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Full Length Article

Healthcare resource utilization and costs among patients with direct oral anticoagulant or warfarin-related major bleeding

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ABSTRACT

Introduction: Direct oral anticoagulants (DOACs) have expanded the options for antithrombotic therapy. DOAC-related major bleeds are associated with favorable outcomes compared to warfarin in clinical trials and routine practice. However, it is unclear whether management of DOAC-associated major bleeding incurs higher resource utilization and costs.

Materials and methods: We screened medical records of patients ≥ 66 years with atrial fibrillation admitted to one of five tertiary care hospitals in Ontario, Canada with a hemorrhage. We abstracted bleeds involving DOACs or warfarin and linked them to administrative databases to capture length of hospital stay, blood product use, procedural interventions, intensive care unit (ICU) utilization and related direct medical costs. To control for confounders, multivariate logistic and linear regressions were used for binary and linear outcomes respectively.

Results: Among 19,061 records screened, 1978 (10.4%) cases involving 1632 patients met criteria of oral anticoagulant-associated bleeding. Baseline characteristics between DOAC and warfarin groups were similar. Blood product costs were higher for DOACs (all comparisons DOACs vs. warfarin, $1456 vs. $1109, mean difference $347, 95% CI $185 to $509), but length of stay and ICU use were similar. Mean direct medical costs did not differ ($9217 vs. $10,790, adjusted relative ratio 0.94, 95% CI 0.84–1.05).

Conclusions: Prior to introduction of DOAC-specific reversal agents, resource utilization and medical costs were comparable between DOAC- and warfarin-associated major bleeds, despite marginally higher blood product costs incurred by the former. Resource intensity associated with anticoagulant-related bleeding remains high, and our data provide measures for cost-effectiveness evaluation of emerging DOAC antidotes.

Atrial fibrillation (AF) affects approximately 33 million individuals worldwide, and is a major risk factor for ischemic stroke [1]. Over 20% of ischemic strokes are associated with AF [2], and these events are associated with higher mortality and residual functional deficits compared to non-AF strokes [3,4]. Annual costs associated with treatment of AF account for 1% of the National Health Service budget in the

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United Kingdom [5]; in the United States, estimates range from $6 to $26 billion annually [6].

While anticoagulants form the cornerstone of stroke prevention in patients with AF, they also constitute the drug class with highest rates of hospitalizations due to adverse events among those aged 65 years and above [7,8]. Warfarin has been the standard of care in AF-related anticoagulation in the past 5 decades and is highly effective [9]; however, direct medical costs of warfarin-associated bleeds are estimated at $11,000 per episode [10]. The advent of direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban and edoxaban represents an expansion of the clinical armamentarium for stroke prevention [11]. Nonetheless, healthcare resource utilization and direct costs of DOAC-related major bleeding are unknown, and comparisons to a contemporaneous warfarin cohort have not been undertaken. Furthermore, while the regulatory approval of idarucizumab and andexanet alfa have addressed the irreversibility of DOACs, these antidotes were evaluated in single-arm studies without comparator groups [12,13]. Given acquisition costs of up to $49,500 U.S. per dose [14], health economic analyses from the management of DOAC-associated major bleeding in the pre-tidote era provide crucial baseline data to identify situations where cost-effectiveness afforded by specific reversal agents are greatest.

Using the Bleeding Effected by Direct Oral Anticoagulants (BLED-AC), a multi-centre cohort involving comprehensive chart review with subsequent administrative data linkage, we demonstrated lower in-hospital mortality associated with DOAC-associated major bleeding in the real-world setting [15]. In this study, we sought to determine healthcare resource use and direct medical costs in the treatment of patients presenting with DOAC-related major bleeds, and to compare them to those of warfarin.

1. Methods

We conducted a retrospective cohort study of patients diagnosed with atrial fibrillation who experienced anticoagulant-related major bleeding using data from the BLED-AC cohort [15]. In the study, hospital medical records were used to identify all cases of oral anticoagulant-associated bleeds involving individuals aged ≥ 66 years presenting to one of five tertiary care hospitals across three cities in Ontario, Canada, with a combined catchment area of approximately 4 million residents. The study spanned October 2010 to March 2015 to correspond with Health Canada's approval for dabigatran, the first DOAC to enter the market for stroke prophylaxis in patients with atrial fibrillation [16]. This study was conducted from the public healthcare system's perspective. All costs were expressed in 2017 Canadian dollars. The study was approved by the research ethics boards at all institutions involved, as well as the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada.

We defined a case of oral anticoagulant-related major bleed as 1) presentation to hospital with documented bleeding; and 2) with use of an oral anticoagulant (warfarin, dabigatran, rivaroxaban or apixaban) within 3 days of presentation; and 3) with documented diagnosis of atrial fibrillation or flutter; and 4) fulfilling one of the following criteria:

a. International Society on Thrombosis and Haemostasis major bleeding definition components (hemoglobin drop ≥ 2 g/dL, involvement of a critical organ [intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome], or fatal bleed) [17]; or
b. transfusion of blood products or use of a specific reversal agent; or
c. resulting in hospitalization.

Exclusion criteria entailed initial hospital presentation that did not involve hemorrhage (biochemical coagulopathy without signs, symptoms or diagnosis of bleeding; bleeding that began in hospital; or peri-procedural anticoagulant bridging); and history of prosthetic heart valve (mechanical or bioprosthetic) given DOAC indications.

1.1. Data sources

We undertook a comprehensive chart review using electronic medical records housed at health records and decision support departments of participating Ontario hospitals. First, charts were identified using a validated computerized algorithm of hospital discharge diagnoses [18]. These cases were then screened manually for use of oral anticoagulation within 3 days of hospital presentation, as well as key exclusion criteria based on available chart data. Thereafter, clinical data from eligible charts were abstracted manually to obtain baseline vital signs, laboratory investigations, type and dose of oral anticoagulant, concomitant medications and blood product data. Validation of chart abstraction across sites demonstrated agreement on all data fields at 98%, representing high-quality data [19].

We then linked the clinical data to healthcare utilization and cost databases housed at the Institute for Clinical Evaluative Sciences (ICES). The linking of databases was performed using a combination of treatment centre code (assigned to each hospital in Ontario by Ministry of Health and Long-Term Care) and medical record number through deterministic linkage, with cross-validation by date of birth and date of admission to identify false linkages. ICES is an independent, non-profit organization funded by the Ontario Ministry of Health and Long-Term Care that links de-identified population-based health information at the individual level.

Four ICES databases were used: the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD: all visits to acute and rehabilitation institutions); National Ambulatory Care Reporting System (NACRS: all emergency department visits); Ontario Case Costing Initiative (OCCI: inpatient direct medical costs); and Ontario Health Insurance Plan (OHIP: physician services and billing). The CIHI-DAD provided comorbid medical conditions not captured in chart review, the number of bleeding-related hospitalizations within 5 years, length of stay (total acute length of stay and those involving the intensive care unit) and intervention codes for each case. CIHI-NACRS was used to determine length of visit for cases presenting to the emergency department. Costs were derived from the OCCI database, which uses hospital Management Information Systems (MIS) method to collect and assign costs at the individual patient level. OCCI tracks costs of services incurred by patients during a hospital visit based on the hospital's production model [20,21]. The model shows how inputs (labour, equipment) are used to produce outputs (nursing, services, tests, radiographic investigations) for the patient. Through OCCI, service costs are estimated and distributed to each patient, such that these costs reflect patient specific costs. In sum, OCCI was used to determine direct medical costs (e.g., nursing, laboratory, transfusion medicine, pharmacy, imaging) associated with inpatient hospitalizations and emergency room visits. All hospitals included in the study participate in the OCCI. OCCI data do not include physician payments, which were captured by the OHIP database.

The quality of data generated by individual hospital decision support units and captured in CIHI-DAD and CIHI-NACRS has been assessed through data re-abstraction and inter-rater reliability studies by the Canadian Institute for Health Information. Agreement on codes representing Most Responsible Diagnosis (used for determination of comorbid conditions) in Ontario was 86% [22]. Data quality of CIHI-NACRS has been assessed through data re-abstraction and inter-rater reliability studies in 2004–2005. For the variable pertaining to main diagnosis, agreement was 86% in the re-abstraction study and 90% in the inter-rater reliability study [23].

1.2. Outcomes

The primary study outcome was healthcare utilization in the form of total acute length of stay (LOS) from the index date (defined as date of initial hospital encounter with hemorrhage), including days within an intensive care unit. Acute LOS included time in the emergency department and inpatient unit and excluded time spent in alternate level of care, defined as bed occupancy by patients who no longer need acute services and awaiting discharge to a not-yet available lower care acuity bed (e.g., community care with supports or long-term care) [24]. Secondary analyses included blood product costs, procedural interventions (codes derived from Canadian administrative study involving warfarin) [25], direct medical costs, hospital spending, and physician cost.

1.3. Statistical analysis

We presented continuous data as a mean and standard deviation or a median with interquartile range (IQR). Dichotomous data were presented as percentages. Differences across DOAC- and warfarin-related bleeds on baseline parameters were compared using standardized differences, an approach frequently used in observational studies; values > 0.1 are generally considered meaningful [26]. To compare LOS and costs between DOAC and warfarin cohorts, we used multivariate linear regression, adjusting for covariates determined a priori. These included age, chronic kidney disease (CKD) status, CHA_2DS_2-VASc and HAS-BLED components (hypertension, congestive heart failure, diabetes, stroke or transient ischemic attack, abnormal liver function, drugs or alcohol use), number of previous admissions for bleeding, and co-morbid disease burden (Charlson comorbidity index). The use of administrative databases for identifying these covariates have been validated [27–30]. Unit blood product costs were derived from published Ontario data [31]. Direct medical costs were composite of hospital spending (including transfusion costs) and physician costs.

Because of the skewed distribution of LOS and cost variables, these were log-transformed for the linear regression. Regression coefficient (on the log scale) and corresponding 95% confidence intervals (CI) were then exponentiated to calculate the relative ratio between the two groups. Rates of dichotomous data, including procedural interventions and rates of intensive care admissions were compared using multivariable logistic regression. In order to account for multiple events representing recurrent bleeds during the study period, sensitivity analysis was performed for each outcome by restricting the regression model to cases with no emergency room presentation or hospital admission for bleeding within 30 days following the index date. Cells with sample sizes of five or less were suppressed to prevent risks of re-identification. A type 1 error rate of 0.05 was used as a threshold for statistical significance. All analyses were completed using SAS Statistical Software (version 9.4, Cary, North Carolina).

2. Results

During the study period, we identified and screened 19,061 consecutive cases with diagnoses of hemorrhage through medical records. Of these, 1978 cases involving 1632 patients were eligible for inclusion in this study (Fig. 1).

Average age was 81, and mean CHA_2DS_2-VASc score was 4.4 with no difference between the DOAC and warfarin cohorts. However, higher proportion of warfarin-treated patients had a documented diagnosis of chronic kidney disease (standard difference 0.29, Table 1). Intracranial hemorrhages comprised 21% of DOAC-associated major bleeds compared to 30% among warfarin cases (standard difference 0.20), while 62% and 42% (standard difference 0.39) of DOAC and warfarin major bleeds involved the gastrointestinal tract.

There was no difference in Charlson comorbidity, median number of physician visits, hospitalizations and emergency department visits in the 2 years prior to the index date between cases of DOAC and warfarin-associated major bleeding (standard difference ≤ 0.10 across all comparisons, Table 1).

Blood product costs and procedural utilization

Average cost of blood products was $1456 ± 1482 for DOACs and $1109 ± 1568 for warfarin, accounting for a mean cost difference of $347 favoring warfarin (95% CI $185 to $509). Among DOAC bleeds, more than half of blood product costs were attributable to use of packed red blood cells, followed by activated prothrombin complex concentrates (Fig. 2). Among warfarin bleeds, packed red blood cells and prothrombin complex concentrates accounted for 89% of blood product costs (Fig. 2).

Among major bleeds involving the gastrointestinal tract, 69.4% of DOAC cases and 64.5% of warfarin cases required endoscopic procedures (adjusted relative ratio 1.27, 95% CI 0.94–1.73). Among intracranial hemorrhages, procedural interventions were required in 30.9% and 36.3% of DOAC and warfarin cases, respectively (adjusted relative ratio 0.84, 95% CI 0.51 to 1.36).

2.1. Length of stay

Average acute LOS was 8.1 ± 7.7 days in the DOAC cohort compared to 10.0 ± 13.0 days in the warfarin group (Table 2). After adjusting for covariates, there was no significant difference in length of stay between DOAC- and warfarin-associated major bleeds (adjusted relative ratio 0.94, 95% CI 0.85–1.03).

2.2. Intensive care unit (ICU) utilization

ICU utilization was similar between DOAC and warfarin cohorts (27.7% vs. 29.0%, adjusted odds ratio 0.95, 95% CI 0.74–1.22). No difference was found in average ICU LOS between the two groups (Table 3).

2.3. Healthcare costs

Mean direct medical costs were $9217 ± 12,771 for treatment of DOAC-associated major bleeds and $10,790 ± 18,130 for warfarin-associated major bleeds. Corresponding median direct medical costs were $5237 (IQR $2866 to $9566) and $5544 (IQR $3068 to $11,136) respectively. After adjusting for covariates, differences between the two groups were not statistically significant (adjusted relative ratio 0.94, 95% CI 0.84–1.05, Table 3). Similar findings were noted when we separately compared hospital and physician costs between the DOAC and warfarin cohorts (Table 3).

Within DOACs, direct medical costs were similar for treatment of dabigatran-associated major bleeding compared to those accrued by anti-Xa inhibitors rivaroxaban and apixaban. Furthermore, no difference was observed when treatment costs were compared across individual DOACs (Supplemental Table 1).

2.4. Sensitivity analysis

Regression analysis restricted to cases with no hospitalization records for bleeding within 30 days of index date demonstrated similar findings to results of the main outcomes. Notably, adjusted beta-coefficients for length of stay, costs, as well as adjusted odds ratios for intensive care and procedural interventions were similar between the DOAC and warfarin groups (Supplemental Table 2).

3. Discussion

Among over 1900 cases of major bleeding related to oral anticoagulants, we found no difference between DOAC- and warfarin-associated bleeding with respect to overall length of stay, requirement for ICU monitoring or total medical costs, despite different anatomical patterns of bleeding at presentation. While blood product costs were higher to manage DOAC-associated hemorrhage, the absolute difference was small and did not alter comparisons of total medical costs.

There is a lack of data comparing healthcare resource utilization

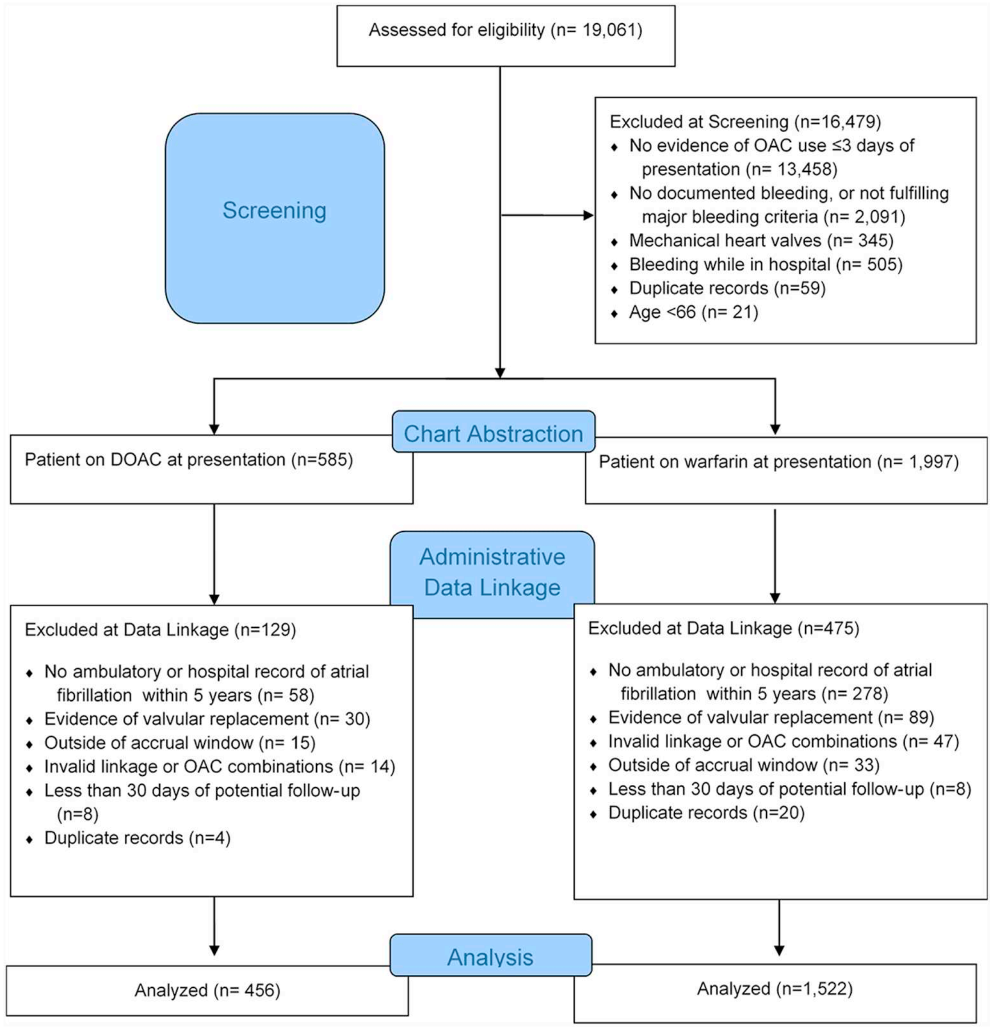

Fig. 1. Flow diagram of included and excluded participants.

and case-specific medical costs associated with management of DOAC- and warfarin-associated major bleeding. Our results are consistent with those observed by Amin et al., who used U.S. Medicare database to compare major bleeding-associated medical costs from 2012 to 2014 between DOACs and warfarin on a per-patient, per-month basis [32]. They found similar or lower monthly costs attributable to major bleeding among DOAC users compared to warfarin users, but they did not include blood product costs, use of ICU or per-episode total medical costs of anticoagulant-associated hospitalizations or emergency department visits in their analysis. Our results are also comparable to data from randomized trials: in the post-hoc analysis of major bleeding in the RE-LY trial, average LOS of 8.4 days and 8.9 days were reported respectively for dabigatran- and warfarin-associated major bleeds [33]. Similarly, median LOS of rivaroxaban and warfarin major bleeds in the ROCKET-AF trial were 5 days and 6 days respectively [34].

Despite prohemostatic agents with high unit costs suggested in the management of severe DOAC-associated bleeding, similar medical costs accrued between DOAC and warfarin groups in our analysis. Several factors likely contributed to this outcome. First, packed red blood cells compromised > 50% of blood product costs in both groups, while supportive measures with bleeding source control spared the use of activated prothrombin complex concentrates and recombinant factor VIIa to < 10% in the DOAC cohort [15]. On the other hand, guideline-concordant use of prothrombin complex concentrates was high among patients presenting with warfarin-associated bleeds [15,35], which increased blood product costs in the warfarin arm. Taken together, this resulted in lower than expected difference in blood product costs. Furthermore, intracranial hemorrhages were seen less frequently among DOAC-associated bleeds in comparison to warfarin [11], thereby reducing the requirement for resource-intensive neurocritical care in the DOAC arm [36]. Though gastrointestinal bleeds were higher in the DOAC cohort with 69% undergoing interventions, resource intensity of endoscopy is markedly less than that of neurosurgical procedures [37].

In our study, more than one in four cases of major hemorrhage required advanced monitoring in an ICU. Procedural interventions were frequently used in gastrointestinal and intracranial hemorrhages, and mean direct medical costs were roughly twice the jurisdictional average ($5346) over the same period [38]. The intensity of care required to manage patients presenting with oral anticoagulant-associated bleeding seen in our study is mirrored by other post-marketing studies to date. In an observational study of 478 rivaroxaban-associated major bleeding events identified by administrative database of the United States (U.S.) military service members and their families, ICU monitoring was required in 43% of cases, with 1 in 4 cases requiring surgical intervention [39]. Similarly, in a single-centre retrospective review of oral anticoagulant-associated bleeds presenting to a U.S. emergency department from 2012 to 2015, 49% of 95 DOAC- and 342 warfarin-associated bleeds were admitted to the ICU [40].

Using this cohort, we previously reported a 5.4% absolute risk difference in inpatient mortality from major bleeding favoring DOACs (9.8% vs. 15.2%) [15]. Taken together with post-marketing data

Table 1
Characteristics of DOAC- and warfarin-associated major bleeding events.

	DOAC (n = 456)		Warfarin (n = 1522)	Standardized difference
Age (mean ± SD)	81.2 ± 7.0		81.2 ± 7.1	0.01
Female (%)	178 (39.0)		617 (40.5)	0.03
DOAC agent	Dabigatran	243	NA	NA
	220 mg (%)	154 (63.3)		
	300 mg (%)	64 (26.3)		
	NR/other (%)	25 (10.3)		
	Rivaroxaban	156		
	10 mg (%)	8 (5.1)		
	15 mg (%)	68 (43.6)		
	20 mg (%)	65 (41.7)		
	NR/other (%)	15 (6.2)		
	Apixaban	59		
	5 mg	34 (57.6)		
	NR/other (%)	25 (42.4)		
Charlson comorbidity				
0	85 (18.6%)		254 (16.7%)	0.05
1	87 (19.1%)		234 (15.4%)	0.10
2+	212 (46.5%)		746 (49.0%)	0.05
No hospitalizations	72 (15.8%)		290 (19.0%)	0.09
CHA_2DS_2-VASC SCORE				
Mean (95% CI)	4.4 (4.3, 4.5)		4.5 (4.4, 4.5)	0.08
HAS-BLED score				
Mean (95% CI)	2.7 (2.6, 2.8)		2.8 (2.7, 2.8)	0.08
Chronic kidney disease (%)				
Yes	69 (15.1%)		408 (26.8%)	0.29
Previous warfarin use (%)				
Yes	133 (29.2%)		NA	NA
Previous bleeds (%)				
Past 30 days	51 (11.2)		144 (9.4)	0.06
Past 90 days	69 (15.1)		230 (15.1)	0
Healthcare encounters over past year				
Physician visits (median [IQR])	25 (15–35)		25 (15–36)	0.02
Hospitalizations (median [IQR])	1 (0–2)		1 (0–2)	0.1
Emergency department visits (median [IQR])	3 (1–5)		3 (1–5)	0.04
Site of bleeding[a]				
Intracranial hemorrhage	97 (21.3%)		455 (29.9%)	0.20
Epidural	0 (0.0%)		≤5 (≤0.3%)	NA[b]
Intraparenchymal	23 (5.0%)		124 (8.1%)	0.12
Intraventricular	6 (1.3%)		34 (2.2%)	0.07
Subarachnoid	34 (7.5%)		93 (6.1%)	0.05
Subdural	61 (13.4%)		290 (19.0%)	0.15
ICH - NOS	0 (0.0%)		9 (0.6%)	0.11
Gastrointestinal	281 (61.6%)		646 (42.4%)	0.39
Upper GI	100 (21.9%)		297 (19.5%)	0.06
Lower GI	141 (30.9%)		264 (17.3%)	0.32
GI - NOS	41 (9.0%)		87 (5.7%)	0.13
Hematoma without compartment syndrome	8 (1.8%)		82 (5.4%)	0.20
Hemarthrosis	0 (0.0%)		15 (1.0%)	0.14
Intramuscular with compartment syndrome	0 (0.0%)		≤5 (≤0.3%)	NA[b]
Retroperitoneal	≤5 (≤0.2%)		20 (1.3%)	NA[b]
Pericardial	≤5 (≤0.2%)		≤5 (≤0.1%)	NA[b]
Hematuria	42 (9.2%)		210 (13.8%)	0.09
Epistaxis	≤5 (≤0.9%)		41 (2.7%)	NA[b]
Hemoptysis	18 (3.9%)		54 (3.5%)	0.02
Pulmonary	≤5 (≤0.7%)		11 (0.7%)	NA[b]
Vaginal	≤5 (≤0.4%)		11 (0.7%)	NA[b]
Other	≤5 (≤1.1%)		11 (0.7%)	0.08
Unknown	≤5 (≤0.9%)		7 (0.5%)	NA[b]

Abbreviations: NA, not applicable; NR, not recorded on chart; ICH, intracranial hemorrhage; NOS, not otherwise specified; DOAC, direct oral anticoagulant; IQR, interquartile range; GI, gastrointestinal.
Notes:
[a] Sites of bleeding are not mutually exclusive.
[b] In accordance with ICES privacy policies, in cases where the number of total users is ≤5, this number has been suppressed to ensure confidentiality. In these cases, related percentages were reported using n ≤ 5. In cases where there is only one record being suppressed, the other record with lowest value has been suppressed as well in order to avoid residual disclosure issues.

demonstrating similar or lower incidence of hemorrhagic complications compared to warfarin [41], our current results provide further signals of safety for this class of agents. With advent of drug-specific reversal agents idarucizumab and andexanet alfa that were approved based on single-arm studies without use of comparator groups [12,13], our resource utilization data from the pre-tidote era with stratification by DOAC type (dabigatran vs. factor Xa inhibitors) will help inform cost-effectiveness analysis to guide the appropriate use of these new agents. Our results also are applicable to health systems in which implementation of DOAC reversal agents are not yet possible due to regulatory approval or high acquisition costs [14,42].

The main strength of our study is the inclusion of standardized

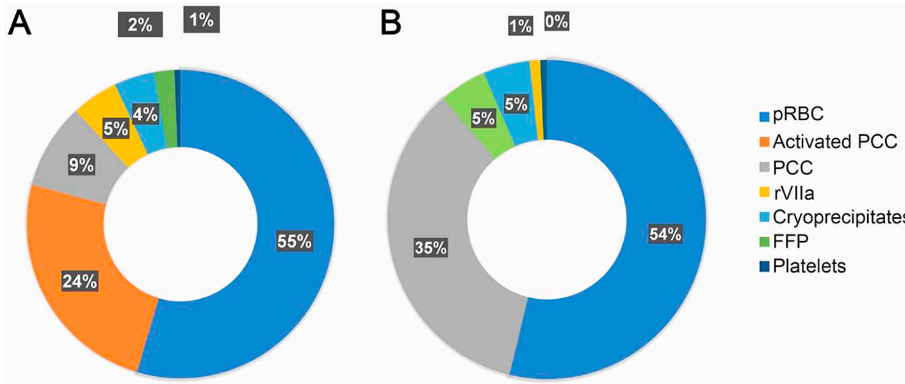

Fig. 2. Distribution of blood product costs for management of major bleeding associated with DOACs (A) and warfarin (B). pRBC, packed red blood cells; PCC, prothrombin complex concentrates; rVIIa, recombinant factor VIIa; FFP, fresh frozen plasma.

Table 2
Total length of stay, rate of ICU utilization and ICU length of stay.

	Unadjusted		Regression-adjusted
	DOACs N = 456	Warfarin N = 1522	DOAC vs. warfarin (95% CI)
Total LOS excl. ALC (days)	Mean (SD) = 8.1 (7.7) Median (IQR) = 5.4 (3.3, 9.5)	Mean (SD) = 10.0 (13.0) Median (IQR) = 6.0 (3.4, 11.0)	0.94 (0.85, 1.03)[a]
ICU utilization (%)	27.7	29.0	0.95 (0.74, 1.22)[b]
ICU LOS (days)	Mean (SD) = 5.2 (5.2) Median (IQR) = 3.4 (2.0, 6.9)	Mean (SD) = 4.7 (6.1) Median (IQR) = 2.9 (1.6, 5.8)	1.13 (0.90, 1.43)[a]

SD, standard deviation; IQR, interquartile range.
[a] Adjusted relative ratio by multivariate linear regression.
[b] Adjusted odds ratio by multivariate logistic regression.

Table 3
Direct medical cost per episode of major bleeding.

	Unadjusted		Regression-adjusted
	DOACs ($) N = 456	Warfarin ($) N = 1522	DOAC vs. warfarin Adjusted relative ratio (95% CI)
Physician cost	Mean (SD) = 1918 (2622) Median (IQR) = 1194 (668, 1961)	Mean (SD) = 1936 (2572) Median (IQR) = 1178 (645, 2158)	1.02 (0.90, 1.16)
Hospital cost	Mean (SD): 7190 (10416) Median (IQR) = 3953 (2166, 7363)	Mean (SD) = 8627 (16035) Median (IQR) = 4127 (2114, 8753)	0.97 (0.86, 1.10)
Total cost	Mean (SD) = 9217 (12771) Median (IQR) = 5237 (2866, 9566)	Mean (SD) = 10,790 (18130) Median (IQR) = 5544 (3068, 11,136)	0.94 (0.84, 1.05)

SD, standard deviation; IQR, interquartile range.

costing methods used to directly measure accrued medical costs, enabling accurate cost comparisons between DOAC- and warfarin-associated cases. As treatment cost of major bleeding is an important modifier of cost-effectiveness involving oral anticoagulants [43], healthcare utilization and direct medical costs specifically attributable to DOACs and warfarin will provide considerable precision to pharmacoeconomic analyses. However, there are limitations. First, inclusion of cases for cost comparison was restricted to those admitted prior to April 2012 due to data availability. However, included cases comprised half of total study cases, and there was no selective exclusion of DOAC- or warfarin-associated cases. In addition, the observational design of our study precluded controlling for confounders that are not captured in our databases. Nonetheless, rates of previous bleeding at baseline were similar between the groups, raw and adjusted outcomes were consistent with each other and data from trials, and sensitivity analyses did not alter our results. Finally, our study only included acute inpatient care costs; therefore costs related to rehabilitation, assistive devices and home care were not part of this analysis.

In conclusion, we observed high healthcare resource utilization in forms of LOS, intensive care utilization and direct medical costs in a large unselected cohort of patients presenting with anticoagulant-associated hemorrhage in routine practice. However, there was no difference between those presenting with DOAC- or warfarin-associated bleeds. Our findings provide useful baseline benchmark to assess the cost-effectiveness implications of drug-specific reversal agents in the healthcare system.

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Disclaimer

The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.07.026.

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