Oral Contraceptives and VTE across the Sentinel data network –An IMEDS Evaluation pilot assessment

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Abstract

Introduction
The risk of venous thromboembolism (VTE) with oral contraceptives (OCs) is well documented. Recently, questions have been raised about an increased risk of VTE of 4th generation OCs (containing drospirenone) compared to 2nd generation (containing levonorgestrel).

Objective
This IMEDS Evaluation pilot used a distributed network of FDA Sentinel data partners to examine the rate of VTE in new users of 2nd and 4th generation OCs using the standardised data analytics capabilities of the IMEDS Evaluation pilot

Methods
The analytic cohort consisted of women aged 15-44 who were new OC users (2nd or 4th generation). Patients with VTE risk factors were excluded.
Dispensings were defined by National Drug Code in outpatient pharmacy claims. VTE was defined by ICD9 codes 415.1 or 453.xx, occurring in the inpatient or emergency department setting.
Nine Sentinel data partners participated. Publicly available Sentinel modular programs were used. Feasibility data were reviewed to inform use of the more complex modular analyses. Consistent with typical FDA use of these programs, the analysis did not include a direct comparison or statistical testing; rather, the results include rates of VTE stratified by age, sex, and year.

Results
Between January 1, 2008 and April 30, 2015 there were 350572 new users of 4th generation OCs and 317363 new users of 2nd generation OCs. There were 158 new VTE events for 4th generation OCs, and 121 for 2nd generation OCs. The rate of VTE events per 10000 person-years was 8.56 for 4th generation and 6.58 for 2nd generation OCs (interquartile range from 5.86 to 9.23 for 4th generation OCs, and from 0 to 7.07 for 2nd generation OCs across the data partners).

Conclusions
In line with the literature, rates of VTE were greater for 4th generation than 2nd generation OCs. Limited variation was seen across data partners, although some partners had few events. Limitations include lack of confounding control, no direct comparisons or matching, and VTE defined only by diagnosis code. The pilot shows the value of the large distributed data network in exploring safety issues by a pharmaceutical sponsor.

Background

The risk of venous thromboembolism (VTE) with oral contraceptives (OCs) is well documented and extensively studied, see for example (1). While several studies evaluating the incidence of VTE and related adverse events among patients exposed to oral contraceptives that have also used large, electronic databases(1,2), none of these have taken advantage of a large distributed network of observational databases such as those available in the FDA's Sentinel network(3).

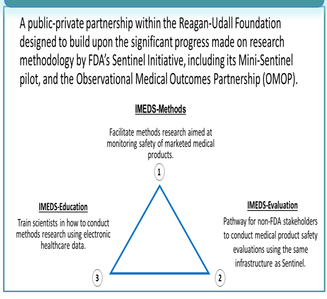
Objectives

The aim of this pilot assessment was to examine new users of second generation and fourth generation oral contraceptives (OCs) with respect to the occurrence of venous thromboembolism (VTE) in the Sentinel data network using the standardised data analytics capabilities of the IMEDS-Evaluation pilot (figure 2)(4).

Methods

The cohort for this analysis consisted of women aged 15-44 who are new users of 2nd generation OCs (levonorgestrel-containing products) and 4th generation (drospirenone-containing) OCs. Patients with evidence of VTE risk factors were excluded: cancer, renal failure, chronic cardiovascular diseases, inflammatory or autoimmmune conditions, epilepsy, anticoagulant use, NuvaRing use major surgery, trauma, or pregnancy.
Dispensings were defined by National Drug Code in outpatient pharmacy claims records. VTE was defined as ICD9 codes 415.1 or 453.xx, occurring in the inpatient or emergency department setting.
Age stratification was conducted into three age groups (15-29, 30-39, 40-44).
Analyses were conducted across nine Sentinel data partners participating in the pilot. Publicly available Sentinel modular programs and summary table query tools (Modular Program QRP version 2.09, Summary Table version 5.0) were used. Summary table data were reviewed to inform use of the more complex modular analyses. Consistent with typical FDA use of these programs, the analysis did not include a direct comparison or statistical testing, rather, the results include rates of VTE stratified by age, sex, and year.

Figure 1. IMEDS Program Overview



Results

As shown in table 1, between 1st January 2008 and April 30th 2015 across the 9 data partners there were 350572 new users of 4th generation OCs and 317363 new users of 2nd generation OCs, leading to 1899922 and 1460766 dispensings respectively. There were a total of 158 new treatment episodes with VTE events for 4th generation OCs, and 121 for 2nd generation OCs. The rates of new episodes with VTE events per 10000 person-years were 8.56 for 4th generation and 6.58 for 2nd generation (details of variation across the data partners see figure 1 and table 2). Rates were slightly higher for both when exclusions were limited to 90 days (9.36 and 7.94 respectively).

Table 1. Oral Contraceptives (OCs) and VTE across participating data partners of the MSDD between January 1, 2008 and April 30, 2015, by Oral Contraceptive Exposure and Exclusion Criteria

	4th Generation OCs	2nd Generation OCs
New Users	350,572	317,363
Dispensings	1,899,922	1,460,766
Days Supplied	62,180,487	63,102,751
Years at Risk	184,485.20	183,852.50
New Episodes w/ Events	158	121
Eligible Members	26,697,378	26,697,378
Member- Years	41768751.5	41852933.9
New Users /Eligible Members (Per 1000 members)	13.13	11.89
Days Supplied/ New User	177.37	198.83
Dispensings/ New User	5.42	4.6
Days Supplied/ Dispensing	32.73	43.2
New Episodes w/ Events /Years at Risk (Per 10000 Years)	8.56	6.58

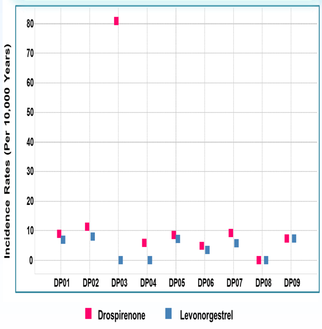
Results (*Cont.*)

Table 2. Summary Statistics Across participating Data Partners of MSDD

	4th Generation OCs			2nd Generation OCs		
	New Users	Eligible Members	Days Supplied/ Dispensing	New Users	Eligible Members	Days Supplied/ Dispensing
Minimum	159.00	23817.00	27.80	314.00	23817.00	33.30
25th Percentile	4040.00	428348.00	30.20	12867.00	428348.00	38.00
Mean	38952.40	2966375.30	39.00	35262.60	2966375.30	47.50
Median	8514.00	653439.00	33.40	13362.00	653439.00	45.30
75th Percentile	21188.00	1840769.00	46.20	15662.00	1840769.00	59.40
Maximum	167929.00	11841843.00	61.00	127269.00	11841843.00	67.50

Note: Minimum and maximum statistics for the three metrics are across all 9 data partners,and do not necessarily refer to the same data partner throughut a row

Figure 2. VTE Incidence Rates Among 4th and 2nd generation OC Users by DP



Conclusion

This rapid analysis approach shows rates of VTE were greater for 4th generation than 2nd generation OCs in line with the literature. Limited variation was seen across data partners, although some partners had few events. Limitations include lack of confounding control, no direct comparisons or matching, and VTE defined solely by diagnosis code. The pilot shows the potential of the large distributed data network in exploring safety issues and the value in leveraging Sentinel data and analytic tools.

Acknowledgement

We wish to thank the participating data partners: Group Health, Harvard Pilgrim, Healthcore, Health Partners, Humana, Marshfield, Meyers Primary Care, Optum and Vanderbilt for their data provision for this pilot, but wish to emphasise that the conclusions are not necessarily those of the data partners themselves.

References

1. Jick SS and RK Hernandez. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ, 2011. 342: p. d2151.
2. Vinogradova Y et al. Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ, 2015. 350: p. h2135.
3. Platt R et al. The new Sentinel Network--improving the evidence of medical-product safety. N Engl J Med, 2009. 361(7): p. 645-7.
4. Toh S et al. Rapid assessment of cardiovascular risk among users of smoking cessation drugs within the US Food and Drug Administration's Mini-Sentinel program. JAMA Intern Med, 2013. 173(9): p. 817-9.

Conflict of Interest: The study was fully funded by Pfizer Inc through the IMEDS program of the Reagan-Udall Foundation for the FDA. Andrew Bate, Rachel Sobel and Robert Reynolds are all shareholders and full time employees of Pfizer Inc. All authors have no conflicts of interest relevant to this study to disclose.