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

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

David Moeny, R.Ph., MPH

Division of Epidemiology
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Disclosures

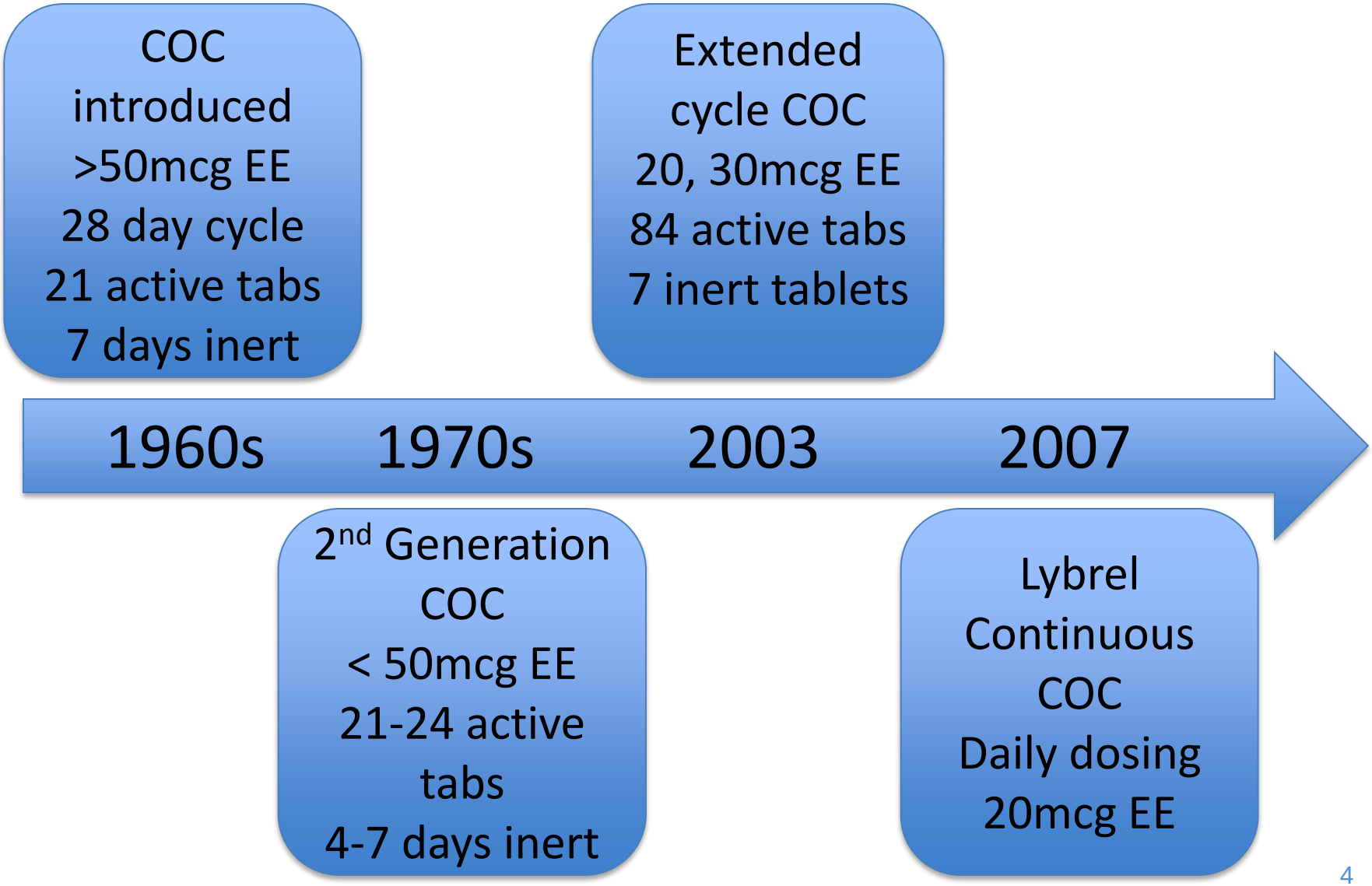
- No relationships to disclose

- 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



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

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

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 • 8 Sentinel Data Partners, 5/2007 – 9/2015 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

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

	Extended / Continuous COC (Yr, %)	Cyclic COC (Yr, %)	Covariate Balance	
			Absolute difference (Yr, %)	Standardized mean difference*
Patients (N)	210,691	522,316		
Mean age (years)	30.4	28.8	1.69	0.20
Other Study COC	3.0%	0.9%	2.07%	0.15
Use of oral non-LNG COC or non-oral hormonal contraceptive in baseline	35.0%	26.9%	8.03%	0.17

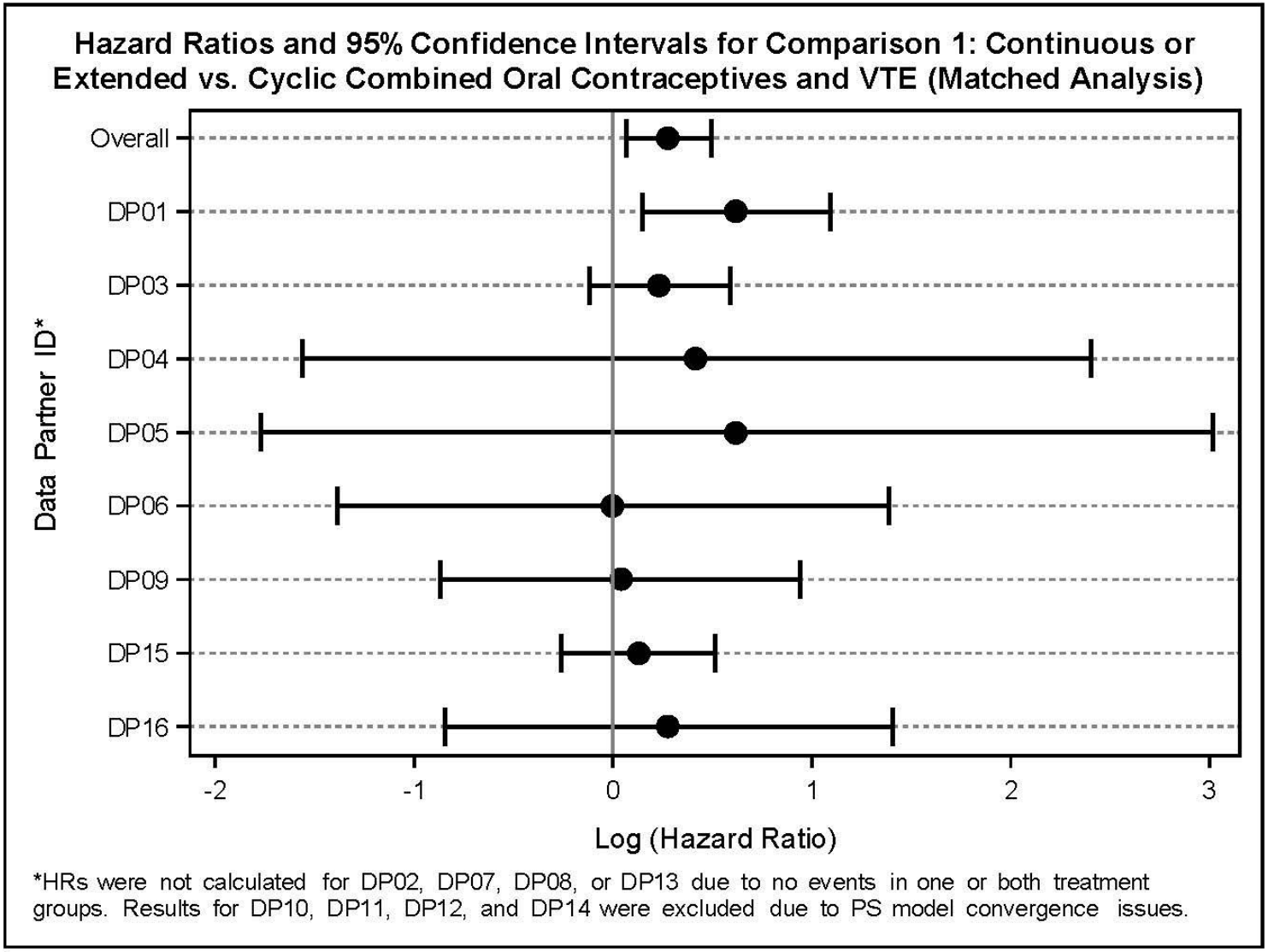
*After matching, the cohorts were highly comparable

Baseline Characteristics Unmatched Cohorts

	Extended / Continuous COC (%, N)	Cyclic COC (%, N)	Covariate Balance	
			Absolute difference (%, N)	Standardized mean difference*
Cardiovascular and Metabolic Conditions	7.2%	4.7%	2.50	0.11
Gynecological conditions	39.7%	32.3%	7.35	0.15
Mean # ambulatory encounters	4.8	3.6	1.16	0.20
Mean # of filled RX	7.0	4.5	2.52	0.35
Mean # of generics	3.3	2.4	0.93	0.31
Mean # of unique drug classes	3.1	2.3	0.87	0.32

*After matching, the cohorts were highly comparable

Risk VTE Continuous/Extended vs. Cyclic COC



Results - Primary analysis
Risk of VTE

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

Results - Secondary Analyses Risk of VTE

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

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

FDA

- Jie Li
- Wei Liu
- Rongmei Zhang
- Rima Izem

Sentinel

- Jane Huang
- Judy Maro
- Genna Panucci
- Darren Toh

Many thanks are due to the Data Partners who provided the data used in this analysis

References

1. American College of Obstetricians and Gynecologists, Practice Bulletin: Non-contraceptive Uses of Hormonal Contraceptives, Number 110, January 2010
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
3. Ekwutosi M. Okoroh, MD, W. Craig Hooper, PhD, Hani K. Atrash, MD, Hussain R. Yusuf, MD, and Sheree L. Boulet, DrPH; Is polycystic ovary syndrome another risk factor for venous thromboembolism? United States, 2003–2008, Am J Obstet Gynecol. 2012 November ; 207(5): 377.e1–377.e8. doi:10.1016/j.ajog.2012.08.007

Backup slides

Lybrel labeling full text

- 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)

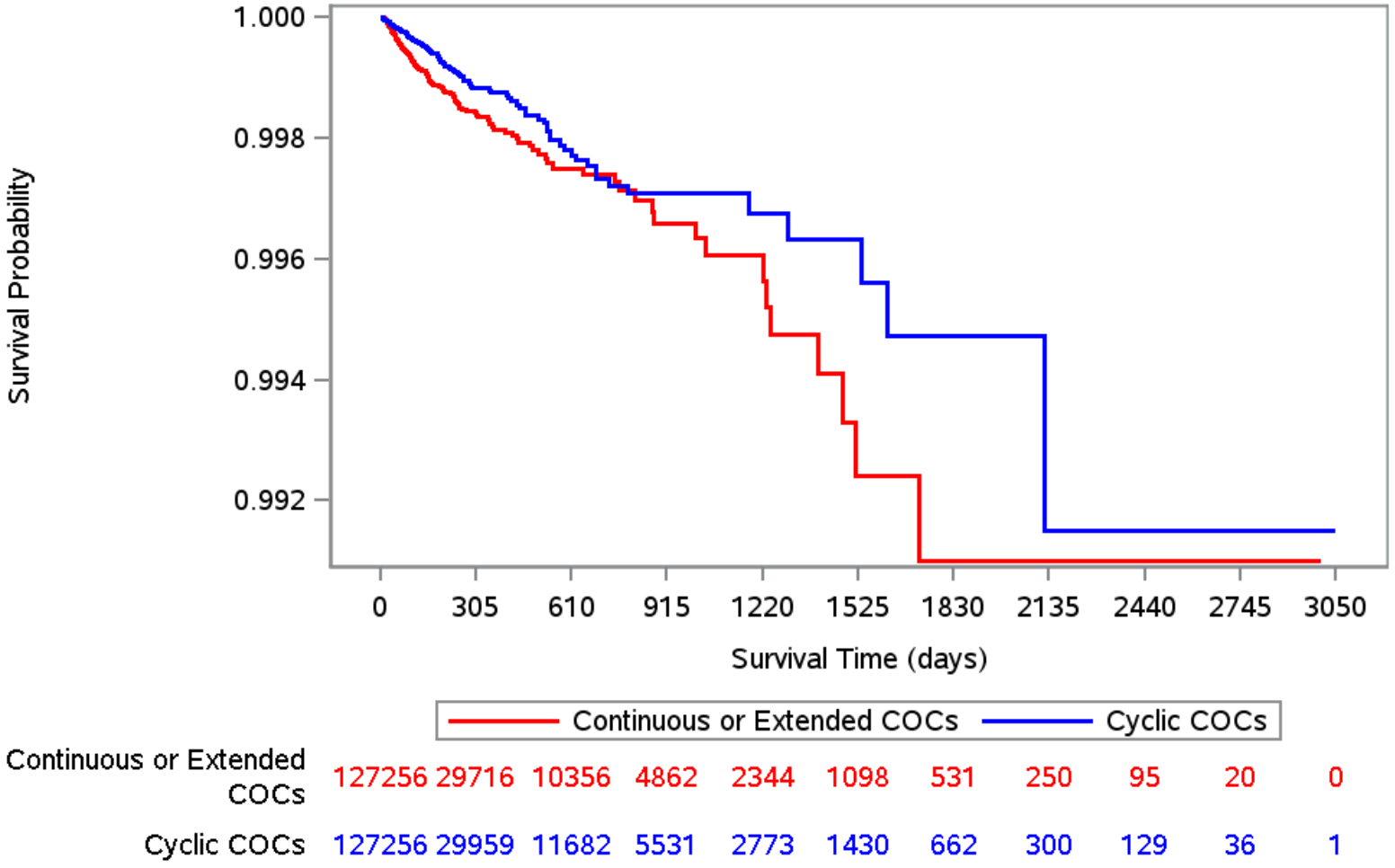
- Utilized covariates assessed at baseline

  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

	Incidence Rate per 10,000 WY 1:1 propensity matched N=203,402/203,402	
	Continuous / extended COC	Cyclic COC
18-24 years	7.1	4.4
25-34 years	12.0	10.4
35-50 years	24.7	17.6
20 mcg EE	16.0	10.1
30 mcg EE	15.6	12.8

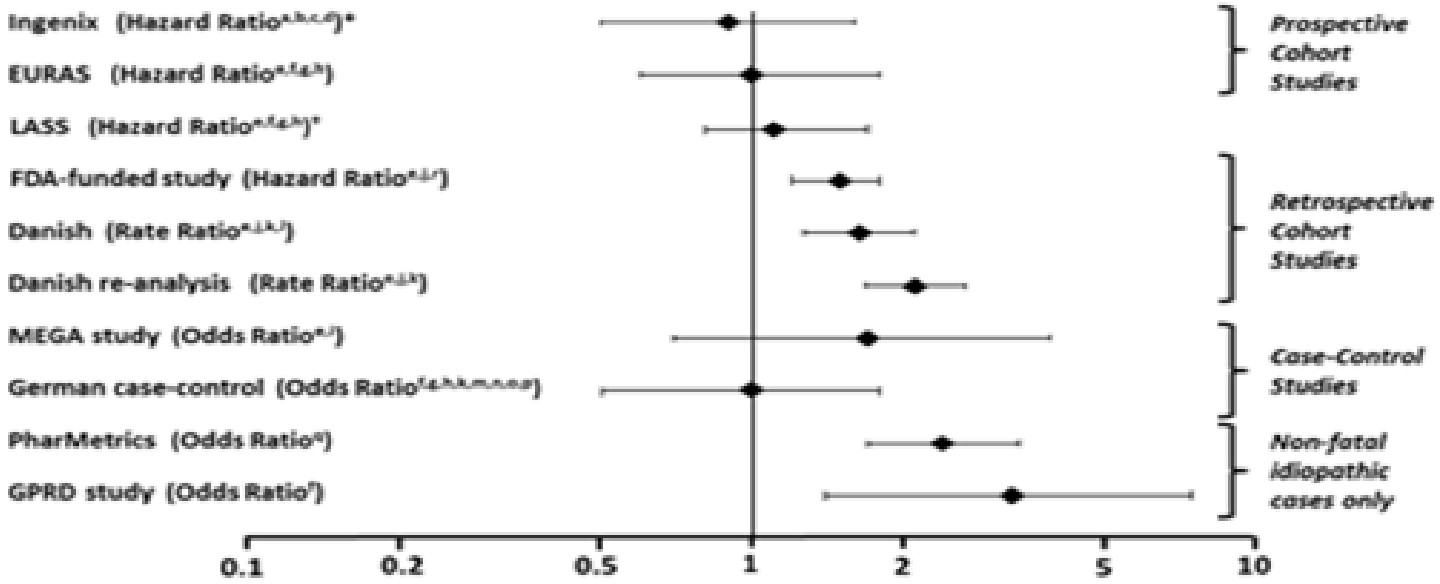
Kaplan Meier Survival Curves for Continuous or Extended COCs and Cyclic COCs with VTE (Strict Incidence Criteria)
from Unconditional Matched Population
With Number of Subjects at Risk



Continuous or Extended COCs	127256	29716	10356	4862	2344	1098	531	250	95	20	0
Cyclic COCs	127256	29959	11682	5531	2773	1430	662	300	129	36	1

Prospective VS. Retrospective studies

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



•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.

8

Source: Label for drospirenone products