Early Use Effects
on the Risk of Venous Thromboembolism
After the Initiation of Oral Contraceptive Use

Jürgen Dinger, Sabine Möhner & Thai Do Minh
Disclosure

► The presented analysis is based on data from the EURAS and LASS studies.

► The EURAS study was a Post-Authorization Safety Study (PASS) that was requested by the EMA to investigate the safety of DRSP/EE.

► The LASS study is an extension of the EURAS study

► The studies were supported by Bayer Schering Pharma AG with an unrestricted grant.

► The studies were supervised by an independent Safety Monitoring and Advisory Council.

► No product specific data will be presented.
### EURAS Study Outline

**Design:** Controlled, prospective, non-interventional, cohort study with active surveillance in 7 European countries  
- participants recruited via gynecologists/PCPs  
- follow-up via direct contacts with study participants

**Exposure:** New use of oral contraceptives – first ever or recurrent use

**Study Period:** 2000 to 2006

**Primary Objective:** To investigate the short and long-term safety of DRSP/EE - in particular the risk of VTE
## Study Population

<table>
<thead>
<tr>
<th>Women</th>
<th>Nos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>enrolled by study centers</td>
<td>59,510</td>
</tr>
<tr>
<td>excluded because of protocol violations</td>
<td>836</td>
</tr>
<tr>
<td>analyzed</td>
<td>58,674</td>
</tr>
</tbody>
</table>

- Refused to sign informed consent
- Enrolled two or more times
- Continued their old OC
- Did not use any OC

**OC exposure:** 112,659 WY  
**Past use:** 25,767 WY  
**Total:** 142,475 WY
LASS

- LASS is an extension of the EURAS study
- The EURAS study had followed OC users for up to 5 years.
- A total of 47,799 out of 58,674 EURAS participants were still in follow-up at the end of the EURAS study.
- LASS is succeeding EURAS and will prolong the follow-up period for another 5 years.
- Primary objective is to investigate the long-term safety of DRSP/EE
- The presented analysis is based on 260,000 WY of observation, 185,000 WY of exposure and 220 confirmed VTE
Objective of the presented analysis

To assess time pattern of the incidence of VTE after initiation of COC use (duration of current use)

- first ever use (starter)
- recurrent use (re-starting and switching with an intake break)
- switching without an intake break
**Outcome Validation**

- All reported VTE were validated via the physician(s) who diagnosed and/or treated the reported condition.

- All reported VTE – confirmed and unconfirmed – were subjected to blinded adjudication by 3 independent experts (1 cardiologist, 1 radiologist, 1 phlebologist).

- All reported VTE – confirmed and unconfirmed – were submitted to FDA and EMA for review.
Why is Duration of Current Use important?

- Progestin/estrogen combinations increase Venous Thromboembolism maximally during the first year of use, after which the risk declines - starter effect/early use effect

- This effect repeats itself at after a period of discontinuation - re-starter effect

- Women at high risk tend selectively to switch to the most recently marketed product - switcher effect

- Relative risk for venous thromboembolism: starters > re-starters/switchers > long-term users
Progestin/Estrogen Combinations: Early Use Effect

HRT: Data from the WHI Study

RR = 3.6

OCS: Data from the Transnational Study

RR ~ 1

Source: S. Suissa
Progestin/Estrogen Combinations: Early Use Effect

MEGA Case-Control Study*

Danish Case Control Study, Lidegaard 2002
EURAS Time to Event Analysis: ‘Early use effect’

VTE Incidence vs. Duration of Use

Exposure (months)

VTE/10,000 WY
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- Relative risk for venous thromboembolism: starters > re-starters/switchers > long-term users
EURAS Study: VTE Incidence by Starter-Switcher* Status

* as defined by the Principal Investigator (L. Heinemann) at the start of the EURAS study; includes re-starters
LASS: Time to Event Analysis for VTE

Definitions*

Starter  Woman who used an OC for the first time in her life

Re-starter  Woman who used the same OC after a pill break of at least 4 weeks

Switcher  Woman who switched from one OC preparation to another OC preparation. Use of the latter preparation may start after a pill intake break or immediately after stop of the first preparation

Recurrent User  Woman who is a re-starter or switcher

LASS: Time to Event Analysis for VTE

Restarters

![Graph showing VTE/10,000 WY vs. Duration of Current Use [months]. The graph indicates a decreasing trend in VTE rate with increased duration of use.]
LASS: Time to Event Analysis for VTE

Switchers without Pill Intake Break Before Switch
LASS: Time to Event Analysis for VTE

Recurrent Use after stopping use for at least 4 weeks

Duration of Current Use [months]

VTE/10,000 WY
### LASS: Time to Event Analysis for VTE

<table>
<thead>
<tr>
<th>User Status</th>
<th>Incidence Rate Ratio: Use ≤ 3 month compared to &gt; 3 month</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starters</strong></td>
<td></td>
</tr>
<tr>
<td>(17,798 WY)</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>Switchers without intake break</strong></td>
<td></td>
</tr>
<tr>
<td>(65,983 WY)</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Recurrent users with intake break ≥4 wks</strong></td>
<td></td>
</tr>
<tr>
<td>(89,729 WY)</td>
<td>1.9</td>
</tr>
<tr>
<td><em>of which</em></td>
<td></td>
</tr>
<tr>
<td><strong>Restarters</strong></td>
<td></td>
</tr>
<tr>
<td>(33,952 WY)</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Switchers with intake break ≥4 wks</strong></td>
<td></td>
</tr>
<tr>
<td>(55,777 WY)</td>
<td>1.7</td>
</tr>
</tbody>
</table>

- [ ] Statistically significant time trend
- [ ] Statistically not significant time trend
VTE Incidence Rate vs. Duration of Current Use

Example:

1995

- No OC
- OC A, 3M
- No OC, 5M
- OC A, 5M
- No OC

Actual Incidence

Danish Cohort Study

Incidence vs. Time
VTE Incidence Rate vs. Duration of Current Use

Example:

2010

No OC

OC A, 3M

OC A, 5M

Incidence vs. time

Incidence

Time
Conclusions

1) Study Methodology: Information on
- duration of current use
- exact start & stop dates
- discontinuation periods
is needed for the evaluation of the VTE risk associated with COC use

2) Counseling of Patients:
- First time OC use & recurrent COC use after an intake break of at least one cycle increases the VTE risk during the first 3 - 6 months of use after which the risk remains fairly stable
- Switching OC preparations without an intake break is not associated with a (substantial) initial excess risk compared to long-term use