DIA

Interplay of Adverse Events, Spontaneous Reporting, and Longitudinal Electronic Health Records for Signal Management

January 27-29
Baltimore, MD

Disclaimer

A manuscript on this topic has been submitted to Drug Safety on behalf of **Real-World Evidence and Big Data Special Interest Group of the International Society of Pharmacovigilance** with the following authors: Salvatore Crisafulli, Gianmario Candore, Andrew Bate, Jeffrey Stuart Brown, Rebecca Chandler, Tarek A Hammad, Samantha Lane, Judith C. Maro, G. Niklas Norén, Antoine Pariente, Mulugeta Russom, Maribel Salas, Andrej Segec, Saad Shakir, Andrea Spini, Sengwee Toh, Marco Tuccori, Eugène van Puijenbroek, Gianluca Trifirò

The views expressed in this presentation are those of the authors and do not necessarily represent the official views of the US FDA and should not be attributed to DIA, its directors, officers, employees, volunteers, members, chapters, councils, Communities or affiliates.

Example presented regarding the Sentinel System: This Sentinel Operations Center (SOC) is funded by the U.S. Food and Drug Administration (FDA) through the Department of Health and Human Services (HHS) contract number 75F40119D10037. This project was supported by Task Order HHSF22301012T under Master Agreement HHSF223201400030I.

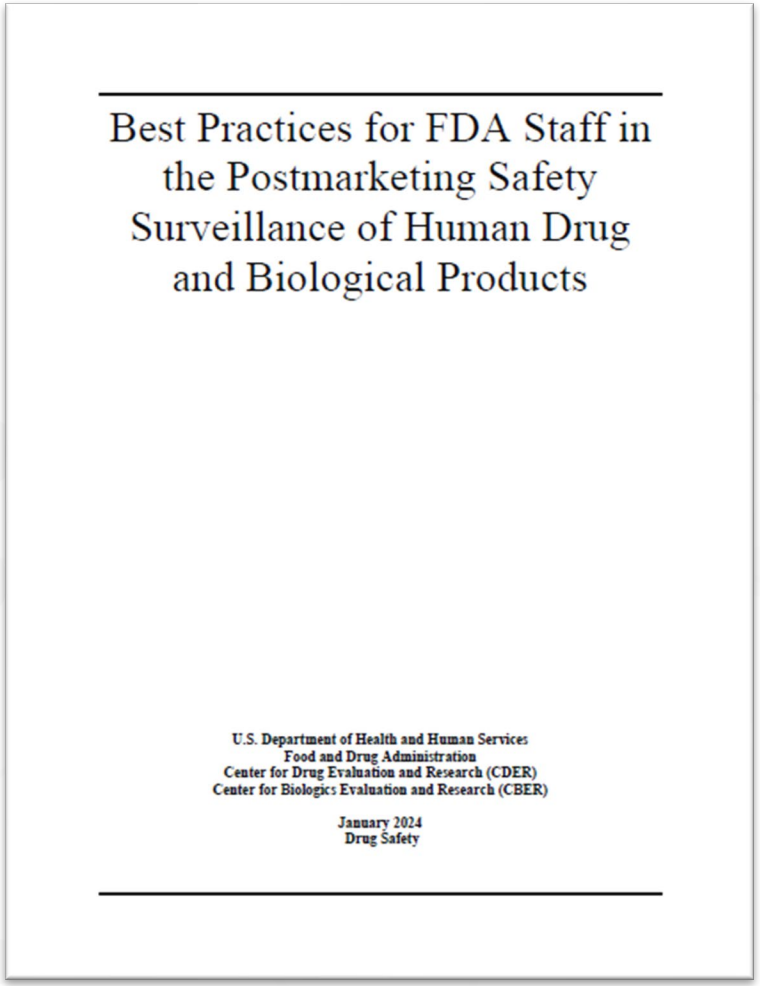
Many thanks are due to those who participated in this work: Sentinel Data Partners who provided data used in the analysis: CVS Health (Aetna), Blue Bell, PA; Carelon Research/Elevance Health, Wilmington, DE; Duke University School of Medicine, Department of Population Health Sciences, Durham, NC, through the Centers for Medicare and Medicaid Services which provided data; HealthPartners Institute for Education and Research, Minneapolis, Minnesota; Humana Healthcare Research Inc., Louisville, KY; Kaiser Permanente Colorado Institute for Health Research, Aurora, CO; Kaiser Permanente Hawai'i, Center for Integrated Health Care Research, Honolulu, HI; Kaiser Permanente Mid-Atlantic States, Mid-Atlantic Permanente Research Institute, Rockville, MD; Kaiser Permanente Northwest Center for Health Research, Portland, OR; Kaiser Permanente Washington Health Research Institute, Seattle, WA; Marshfield Clinic Research Institute, Marshfield, WI; OptumInsight Life Sciences Inc., Boston, MA; Vanderbilt University Medical Center, Department of Health Policy, Nashville, TN, through the TennCare Division of the Tennessee Department of Finance & Administration which provided data.

Two Complementary Data Streams for Pharmacovigilance: Spontaneous Reporting Systems & Longitudinal Health Data

DIA

Signal Identification – Routine Pharmacovigilance

- Risk-based approach for surveillance
  - Product focus
    - New Molecular Entities (NMEs) and other novel medications
  - Event focus
    - Serious, unlabeled adverse events
    - Adverse events of special interest (AESI)
- Spontaneous reports, literature, and periodic safety reports are the main data sources surveilled


Best Practices for FDA Staff in the Postmarketing Safety Surveillance of Human Drug and Biological Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

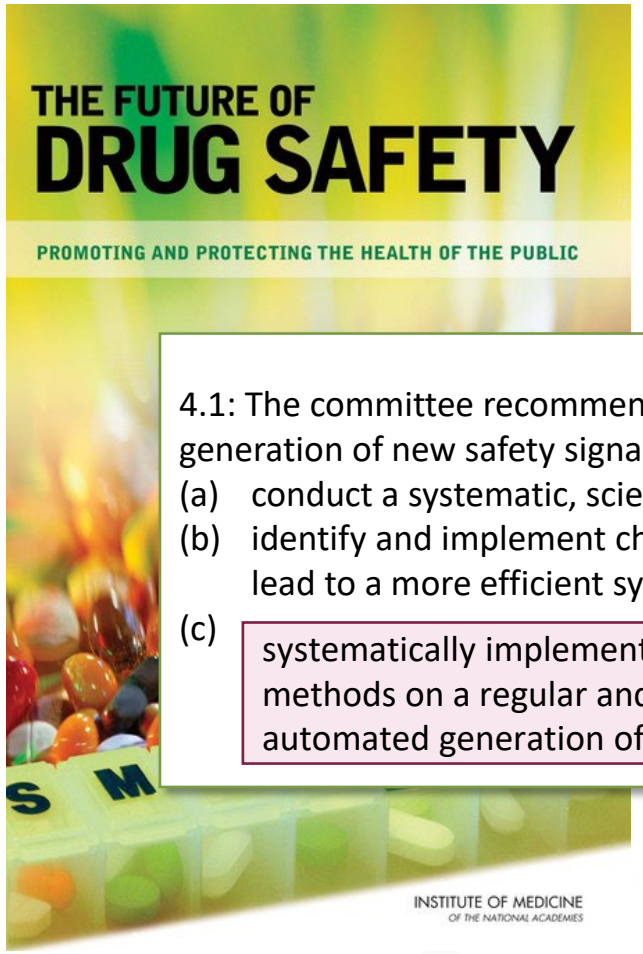
January 2024
Drug Safety

DIA

Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff. January 2024. https://www.fda.gov/media/130216/download

Institute of Medicine Drug Safety System Assessment : Longitudinal Health Data for Signal Generation

- In 2006, the FDA requested that the Institute of Medicine **examine the system of drug safety in the US**
- Institute of Medicine published "The Future of Drug Safety: Promoting and Protecting the Health of the Public" in 2007 calling for a comprehensive approach to drug safety



4.1: The committee recommends that in order to improve the generation of new safety signals and hypotheses, CDER

(a) conduct a systematic, scientific review of the AERS system,

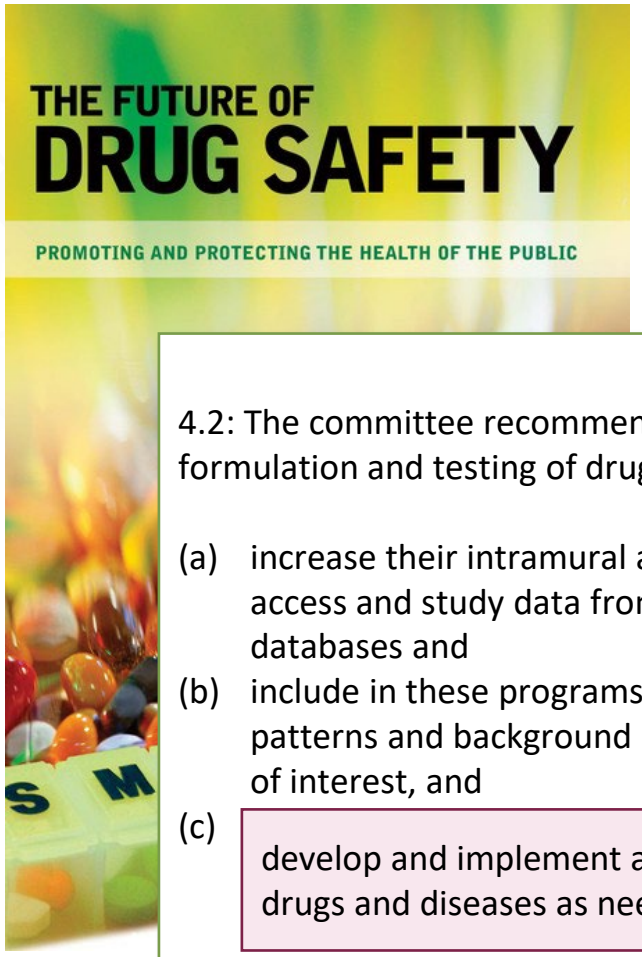
(b) identify and implement changes in key factors that could lead to a more efficient system, and

(c) systematically implement statistical-surveillance methods on a regular and routine basis for the automated generation of new safety signals

Committee on the Assessment of the US Drug Safety System; Board on Population Health and Public Health Practice; Institute of Medicine. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*; Stratton, K., Baciu, A., Burke, S. P., Eds.; National Academies Press: Washington, D.C., 2007. https://doi.org/10.17226/11750.

Institute of Medicine Drug Safety System Assessment: Longitudinal Health Data for Signal Refinement/Evaluation

- In 2006, the FDA requested that the Institute of Medicine **examine the system of drug safety in the US**
- Institute of Medicine published "The Future of Drug Safety: Promoting and Protecting the Health of the Public" in 2007 calling for a comprehensive approach to drug safety



4.2: The committee recommends that in order to facilitate the formulation and testing of drug safety hypotheses, CDER

(a) increase their intramural and extramural programs that access and study data from large automated healthcare databases and

(b) include in these programs studies on drug utilization patterns and background incidence rates for adverse events of interest, and

(c) develop and implement active surveillance of specific drugs and diseases as needed in a variety of settings.

Committee on the Assessment of the US Drug Safety System; Board on Population Health and Public Health Practice; Institute of Medicine. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*; Stratton, K., Baciu, A., Burke, S. P., Eds.; National Academies Press: Washington, D.C., 2007. https://doi.org/10.17226/11750.

Two Complementary Data Streams for Pharmacovigilance: Spontaneous Reporting Systems & Longitudinal Health Data

SRS Limitations	LHD Strengths
• Cannot determine incidence rates	• Estimates of population exposure available • Risk quantification possible
• Vulnerable to underreporting and reporting bias	• Exposure/event capture at the level of patient and based on billed medical encounters
• Adverse events associated with long latency, worsening disease, or high background rates difficult to evaluate	• Longitudinal capture of medical history • Ability to control for confounding

DIA

SRS = Spontaneous Reporting Systems; LHD = Longitudinal Health Data

Two Complementary Data Streams for Pharmacovigilance: Spontaneous Reporting Systems & Longitudinal Health Data

SRS Strengths	LHD Limitations
• Detecting serious rare events, particularly obvious drug-induced events	• Need sufficient exposures & outcomes
• Captures all products and use settings; can provide patient perspectives	• Capture based on billed medical encounters
• Near real-time data from reporters available for analysis	• Claims maturation period; data lags

DIA

SRS = Spontaneous Reporting Systems; LHD = Longitudinal Health Data

Early Examples of the Interplay: EU-ADR and extensions of Multi-Gamma Poisson Shrinker Methods

Exploratory Comparison: Keep the Statistical Method, Change Data Input

- First extensions of **Disproportionality Analyses** to Longitudinal Data mostly focused on changing the nature of the "expected count" to reflect a different denominator (one made possible by databases)

Research Article | Published: 09 December 2014

Evaluating performance of electronic healthcare records and spontaneous reporting data in drug safety signal detection

Vaishali K. Patadia, Martijn J. Schuemie, Preciosa Coloma, Ron Herings, Johan van der Lei, Sabine Straus, Miriam Sturkenboom & Gianluca Trifirò

[1]Schuemie 2011 (https://pubmed.ncbi.nlm.nih.gov/20945505/); Schuemeie 2012 (https://pubmed.ncbi.nlm.nih.gov/25487079/), Patadia 2015 (https://pubmed.ncbi.nlm.nih.gov/25487079/)

EU-ADR Comparative Papers – Main Takeaways Using Known Positive Comparisons

- Longitudinal databases + extensions of disproportionality analysis excelled for outcomes that had high background rates and when there was not an obvious drug-induced effect
  - These are precisely the known weaknesses of spontaneous reporting databases.
  - Specific Example: Vioxx and acute myocardial infarction (AMI). Detected using longitudinal databases, not spontaneous reporting systems.
  - By contrast, bullous eruption (i.e., a drug-induced effect) does best in spontaneous reporting systems.

Examples of the Interplay: Longitudinal Health Data in both Signal Identification and Signal Refinement/Evaluation

Sentinel Signal Identification- Untargeted Use of Longitudinal Data

- Credible source of signals? ✓
  - Conceptual support, demonstration projects
- Signal tools are scalable and rapid? ✓
  - Foundational methods/infrastructure projects completed
  - Enhancements implemented to facilitate Sentinel Signal Identification
- Integrated into PV system efficiently?
  - Pilots and ongoing projects are informing process development
  - Expect tools and approaches will continue to evolve

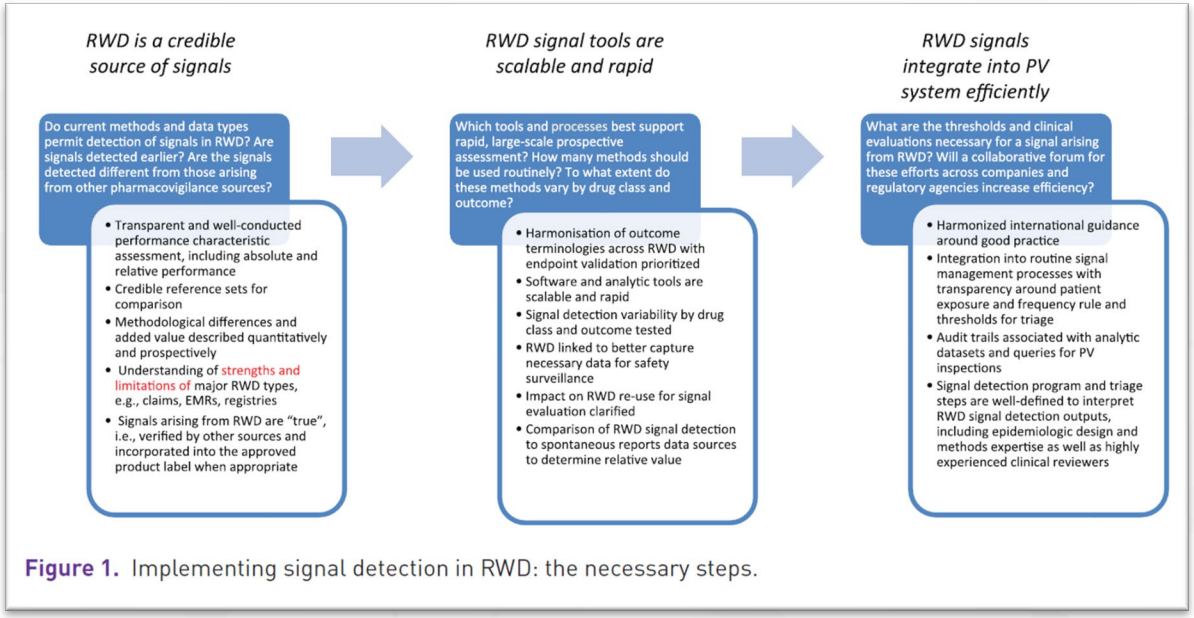


Figure 1. Implementing signal detection in RWD: the necessary steps.

Bate A, et al. Ther Adv Drug Saf. 2019; 10: 2042098619864744.

Signal Identification for Ozempic (semaglutide)

Background

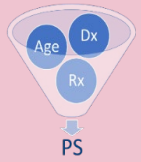
Ozempic

VS.

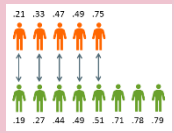
Sitagliptin

Is there an increase in frequency of adverse events during Ozempic use as compared to sitagliptin?

Methods



1:1 PS Match & hdPS match

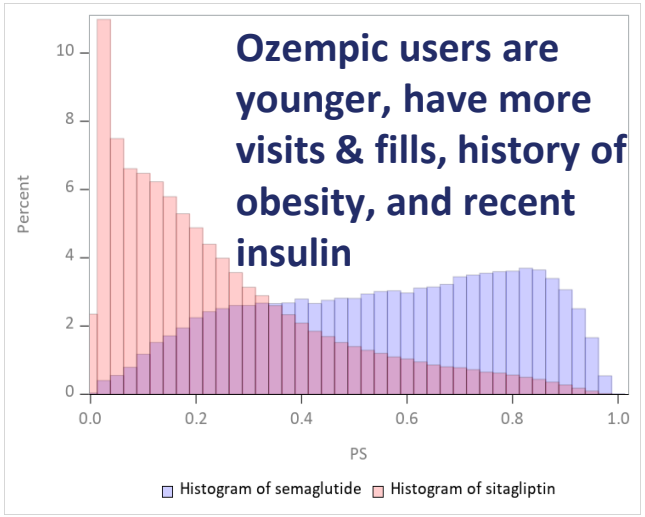


Analysis and Findings

Sentinel Distributed Database

- Scanned ~83,000 non-pregnancy and non-cancer outcomes
- Sensitivities based on encounter setting

Jan. 2018 – Feb. 2022



134,007 1:1 Matched Pairs with Conventional PS
118,161 1:1 Matched Pairs with Conventional + hdPS

Ozempic users less adherent, more likely to stop treatment after a single dispensing

Significant Alerts: Nausea/Vomiting, Diarrhea, Constipation, GI distress / pain, Obesity, Abnormal Weight Loss, Metabolic Issues, Sleep Apnea

Conclusions: All of the alerts observed were either labeled adverse events, or comorbid conditions of people likely using Ozempic not only for glucose control but also for weight loss. None of the alerts required further follow-up.

https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/outcome-monitoring-following-ozempic-use-patients-type-2

PHARMACOTHERAPY
accp American College of Clinical Pharmacy

Volume 40, Issue 11
November 2020
Pages 1099-1107

Original Research Article

Complementary Use of U.S. FDA's Adverse Event Reporting System and Sentinel System to Characterize Direct Oral Anticoagulants-Associated Cutaneous Small Vessel Vasculitis

References Related Information

PDS Pharmacoepidemiology & Drug Safety
ispe Official Journal of the International Society for Pharmacoepidemiology

Volume 31, Issue 11
November 2022
Pages 1164-1173

ORIGINAL ARTICLE

A cohort study to assess risk of cutaneous small vessel vasculitis among users of different oral anticoagulants

Adebola Ajao, Austin Cosgrove, Efe Eworuke, Mohamed Mohamoud, Rongmei Zhang, Oren Shapira, Joy Kolonoski, John G. Connolly

First published: 31 July 2022 | https://doi.org/10.1002/pds.5514 | Citations: 1

References Related Information

Recommended

Novel Oral Anti-Coagulant (NOAC)-Cutaneous Small Vessel Vasculitis (CSVV) Chronology

- **NOAC-CSVV signal identified in routine literature search, prompted a case series analysis in FAERS.**
  - 50 cases of CSVV reported with rivaroxaban (n=26), apixaban (n=14), dabigatran (n=9), and edoxaban (n=1).
  - Approximately 50% of the cases reported time to onset within 10 days after DOAC exposure.
  - Hospitalization occurred in most of the cases (n=37). Switching of the offending agent after the development of CSVV was reported (n=26).
  - Three rivaroxaban (n=3) cases and one dabigatran case (n=1) reported positive rechallenge.
  - 50% were treated with corticosteroids after discontinuation of the suspected DOAC.

https://pubmed.ncbi.nlm.nih.gov/33090530/

Novel Oral Anti-Coagulant (NOAC)-Cutaneous Small Vessel Vasculitis (CSVV) Chronology

- **Routine descriptive query initiated in the Sentinel System among 17 Data Partners from January 1, 2010, to June 30, 2018**
  - 3659 CSVV cases identified with prior DOAC exposure, with 85% of events occurring within 10 days.
  - Skin biopsy up to 14 days before or after the CSVV diagnosis occurred in 704 patients (19.2%).
  - Corticosteroid treatment within 90 days after CSVV diagnosis occurred in 1123 patients (30.7%).

- **Patient profiles analyzed to develop a case algorithm in claims-based data (ICD-9/10-CM code for hypersensitivity angiitis, vasculitis of the skin, or allergic purpura in outpatient setting with corticosteroid treatment within 90 days of diagnosis).**

https://pubmed.ncbi.nlm.nih.gov/33090530/

Longitudinal Data Allows for Rich and Sophisticated Confounding Control

TABLE 1 Baseline characteristics of new initiators of direct oral anticoagulants and warfarin after propensity score matching

	Rivaroxaban	Warfarin	SMD	Dabigatran	Warfarin	SMD	Apixaban	Warfarin	SMD
Number of patients	320 363	320 363	-	142 197	142 197	-	503 885	503 885	-
Baseline comorbidities, %									
Charlson Comorbidity Score, mean*	2.6	2.6	0.005	2.4	2.4	0.011	3.1	3.1	0.006
Autoimmune diseases*	5.1	5.2	0.001	5.3	4.8	0.025	5.6	5.6	0.002
Blood disorders*	19.1	19.1	0.000	17.2	16.7	0.014	23.8	23.6	0.005
Viral infections*	1.3	1.3	0.003	1.3	1.2	0.013	1.3	1.3	0.001
Chronic bacteremia*	0.8	0.8	−0.003	0.6	0.6	−0.004	1.1	1.1	0.001
Anti-infectives*	30.1	29.6	0.012	28.6	27.5	0.024	30.9	30.7	0.004
Non-steroidal anti-inflammatory drugs (NSAIDS)*	6.4	6.2	0.006	7.2	6.6	0.026	5.5	5.5	−0.000
Psychoactive drugs*	4.3	4.2	0.006	3.9	3.5	0.020	4.5	4.5	0.001
Cardiovascular and diuretic drugs*	61.6	61.6	0.001	62.6	62.7	−0.003	64.5	64.8	−0.007
Beta-adrenergic receptor agonists*	10.7	10.5	0.007	10.3	9.5	0.029	11.2	11.2	0.001
Anticonvulsants*	0.6	0.7	−0.004	0.8	0.7	0.010	0.6	0.6	−0.003

https://pubmed.ncbi.nlm.nih.gov/35909259/, Asterisk indicates included in the propensity score model

NOAC-CSVV Inferential Analyses: No Significant Risk in 6 Pairwise Comparisons of NOACs and Warfarin

TABLE 3 Propensity score matched unconditional analysis of incidence of CSVV by DOACs and warfarin

	Number of new users	Number of events	Incidence rate per 10 000-person years	Hazard ratio (95% CI)	*p*-Value
Rivaroxaban	320 363	53	4.1	0.94 (0.64, 1.39)	0.765
Warfarin	320 363	51	4.5		
Dabigatran	142 197	26	5.1	1.17 (0.67, 2.06)	0.576
Warfarin	142 197	23	4.6		
Apixaban	503 885	75	3.8	0.85 (0.62, 1.16)	0.298
Warfarin	503 885	82	4.6		
Rivaroxaban	125 338	25	4.9	0.86 (0.49, 1.50)	0.586
Dabigatran	125 338	24	5.6		
Rivaroxaban	331 796	55	4.1	0.99 (0.68, 1.45)	0.977
Apixaban	331 796	54	4.2		
Dabigatran	125 718	24	5.6	1.70 (0.90, 3.21)	0.099
Apixaban	125 718	16	3.3		

Abbreviations: CSVV, cutaneous small vessel vasculitis; DOACs, direct oral anticoagulants.

https://pubmed.ncbi.nlm.nih.gov/35909259/

Eliquis (Apixaban), Pradaxa (Dabigatran), and Xarelto (Rivaroxaban) & Cutaneous Small-Vessel Vasculitis

Study Summary:

Cases of cutaneous small-vessel vasculitis (CSVV) associated with direct oral anticoagulants (DOACs) were reported in DOAC premarket trials and to the FDA Adverse Events Reporting System (FAERS) post approval. FDA conducted a study in Sentinel to characterize CSVV cases among patients with atrial fibrillation treated with DOACs. Additional studies in Sentinel explored incidence rates for DOACs, warfarin, and allopurinol as positive control and compared adjusted CSVV risk in new users of DOACs and warfarin. No statistically significant differential CSVV risk was observed among new users of DOACs and warfarin. FDA did not take regulatory action at this time, based on available information.

DIA

https://www.sentinelinitiative.org/studies/drugs/eliquis-apixaban-pradaxa-dabigatran-and-xarelto-rivaroxaban-1

Takeaways

- **Multiple data sources contribute to FDA's pharmacovigilance efforts.**
- **Spontaneous reporting systems are complemented by longitudinal databases.**
  - Both offer unique strengths and are best appreciated when leveraged in concert for signal management
- **Interdisciplinary teams, along with clear communication and knowledge sharing across them, are essential for effectively integrating data in signal management.**

Acknowledgements

U.S. Food and Drug Administration

Adebola Ajao
Michael Blum
Catherine Corey
Christine Chamberlain
Efe Eworuke
José Hernández-Muñoz
Lois La Grenade
Yong Ma
David Moeny
Mohamed Mohamoud
Monica Muñoz
Veronica Sansing-Foster
Danijela Stojanovic
Lockwood Taylor
Daniel Woronow
Rongmei Zhang

Sentinel Operations Center

Sarah Alam
Justin Bohn
Jillian Burk
Amanda Carruth
Whitney Chlon
John Connolly
Austin Cosgrove
Elizabeth Dee
Meredith Epperson
Casie Horgan
Jane Huang
Joy Kolonoski
Judith Maro
Jim Marshall
Alexander Peters
Ryan Schoeplein
Oren Shapira
Liz Siranosian
Emma Whited

Thank You

Questions?

DIA