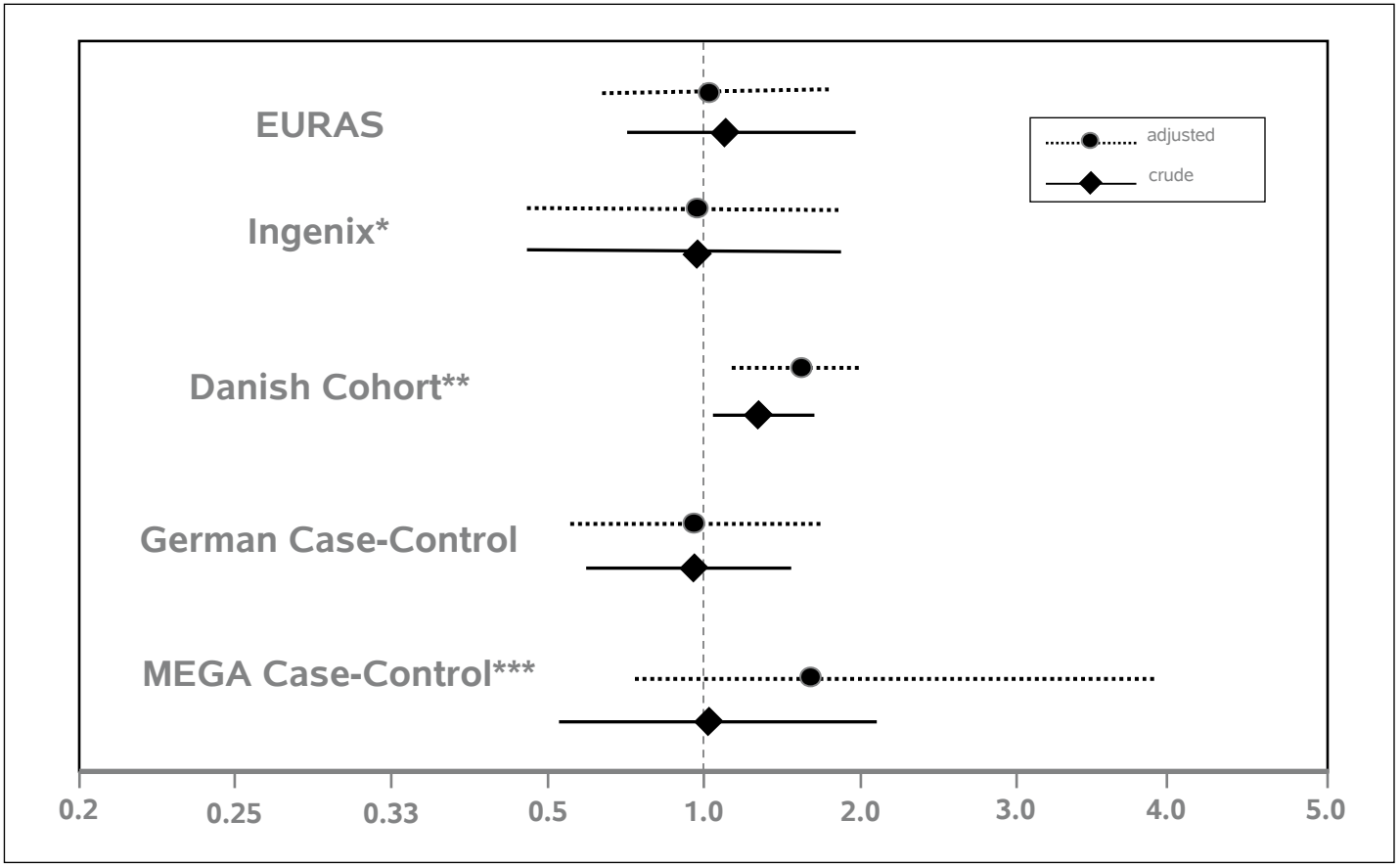
Crude and Adjusted Risk Estimates
► DRSP vs. LNG*



* no adjusted risk estimates calculated because of propensity score matching; comparison vs. other progestins incl. levonorgestrel
**crude risk estimate and 95% confidence intervals are based on our own calculations derived from table 2
***crude risk estimate and 95% confidence intervals are based on our own calculations derived from table 3

BSP Phase 4 Commitments: Two Large Cardiovascular Safety Studies for DRSP

EURAS Study

- Large, European Multinational (60,000 women; 140,000 WY)
- Prospective (2000 -2005)
- Non-interventional
- Active Surveillance
- Controlled Cohort Study

Dinger Contraception 2007

INGENIX Study

- Large, US (67,000 women; 42,000 WY)
- Prospective (2001 -2004)
- Controlled cohort database study
- Propensity score matching

Seeger Ob/Gyn 2007

Compare Yasmin's cardiovascular safety to other OCs

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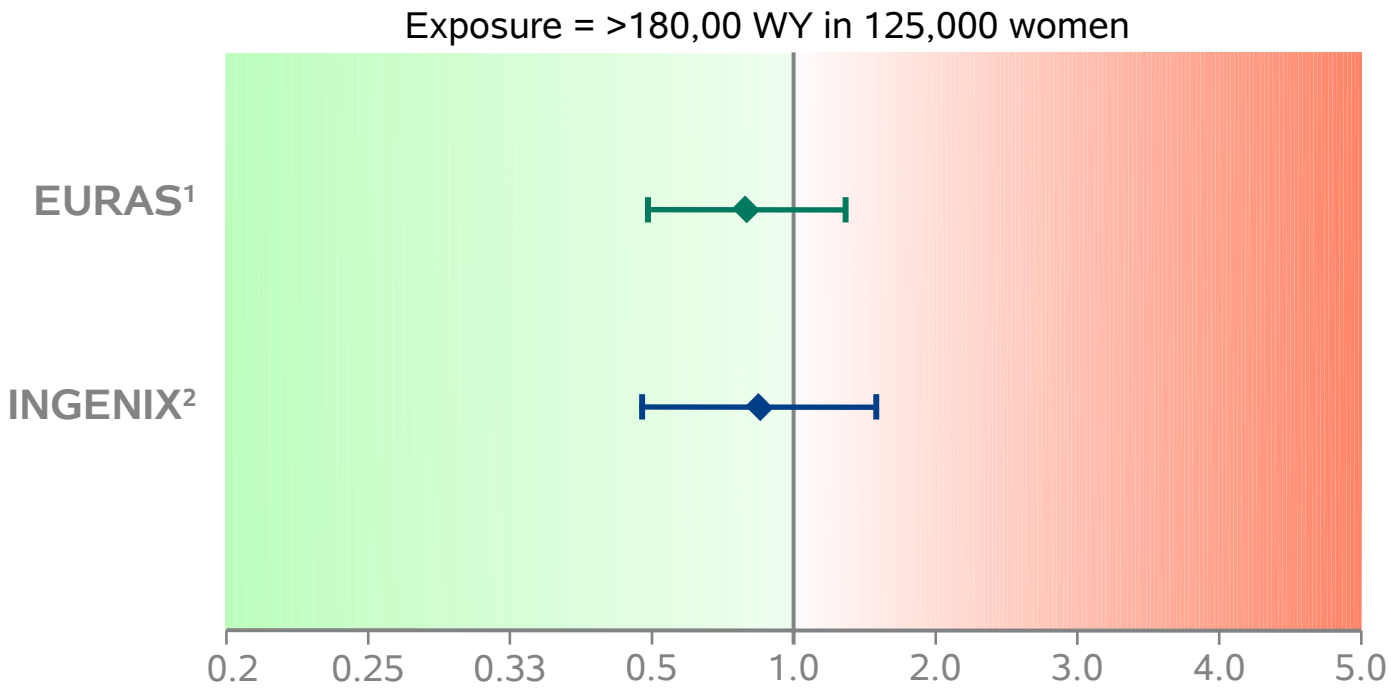
VTE Risk for Yasmin : EURAS & Ingenix Studies

Yasmin vs Other OCs



VTE Rate Ratios ITT Analysis (95% CI)

[1]Dinger Contraception 2007 and [2]Seeger Obst & Gyn 2007

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Van Hylckama Vlieg A et al *

- **Design**: Large, population-based, case-control study of VTE cases in NL
- **Objective**: To investigate risk factors for VTE and to assess the risk of thrombosis associated with the combination of risk factors.
- **This analysis**: post hoc sub analysis of women aged 18 -50
- **Results:**
  - COCs increased the risk of VTE 5-fold compared with non-use
  - The risk clearly differed by type of progestin and dose of estrogen
  - Confirmed highest risk of VTE during the first months of COC use irrespective of the type of COC used

*Van Hylckama Vlieg A et al. BMJ 2009:339:b2921.

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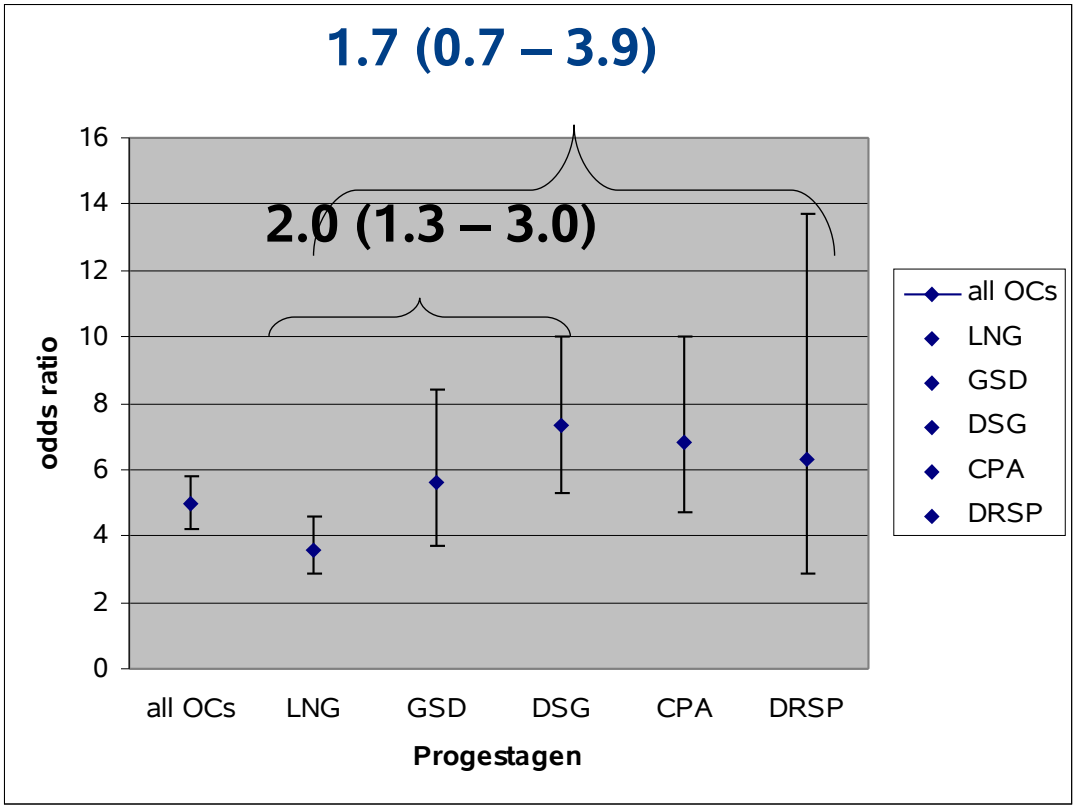
Van Vlieg A et al: Risk for VTE vs No Use (OR with 95%CIs) for the various progestins

Dutch MEGA case-control study



Adjusted for age and period of inclusion

Lidegaard Ø et al *

- All fertile Danish women were followed from 1995 to 2005 in a retrospective national database cohort study
- National exposure and event datasets were linked
  - Exposure Data: Redeemed prescription data for COCs
  - Event Data: All first ever use events of VTE (hospital discharge diagnoses)
- Results:
  - Risk of VTE in all COC users decreases with duration of use and by decreasing estrogen dose
  - For the same dose of estrogen and the same duration of use, so-called 3rd generation COCs and drospirenone were associated with a significantly higher risk of VTE than so-called 2nd generation COCs

*Lidegaard Ø et al. BMJ 2009;339:b2890.

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Lidegaard et al: BSP Assessment

Major questions about the cohort comparisons for VTE risk because:

1. Missing risk factor information: BMI & family history.
1. Misclassification of duration of use: systematically overestimated short term use for LNG but not for DRSP
2. Both created a significant bias in favor of LNG

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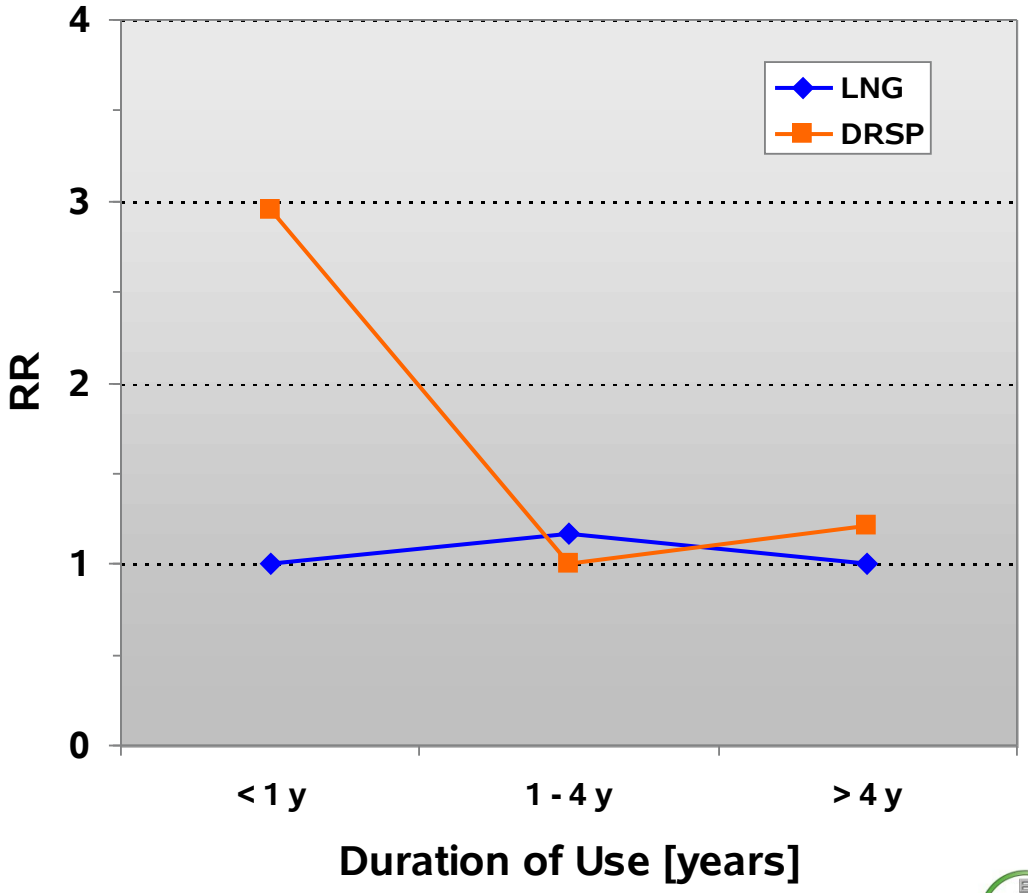
No first year effect for LNG but for DRSP: Impact of “censored duration of use“ data?



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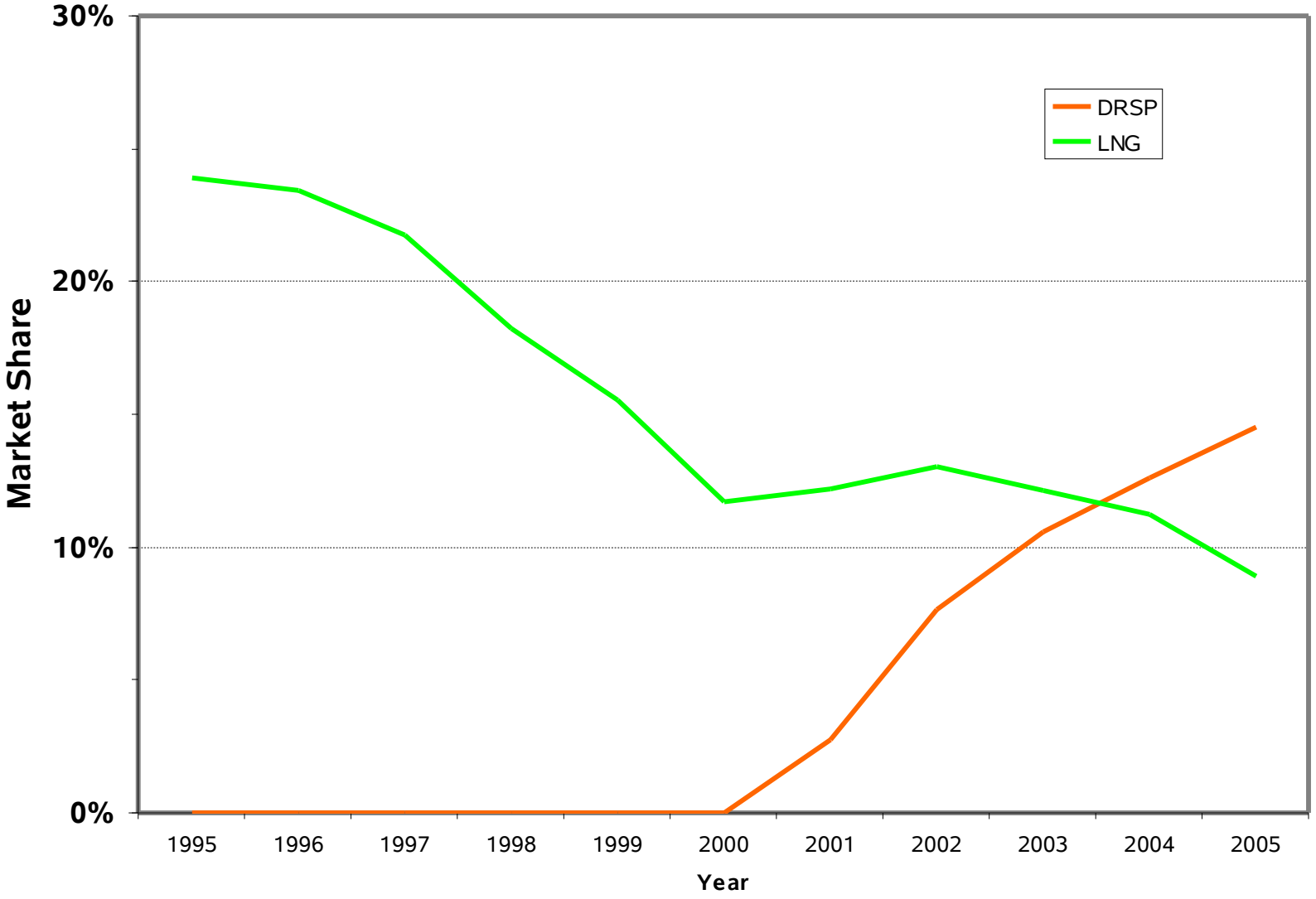
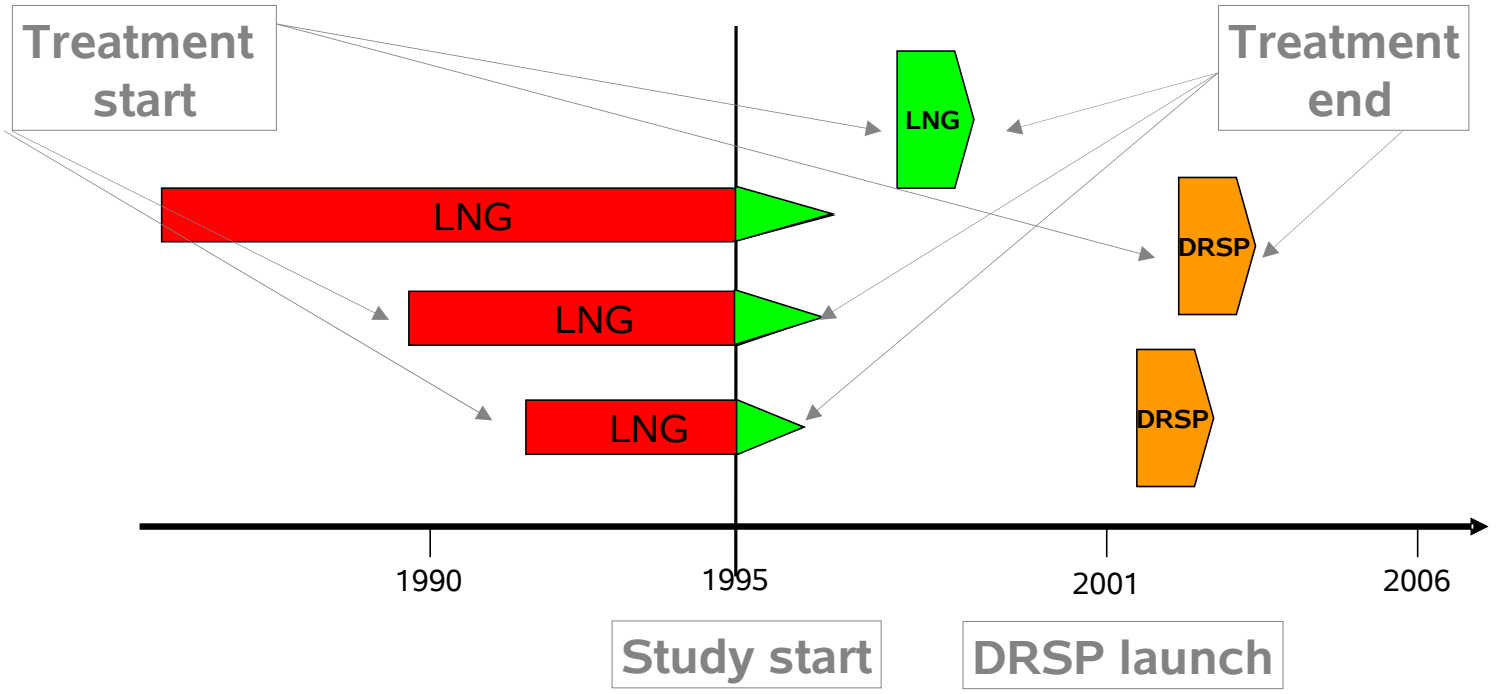
Secular Changes in OC Prescriptions in Danish OC Users during Study



Potential Misclassification of Duration of Use in LNG Users in the Danish Cohort Study

Incorrectly classified as short term users

Correctly classified as short term users



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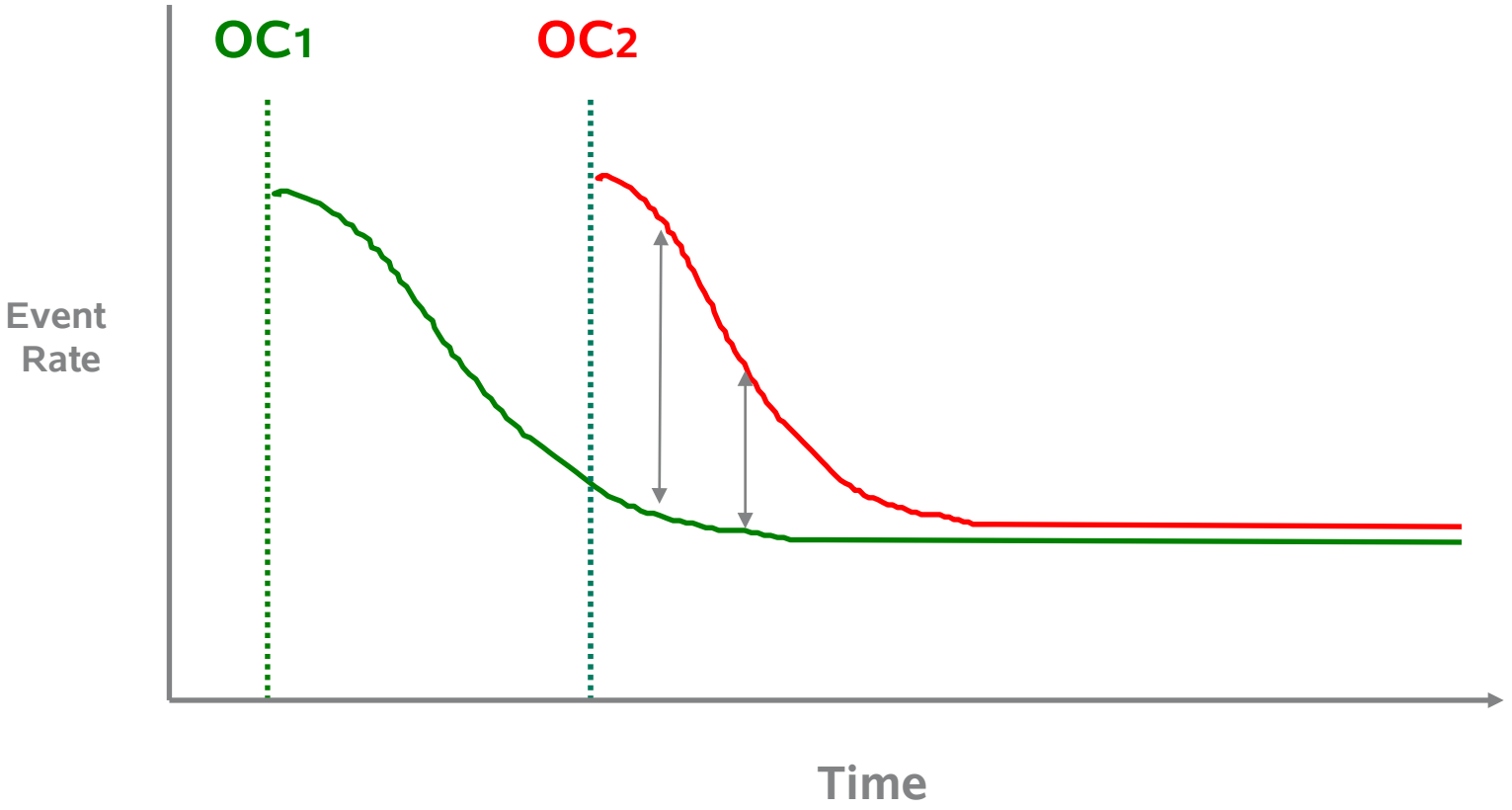
Failure to account for differences VTE prevalence in short term and long term users introduces bias



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BSP Assessment of Recent BMJ Studies

- Neither study adequately accounted for major confounding factors (e.g., body weight and family history of VTE).
- The progestin comparison results in Van Vlieg A et al were not statistically significant.
- Lidegaard Ø et al did not adjust appropriately for duration of treatment: methodology creates a significant bias in favor of LNG.
- These studies are not consistent with the large amount of data generated in post-marketing trials.

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EURAS OC and Ingenix Yasmin studies

Both studies were:

- sponsored by BSP but specifically designed after extensive discussion with European and US Health Regulators
- study concept, conduct, analysis and reporting were performed by two different independent investigator groups, using two different methodologies and in two geographically different populations.

Design:

- sufficiently powered
- compared short term use with short term use
- EURAS by adequately control for confounding factors
- INGENIX by using prospensity score matching.

- Dinger et al. Contraception, 75, 2007, 344– 354.
- Seeger et al. Obstetrics & Gynecology, Vol. 110, No. 3,September 2007, 587 – 593.

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EURAS OC and Ingenix Yasmin studies

The results of both studies were:

- assessed with a blinded medical adjudication process.
- overseen by independent Data Safety Monitoring Boards
- all case reports were submitted to Health Authorities for review.

This is why in our view, the results of these studies are less vulnerable to bias and confounding compared to the studies published in the BMJ in August 2009.

- Dinger et al. Contraception, 75, 2007, 344– 354.
- Seeger et al. Obstetrics & Gynecology, Vol. 110, No. 3,September 2007, 587 – 593.

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EURAS and Ingenix Yasmin Studies: Robust data on the cardiovascular safety of OCs

Both studies confirm:

- Yasmin's cardiovascular profile is well established
- The risk for VTE is the same for all modern lose-dose OCs, including DRSP and LNG

The EURAS study also confirms:

- VTE is a rare event among women using OCs, and the risk for VTE is lower than during pregnancy/delivery
- Risk factor information is important in deciding whether an OC is suitable contraceptive choice for an individual woman

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