Emergency Visits for Oral Anticoagulant Bleeding

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Bleeding Related to Oral Anticoagulants: US Emergency Department Visits, 2017

INTRODUCTION

Warfarin was the mainstay of outpatient antithrombotic management for decades, but in 2010, direct-acting oral anticoagulants (DOACs) were introduced with fixed dosing and without requirements for laboratory monitoring.[1] Clinical trials suggested lower rates of major bleeding with DOACs than with warfarin.[2, 3] The number of patients prescribed DOACs has been increasing, yet the number treated for emergent DOAC-related bleeding in the USA is unknown.[4]

METHODS

We estimated emergency department (ED) visits for oral anticoagulant-related bleeding using the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, an active public health surveillance system based on a nationally representative, size-stratified probability sample of US hospitals. As described previously, trained abstractors record clinician-diagnosed adverse drug events (ADEs) directly from the medical record.[5] Each NEISS-CADES case is assigned a sample weight based on hospital sampling design and inverse probability of selection. We used the SAS (v9.4) SURVEYMEANS procedure to calculate national estimates of ED visits, with corresponding 95% confidence intervals (CIs), accounting for sample weights and complex sample design. NEISS-CADES data collection is considered public health surveillance and exempted from IRB review.

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National estimates of prescriptions dispensed at outpatient retail and long-term care pharmacies were obtained from the 2017 IQVIA National Prescription Audit (NPA).[5] Rates of ED visits were calculated by dividing the ED visit estimate (from NEISS-CADES) by dispensed prescription estimates (from NPA). Because of the large sample size, the variance of NPA estimates was considered negligible.

RESULTS

Based on 3661 surveillance cases, oral anticoagulant-related bleeding caused an estimated 235,651 (95% CI, 127,032–344,270) ED visits in 2017, accounting for 15.5% (95% CI, 11.7–19.3%) of all ED visits for ADEs. The proportion of visits involving DOACs-related bleeding increased from 2.3% (95% CI, 0.9–3.7%) in 2011 to 37.9% (95% CI, 32.7–43.1%) in 2017 (Fig. 1). In 2017, 49.3% of DOAC-related bleeding visits involved rivaroxaban, 41.8% involved apixaban, and 8.9% involved dabigatran (Table 1).

In 2017, approximately one-half (51.1%) of oral anticoagulant prescriptions filled in outpatient retail and long-term care pharmacies were for DOACs. Accounting for prescribing frequency, in 2017, the estimated rate for DOAC-related bleeding was 55.3 (95% CI, 24.9–85.7) and for warfarin-related bleeding, 94.7 visits per 10,000 dispensed prescriptions (95% CI, 54.7–134.7).

There were no statistically significant differences in patient sex or age among visits for DOACs compared with warfarin. Adults aged ≥ 65 years were involved in 80.1% of ED visits for DOAC-related bleeding and 77.3% of ED visits for warfarin-related bleeding. Among adults aged ≥ 65 years, DOAC-related bleeding contributed to 11.8% (95% CI, 9.1–14.5%) of ED visits for ADEs from all drugs, while warfarin-related bleeding contributed to 18.6% (95% CI, 15.7–21.5%). A nominally higher proportion of DOAC bleeding visits involved gastrointestinal bleeding or epistaxis compared with warfarin, and a nominally lower proportion involved central nervous system bleeding, but differences were not statistically significant (Table 1). A similar proportion of bleeding visits resulted in hospitalization for both DOACs and warfarin (51.1% vs. 47.3%).

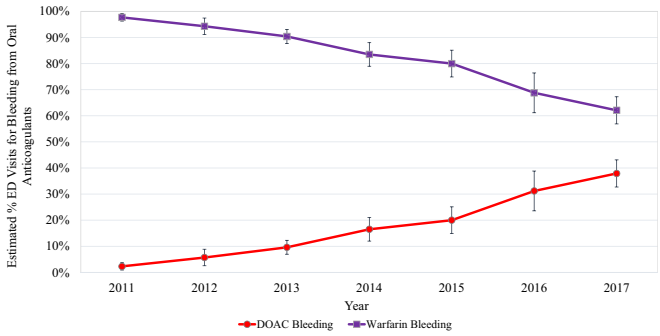

Figure 1 US emergency department visits for oral anticoagulant-related bleeding, by year, 2011–2017. Estimates from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project, CDC. Excludes *n* = 40 cases implicating both warfarin and a DOAC (2011, *n* = 2 cases; 2013, *n* = 3 cases; 2014, *n* = 7 cases; 2015, *n* = 8 cases; 2016, *n* = 9 cases; 2017, *n* = 11 cases). DOAC, direct-acting oral anticoagulant.

DISCUSSION

Despite the introduction of a new class of agents with lower rates of major bleeding in clinical trials, anticoagulant-related harm continues to contribute to a large proportion of US ED visits for adverse drug events. Although the rate of DOAC-related bleeding is nominally lower than the rate for warfarin, DOACs are implicated in nearly 40% of estimated visits for oral anticoagulant-related bleeding, with hospitalization rates comparable with those for warfarin. With further increases in DOAC use, DOAC-related bleeding will likely continue to increase in the future, unless prevention approaches are adopted.

Anticoagulants are essential for the prevention and treatment of thromboembolic disorders and not all anticoagulant-related bleeding is preventable; however, lessons learned from decades of addressing warfarin-associated bleeding suggest that there may be similar opportunities for DOACs, particularly among older adults who are most vulnerable to anticoagulant ADEs. Future studies could identify a subset of patients who would benefit from specialized management.[6]

These data likely underestimate the number of oral anticoagulant-related bleeds because only events diagnosed and treated in EDs are included. Additionally, events

Table 1 US Emergency Department Visits for Oral Anticoagulant-Related Bleeding, by Case Characteristics, 2017

Case characteristic	ED visits for bleeding					
	DOAC			Warfarin		
	Cases (no.)	National estimate		Cases (no.)	National estimate	
		%	(95% CI)		%	(95% CI)
Patient age group (years)						
0–17	0	~	~	5	~	~
18–34	18	~	~	39	1.2	(0.6–1.8)
35–49	66	4.5	(3.0–5.9)	103	4.9	(3.9–5.9)
50–64	221	14.4	(12.4–16.5)	367	16.4	(13.7–19.2)
65–79	600	44.7	(40.9–48.5)	863	40.1	(37.3–42.9)
80+	522	35.4	(31.0–39.8)	846	37.2	(33.5–41.0)
Patient sex						
Female	712	48.8	(44.0–53.6)	1019	45.9	(42.9–48.9)
Male	715	51.2	(46.4–56.0)	1204	54.1	(51.1–57.1)
Drug*						
Rivaroxaban	696	49.3	(42.3–56.3)			
Apixaban	617	41.8	(36.5–47.0)			
Dabigatran	113	8.9	(3.7–14.2)			
Bleeding manifestation†						
Central nervous system bleeding‡	79	4.3	(2.3–6.3)	131	5.3	(4.0–6.7)
Pulmonary bleeding	41	2.6	(1.6–3.7)	65	3.1	(1.3–4.9)
Gastrointestinal bleeding	522	40.2	(30.5–50.0)	649	29.7	(23.9–35.6)
Genitourinary bleeding	123	9.1	(5.4–12.8)	189	9.0	(5.8–12.1)
Epistaxis	252	21.2	(13.1–29.3)	390	19.6	(14.6–24.6)
Skin/wound or other minor bleeding	303	17.6	(9.6–25.6)	610	25.8	(18.0–33.5)
Other types of hemorrhage	107	4.9	(2.1–7.7)	189	7.5	(5.5–9.5)
Discharge disposition						
Admitted/transferred to another facility	736	48.9	(39.6–58.1)	1,063	45.5	(37.8–53.1)
Observation admission	31	2.2§	(0.0–4.5)	47	1.9§	(0.4–3.3)
Not hospitalized‖	660	48.9	(40.7–57.0)	1113	52.7	(45.5–59.9)
Total	1427			2223		

Case counts and national estimates are from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project, CDC. Estimates based on < 20 cases are considered statistically unstable and are not shown (~). Excludes n = 11 cases in which both a DOAC and warfarin were implicated in the ED visit

DOAC direct-acting oral anticoagulant, CI confidence interval

**Not shown: n = 1 case involving edoxaban-related bleeding*

†Bleeding manifestations are mutually exclusive and were assigned hierarchically. For example, an ED visit in which a patient experienced both hematemesis and hematuria while on an anticoagulant would be categorized as gastrointestinal bleeding

‡Includes epidural or subdural hematoma, hemorrhagic stroke, and intracerebral or subarachnoid hemorrhage

§Coefficient of variation > 33%

‖Defined as treated and released, or left without being seen/left against medical advice

involving anticoagulants without overt bleeding (e.g., elevated international normalized ratio levels) and fatalities were not included. These data cannot be used for direct comparisons among agents and additional data which may be used for risk adjustment (e.g., current medical comorbidities) are incomplete based on ED documentation.

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Author Contributions *Dr. Geller had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.*
Study concept and design: Geller, Shehab, Budnitz
Acquisition of data: all authors
Analysis and interpretation of data: all authors
Drafting of the manuscript: Geller, Shehab, Budnitz
Critical revision of the manuscript for important intellectual content: all authors
Statistical analysis: Geller
Administrative, technical, and material support: all authors
Study supervision: Geller, Shehab, Budnitz

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Compliance with Ethical Standards:

Federal government employees led or participated in all aspects of the project, including design and conduct of the project; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The findings and conclusions in this study are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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