Incidence of Severe Abnormal Uterine Bleeding Following Oral Anticoagulant Use

Ting-Ying Huang[1], Laura Hou[1], Abby Anderson[2], Hui-Lee Wong[3], Rongmei Zhang[2], Peter Waldron[2], David Moeny[2], Audrey Gassman[2], Efe Eworuke[2]

[1] Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts 02215
[2] Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland 20993
[3] Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland 20993

BACKGROUND AND OBJECTIVE

- Recent reports have led to concerns over clinically relevant gynecologic adverse events - specifically, uterine bleeding requiring medical intervention - among women of reproductive age who were exposed to oral anticoagulants (OAs)
- This study aimed to estimate the incidence rate of severe abnormal uterine bleeding (SAUB) among OA users, including non-vitamin K oral anticoagulants (NOACs) and warfarin, in the United States

METHODS

- Design: retrospective new user cohort, female only
- Data source: Sentinel Distributed Database, a curated database composed of medical encounter data and outpatient pharmacy dispensing records contributed by 17 data partners of national and regional health insurers and integrated health care delivery networks in the US
- Query period: October 19, 2010 through September 30, 2015
- OA exposures: rivaroxaban, apixaban, dabigatran, or warfarin
  - Exposure washout: no use of rivaroxaban, apixaban, dabigatran, edoxaban, or warfarin (evidenced by dispensing days supply) in the 183 days before the index dispensing date (index date, or Day 0)
- Health outcomes of interest: three types of SAUB in non-institutional care settings were separately assessed, each defined as vaginal bleeding (VB) diagnosis followed by below management -
  1. **$SAUB_{med}$**: same-day insertion of intrauterine device or vaginal packing, initiation of oral contraception (combined or progestin-only oral contraceptives) or an antifibrinolytic drug
  2. **$SAUB_{trans}$**: same-day red blood cell transfusion
  3. **$SAUB_{surg}$**: within 30 days, hysterectomy, hysteroscopic polypectomy, hysteroscopic/laparoscopic/abdominal myomectomy, dilation and curettage (with or without hysteroscopy), thermal/cryo/resection endometrial ablation, uterine artery embolization, or hysteroscopy not otherwise assessed
- Inclusion: in the 183 days before and including index date,
  a) continuously enrolled in health and prescription drug insurance plans,
  b) a diagnosis of venous thromboembolism or atrial fibrillation/flutter, and
  c) no history of joint replacement, hysterectomy, or qualifying VB management of respective SAUBs

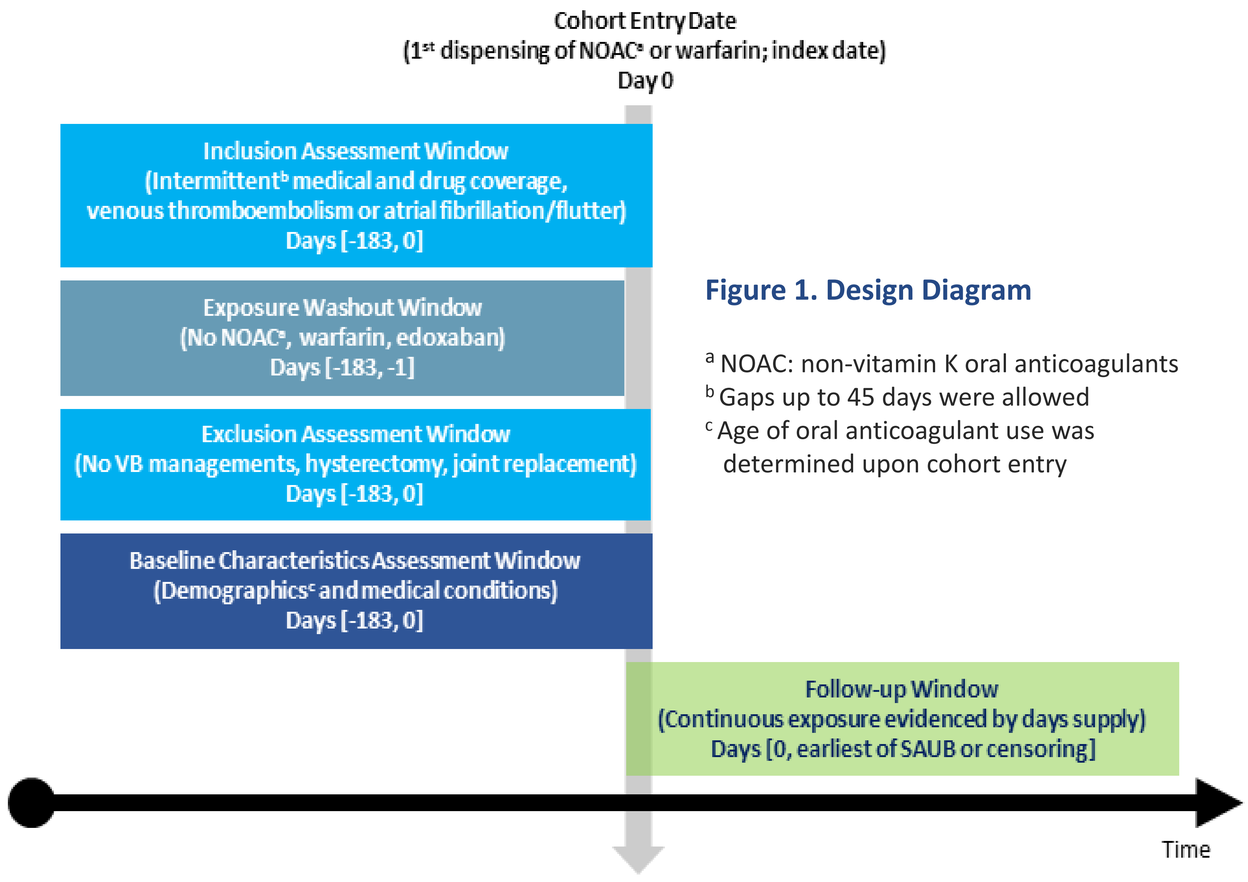


Figure 1. Design Diagram

[a] NOAC: non-vitamin K oral anticoagulants
[b] Gaps up to 45 days were allowed
[c] Age of oral anticoagulant use was determined upon cohort entry

- Follow-up: individual OA new users contributed at-risk time from the index date of their first valid exposure until the earliest occurrence of: SAUB (upon VB management), disenrollment, exposure episode end, query period end, or recorded death
  - At-risk time was determined by cumulative dispensing days supply, with a 3-day maximum gap allowed for late refills and a 3-day extension period attached to the end of the last dispensing
- Statistical analysis: SAUB incidence and incidence rate overall and by pre- and post-menopausal age group, estimated using Sentinel's Query Request Package, Cohort Identification and Descriptive Analysis module version 7.3.4
- Medical conditions and drug utilization were identified via International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), Healthcare Common Procedure Coding System, Current Procedural Terminology, Revenue Center codes, or National Drug Codes recorded in insurance claims
- This study was conducted as part of the public health surveillance activities under the auspices of the US Food and Drug Administration and therefore not under the purview of Institutional Review Boards

RESULTS

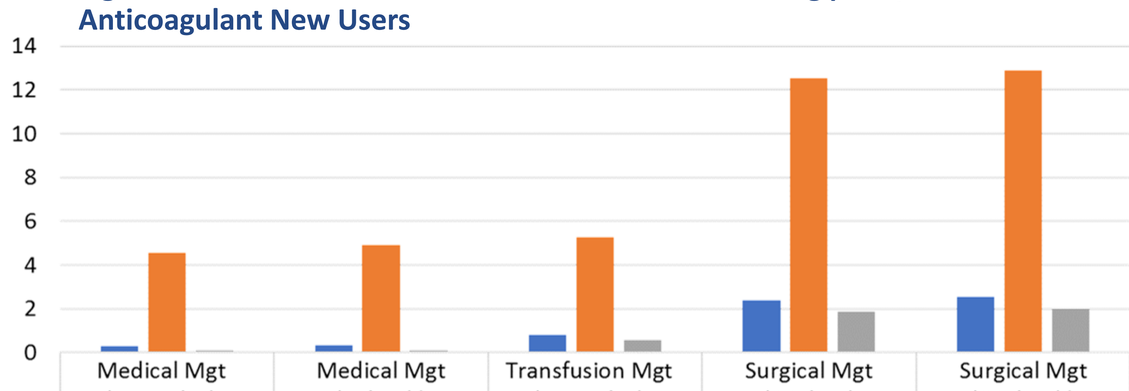
Table 1. Baseline Characteristics for Female New Users of Oral Anticoagulants (n=1,050,192)

	n/mean	%/std
Age	75.3	11.5
≤50 years	50,317	4.8%
51+ years	999,875	95.2%
Warfarin as index exposure	697,836	66.4%
Gynecological disorders[a]	29,837	2.8%
Vaginal bleeding[b]	14,497	1.4%
Cardiovascular and antidiabetic agents	962,346	91.6%
Bleed risk medications[c]	616,093	58.7%
Inhibitors/substrates of cytochrome P450 3A4	690,979	65.8%
Inducers of cytochrome P450 3A4	65,097	6.2%

[a] Adenomyosis, endometrial hyperplasia, endometriosis, gynecological cancers, ovarian cyst, uterine fibroids, uterine or cervical polyp, Von Willebrand's disease;
[b] Vaginal bleed, disorders of menstruation and abnormal bleeding from female genital tract, pre- and post-menopausal bleed;
[c] Aspirin, antiplatelets, prescription nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), heparin, low molecular weight heparin, fondaparinux, cephalosporins

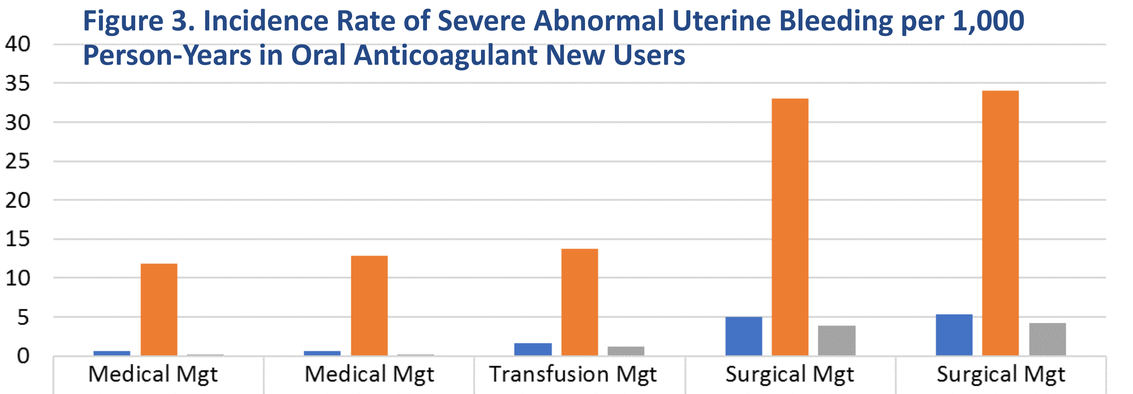
- Of 1,050,192 OA new users, most were 51 years or older and initiated anticoagulation with warfarin
- When stratified by age group, the SAUB incidence rates in reproductive-aged (≤50 years) women were elevated to 11.8, 13.7, and 33.0 per 1,000 person-years for $SAUB_{med}$, $SAUB_{trans}$ and $SAUB_{surg}$ respectively; all estimates were consistently higher than those observed in women of menopausal age (51+ years)
- $SAUB_{surg}$ was notably more common than $SAUB_{med}$ and $SAUB_{trans}$ in all age groups

Figure 2. Incidence of Severe Abnormal Uterine Bleeding per 1,000 Oral Anticoagulant New Users



	Medical Mgt (same day)	Medical Mgt (5 days)*	Transfusion Mgt (same day)	Surgical Mgt (30 days)	Surgical Mgt (60 days)*
All age	0.3	0.3	0.8	2.4	2.5
≤ 50 years	4.6	4.9	5.3	12.5	12.9
51+ years	0.1	0.1	0.6	1.9	2.0

Figure 3. Incidence Rate of Severe Abnormal Uterine Bleeding per 1,000 Person-Years in Oral Anticoagulant New Users



	Medical Mgt (same day)	Medical Mgt (5 days)*	Transfusion Mgt (same day)	Surgical Mgt (30 days)	Surgical Mgt (60 days)*
All age	0.6	0.7	1.7	5.0	5.3
≤50 years	11.8	12.8	13.7	33.0	34.0
51+ years	0.2	0.2	1.2	3.9	4.2

* Sensitivity analysis by varying window allowed for vaginal bleeding management

CONCLUSIONS

- Real-world patients on OA therapy may experience clinically significant, serious adverse gynecologic outcomes
- Our findings are important because medical practitioners should be aware of potential SAUB cases, especially in premenopausal women - a frequently underrepresented subgroup in clinical trials used for new drug approval
- Further studies are warranted to understand the true SAUB risk among OA users and to determine whether the class-wide association exists

CONFLICTS OF INTEREST

- All authors disclose no conflict of interest. This project was supported by Master Agreement HHSF223201400030I from the US Food and Drug Administration
- The views expressed in this presentation are the authors' and do not necessarily reflect the views of the US Food and Drug Administration

ACKNOWLEDGEMENTS

We thank the data partners who provided data or medical records used in the analysis: Aetna, a CVS Health company, Blue Bell, PA; Blue Cross Blue Shield of Massachusetts, Boston, MA; Duke University School of Medicine, Department of Population Health Sciences, Durham, NC, through the Centers for Medicare and Medicaid Services which provided data; Harvard Pilgrim Health Care Institute, Boston, MA; HealthCore, Inc., Translational Research for Affordability and Quality, Alexandria, VA; HealthPartners Institute, Minneapolis, Minnesota; Humana Healthcare Research Inc., Louisville, KY; Kaiser Permanente Colorado Institute for Health Research, Aurora, CO; Kaiser Permanente Center for Integrated Health Care Research Hawai'i, Honolulu, HI; Kaiser Permanente Mid-Atlantic States, Mid-Atlantic Permanente Research Institute, Rockville, MD; Kaiser Permanente Northern California, Division of Research, Oakland, CA; Kaiser Permanente Northwest Center for Health Research, Portland, OR; Kaiser Permanente Washington Health Research Institute, Seattle, WA; Marshfield Clinic Research Institute, Marshfield, WI; Meyers Primary Care Institute, Worcester, MA; 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.