Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year

Venous thromboembolism (VTE) after continuous or extended cycle oral contraceptive use

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Disclosures

• No relationships to disclose

• The views expressed in this presentation are those of the presenter and do not necessarily reflect those of the FDA
Combined Oral Contraceptives

• Combined oral contraceptives (COCs) contain
  – Estrogen-typically ethinyl estradiol (EE)
  – Progestin-levonorgestrel (LNG), others

• FDA approved for contraception
  – Product selection based on
    • Patient preference, physician assessment
    • Secondary indications: acne, premenstrual dysphoric disorder (PMDD)

• Professional guidelines recommend COC use for non-contraceptive uses
COC therapy has evolved

1960s
- COC introduced
- >50mcg EE
- 28 day cycle
- 21 active tabs
- 7 days inert

1970s
- 2nd Generation COC
- < 50mcg EE
- 21-24 active tabs
- 4-7 days inert

2003
- Extended cycle COC
- 20, 30mcg EE
- 84 active tabs
- 7 inert tablets

2007
- Lybrel
- Continuous COC
- Daily dosing
- 20mcg EE
COC and Venous Thromboembolism (VTE)

• Estrogen in COC shown to increase risk of VTE
• Risk may differ by progestin type
• VTE information given in class wide labeling
  – Rate in COC users 3-9 / 10,000 woman-years (WY)
  – Risk increased in women with conditions predisposing for VTE
• VTE risk increase: surgery, trauma, obesity, history of VTE, obesity, polycystic ovary syndrome (PCOS)²,³

Source: FDA class labeling for oral contraceptives, unless otherwise noted
Continuous COC approval

• Lybrel was first continuous COC approved in US
• Concern whether risk profile was different
  – Continuous dosing of EE
• Post-Marketing Requirement (PMR)
  – Claims database safety study to evaluate risk of venous thromboembolism (VTE)
  – Lybrel vs cyclic COC containing 20mcg EE
Market changes and PMR Impact

• Lybrel approved in 2007
• Generics of continuous COCs arrived on the market in 2011
• Lybrel ceased marketing in 2012 due to declining market share
• PMR terminated early, results added to labeling
# Labeling of Lybrel PMR Results

<table>
<thead>
<tr>
<th>Cohort</th>
<th>(representative product approval date)</th>
<th>Idiopathic VTE Crude Incidence / 10,000 woman years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous EE 20mcg + LNG (2007) n=12,281</td>
<td></td>
<td>17.6</td>
</tr>
<tr>
<td>Cyclic EE 20mcg + progestin (1970 +)</td>
<td></td>
<td>8.8</td>
</tr>
<tr>
<td>Cyclic EE 20mcg + LNG (1970 +)</td>
<td></td>
<td>5.1</td>
</tr>
</tbody>
</table>

Source: Lybrel package insert
Generics remain on the market- Is there a public health concern?

• FDA unable to impose a safety study on generic manufacturers

• Sentinel analysis initiated in October 2016
Design Overview

Design
- Retrospective new user cohort
  5 in continuous (Lybrel-only) analysis

Exposure
- New use COC 20/30 mcg EE + LNG only
- Continuous and extended vs Cyclic

Outcome
- Hospitalized VTE (all but one analysis)
- Outpatient (VTE Dx + anticoagulation treatment) or Hospitalized VTE

Inclusion
- Women aged 18-50 years
- 6 months prior continuous insurance eligibility

Exclusion
- VTE, HIV/AIDS, anticoagulant use, cancer, pregnancy, organ failure / transplantation
Follow-up

- COC Rx linked into episodes with 30 day gap allowed
- 30 day at risk period after therapy
- Follow-up begins on first dispensing of COC

Censoring

- First Occurrence of: VTE diagnosis, dispensing of a comparator drug or other hormonal contraceptive, pregnancy start date (derived from livebirth delivery date), disenrollment, evidence of death, end of exposure episode, or end of query period (9/30/2015).
## Analysis

### Analysis
- Cox proportional hazards
- 1:1 propensity score matched on demographics, comorbidities, healthcare utilization, use of other hormonal contraceptives

### Secondary Analysis
- Continuous vs. Cyclic
- No prior hormonal contraceptive use in baseline

### Subgroup Analyses
- EE 20 mcg / 30 mcg
- By age (18-24, 25-34, 35-50 years)
- Follow-up period, 90 and 183 days
### Baseline Characteristics

#### Unmatched Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Extended / Continuous COC (Yr, %)</th>
<th>Cyclic COC (Yr, %)</th>
<th>Covariate Balance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients (N)</strong></td>
<td>210,691</td>
<td>522,316</td>
<td></td>
</tr>
<tr>
<td><strong>Mean age (years)</strong></td>
<td>30.4</td>
<td>28.8</td>
<td>1.69</td>
</tr>
<tr>
<td><strong>Other Study COC</strong></td>
<td>3.0%</td>
<td>0.9%</td>
<td>2.07%</td>
</tr>
<tr>
<td><strong>Use of oral non-LNG COC or non-oral hormonal contraceptive in baseline</strong></td>
<td>35.0%</td>
<td>26.9%</td>
<td>8.03%</td>
</tr>
</tbody>
</table>

*After matching, the cohorts were highly comparable*
## Baseline Characteristics
### Unmatched Cohorts

<table>
<thead>
<tr>
<th>Condition</th>
<th>Extended / Continuous COC (%)</th>
<th>Cyclic COC (%)</th>
<th>Covariate Balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular and Metabolic Conditions</td>
<td>7.2%</td>
<td>4.7%</td>
<td>2.50</td>
</tr>
<tr>
<td>Gynecological conditions</td>
<td>39.7%</td>
<td>32.3%</td>
<td>7.35</td>
</tr>
<tr>
<td>Mean # ambulatory encounters</td>
<td>4.8</td>
<td>3.6</td>
<td>1.16</td>
</tr>
<tr>
<td>Mean # of filled RX</td>
<td>7.0</td>
<td>4.5</td>
<td>2.52</td>
</tr>
<tr>
<td>Mean # of generics</td>
<td>3.3</td>
<td>2.4</td>
<td>0.93</td>
</tr>
<tr>
<td>Mean # of unique drug classes</td>
<td>3.1</td>
<td>2.3</td>
<td>0.87</td>
</tr>
</tbody>
</table>

*After matching, the cohorts were highly comparable*
Risk VTE Continuous/Extended vs. Cyclic COC

Hazard Ratios and 95% Confidence Intervals for Comparison 1: Continuous or Extended vs. Cyclic Combined Oral Contraceptives and VTE (Matched Analysis)

Data Partner ID:
- Overall
- DP01
- DP03
- DP04
- DP05
- DP06
- DP09
- DP15
- DP16

Log (Hazard Ratio)

*HRs were not calculated for DP02, DP07, DP08, or DP13 due to no events in one or both treatment groups. Results for DP10, DP11, DP12, and DP14 were excluded due to PS model convergence issues.
# Results - Primary analysis

## Risk of VTE

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Unmatched Hazard Ratio (95% CI) N=210,691/ 522,316</th>
<th>Matched Hazard Ratio (95% CI) N=203,402/203,402</th>
<th>Incidence Rate Difference per 10,000 WY, Matched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous &amp; extended vs cyclic</td>
<td>1.84 (1.53, 2.21)</td>
<td>1.32 (1.07, 1.64)</td>
<td>3.5</td>
</tr>
<tr>
<td>20 vs 20 mcg EE</td>
<td>2.19 (1.53, 3.14)</td>
<td>1.60 (0.94, 2.71)</td>
<td>5.8</td>
</tr>
<tr>
<td>30 vs 30 mcg EE</td>
<td>1.55 (1.20, 1.99)</td>
<td>1.23 (0.88, 1.73)</td>
<td>2.8</td>
</tr>
<tr>
<td>18-24 years</td>
<td>2.40 (1.54, 3.75)</td>
<td>1.66 (0.95, 2.90)</td>
<td>2.7</td>
</tr>
<tr>
<td>25-34 years</td>
<td>1.57 (1.12, 2.20)</td>
<td>1.19 (0.81, 1.74)</td>
<td>1.6</td>
</tr>
<tr>
<td>35-50 years</td>
<td>1.47 (1.14, 1.90)</td>
<td>1.38 (1.03, 1.85)</td>
<td>7.1</td>
</tr>
</tbody>
</table>
## Results - Secondary Analyses

### Risk of VTE

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Hazard Ratio (95% CI), Unmatched</th>
<th>Hazard Ratio (95% CI), Matched</th>
<th>Incidence Rate Difference per 10,000 WY, Matched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous (Lybrel) regimen vs. Cyclic (5 data partners)</td>
<td>2.92 (1.80, 4.74)</td>
<td>1.45 (0.70, 2.99)</td>
<td>8.2</td>
</tr>
<tr>
<td>Follow-up Period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-90 days</td>
<td>1.92 (1.43, 2.58)</td>
<td>1.37 (0.98, 1.93)</td>
<td>4.8</td>
</tr>
<tr>
<td>1-183 days</td>
<td>2.01 (1.58, 2.56)</td>
<td>1.47 (1.11, 1.94)</td>
<td>5.4</td>
</tr>
<tr>
<td>Outpatient and hospitalized VTE</td>
<td>1.76 (1.52, 2.04)</td>
<td>1.30 (1.10, 1.53)</td>
<td>5.1</td>
</tr>
<tr>
<td>No Prior hormonal contraceptive in baseline</td>
<td>2.03 (1.64, 2.52)</td>
<td>1.49 (1.17, 1.92)</td>
<td>6.4</td>
</tr>
</tbody>
</table>
Limitations

- Incomplete information on smoking, obesity and lifestyle factors
- Incomplete information on reasons for COC use
  - COC used frequently for non-contraceptive uses
  - Inability to reliably capture comorbidities and indication(s) for use
    - Unable to capture physician prescribing rationale and intent
- No adjustment for prior lifetime use, switching, non-live birth pregnancies, trauma, surgery
- Non-cyclic use of cyclic products
Interpretation

• Assessment showed small increase in VTE risk
• VTE risk likely overestimated, due to residual confounding
  – Estimates decreased substantially with adjustment
  – Known risk factors for VTE not controlled: BMI, smoking, lifestyle
• Absolute risk difference is small- 3.5 / 10,000 WY in primary analysis
Conclusions

• Sentinel assessment allowed FDA follow-up on incomplete sponsor safety study
• Largest study to date evaluating continuous / extended COC safety
• Results indicate no substantial increase in risk with continuous and extended cycle products
• FDA is evaluating the results in light of the current body of knowledge to determine whether additional regulatory action is needed
Acknowledgements

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• Judy Maro
• Genna Panucci
• Darren Toh

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References


2. Steven T. Bird, PharmD MS, Abraham G. Hartzema, PhD PharmD, James M. Brophy, PhD MD, Mahyar Etminan, PharmD MS, and Joseph A.C. Delaney, PhD; Risk of venous thromboembolism in women with polycystic ovary syndrome: a population-based matched cohort analysis; CMAJ. 2013 Feb 5; 185(2): E115–E120

Backup slides
A post-marketing observational study evaluated the risk of venous thromboembolism with Lybrel use in two large US automated healthcare claims databases. The study was not completed as planned due to low accrual of Lybrel users in these databases and discontinuation of the product from the market due to low usage. At study discontinuation, the crude incidence rate of venous thromboembolism among Lybrel users (n=12,281) was 17.6 per 10,000 person-years, compared to 8.8 per 10,000 person-years among the users of cyclic oral contraceptives containing 20 mcg of ethinyl estradiol and a progestogen, and 5.1 per 10,000 person-years among the users of cyclic oral contraceptives containing the progestin levonorgestrel and 20 mcg of ethinyl estradiol. Adjustment for important risk factors or confounders (such as obesity, cardiovascular disease and other diseases) for venous thromboembolism could not be performed due to the small sample size. Although the study results suggest an elevated risk of venous thromboembolism with current Lybrel use compared to cyclic oral hormonal contraceptive use, reliable interpretation of the results is significantly limited due to the small sample size and concerns over unmeasured and uncontrolled confounding, as well as questions about the suitability of the comparator selection and the validity of the venous thromboembolism definition.
Propensity score (PS)

• Utilized covariates assessed at baseline

Age, year, comorbidity score, health service utilization, drug utilization, use of any non-study hormonal contraceptive, use of the other study group drug, gynecological conditions, hypercoagulable states and coagulation defects, cardiovascular and metabolic conditions, cardiac conditions, venous catheterization, renal conditions, inflammatory conditions, obesity and overweight, tobacco use, immobility, and surgery
## Results - Incidence Rate of VTE

<table>
<thead>
<tr>
<th></th>
<th>Incidence Rate per 10,000 WY</th>
<th>1:1 propensity matched</th>
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<td>12.8</td>
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Prospective VS. Retrospective studies

VTE Risk for Drospirenone- relative to LNG-containing or Other Birth Control Pills

- Ingenix (Hazard Ratio$^{a,b,c,d}$)
- EURAS (Hazard Ratio$^{e,f,g}$)
- LASS (Hazard Ratio$^{h,i,j}$)
- FDA-funded study (Hazard Ratio$^{k,l}$)
- Danish (Rate Ratio$^{a,l,j}$)
- Danish re-analysis (Rate Ratio$^{a,l,j}$)
- MEGA study (Odds Ratio$^{n,j}$)
- German case-control (Odds Ratio$^{f,e,h,k,m,n,o,p}$)
- PharMetrics (Odds Ratio$^{a}$)
- GPRD study (Odds Ratio$^{a}$)

*Risk ratios displayed on logarithmic scale; risk ratio < 1 indicates a lower risk of VTE for DRSP; > 1 indicates an increased risk of VTE for DRSP.

Source: Label for drospirenone products