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Management of Acute Venous Thromboembolism Amongst Patients Discharged from Hospital

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ABSTRACT:

Objective: To determine anticoagulant therapy at hospital discharge for patients with acute venous thromboembolism (VTE) and secondarily, to describe factors affecting choice of therapy.

Design: A retrospective chart review.

Setting: Hospitals in Edmonton, Alberta (N=4), Regina, Saskatchewan (N=2) and rural Alberta (N=3) from April 2014 to March 2015.

Participants: All patients discharged with an acute VTE were screened. Those with atypical clots, another indication for anticoagulation, pregnancy/breastfeeding or lifespan < 3 months were excluded.

Interventions: None.

Primary and secondary outcomes: Primarily, we identified the proportion of patients discharged from hospital with acute VTE that were prescribed either traditional therapy (parenteral anticoagulant ± warfarin) or a direct acting oral anticoagulant (DOAC). Secondarily, management based on setting, therapy choice based on DVT versus PE, clot burden and renal function was compared. DOAC dosing was assessed (when prescribed), length of hospital stay based on therapy was compared, and planned follow-up in the community was described.

Results: Amongst the 695 patients included, most were discharged following a diagnosis of PE (82.9%) on traditional therapy (parenteral anticoagulant +/- warfarin) (70.2%) with follow-up by either a family doctor (51.5%) or specialist/clinic (46.9%) post-discharge. Regional variation was most evident between urban and rural sites. Of those prescribed a DOAC (28.3%), the majority were dosed appropriately (85.8%). DOAC use did not differ between those with DVT and PE, was proportionately higher for less severe clots, and declined with worsening renal function. Patients prescribed DOACs vs traditional therapy had shorter length of stays (4 versus 7 days, respectively).

Conclusions: Uptake of DOAC therapy for acute VTE was modest and may have been influenced by the timing of the audit in relation to the approval of these agents for this indication. Future audits should occur to assess temporal changes and ongoing appropriateness of care delivery.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study consists of a large cohort of patients discharged with acute DVT or PE from 2 urban areas and 3 rural sites throughout an entire year, thereby providing a good reflection of practice patterns.
- All patient charts were reviewed for inclusion, thereby enabling accurate data capture of the acute VTE population.
- Although this audit occurred early in the licensing of DOACs for VTE, these data offer a benchmark for future usage as guidelines more aggressively incorporate the utilization of DOACs in this population.
- Given our study design, we were not able to collect data for patients following discharge from hospital, thereby prohibiting the assessment of patient outcomes.

FUNDING STATEMENT

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COMPETING INTEREST STATEMENT

TJB has received honoraria for an advisory board for BMS-Pfizer and Boehringer Ingelheim, as well as honoraria for speaking from Bayer. TJB has received unrestricted grants from Pfizer and Bayer. BR has served on advisory boards, given sponsored lectures using his own slides and received travel expense remuneration for Bayer, Baxter, Beohringer-Ingelheim, CSL-Behring, Pfizer, Sanofi, Servier and Shire. In lieu of honoraria for these activities, the companies have given financial contributions to the University of Alberta. BR reports grants from Novo Nordisk, CSL-Behring and Baxter, all outside of this submitted work. JB has received speaker honoraria from Boehringer Ingleheim in the past two years. WS has

received honoraria from Bayer, Pfizer, Bristol Myers Squibb and Boehringer Ingleheim. He has served as a consultant or on an Advisory Board for Bayer and Pfizer/Bristol Myers Squibb and he has received an unrestricted research grant from Pfizer.

INTRODUCTION

After over half a century of vitamin K antagonists as the only available oral anticoagulant therapy, several direct oral anticoagulants (DOACs) have been approved within the past 5 years for the acute treatment of venous thromboembolism (VTE).[1-4] The DOACs (rivaroxaban, dabigatran, apixaban and edoxaban) offer advantages over the traditional therapy of an injectable anticoagulant (typically low molecular weight heparin [LMWH]) overlapped with warfarin.[5] Unlike warfarin therapy, all DOACs have standardized dosing regimens that lack the need for routine coagulation monitoring and offer a therapeutic effect within hours of administration. Rivaroxaban and apixaban do not require initial therapy with an injectable anticoagulant, further streamlining care delivery. Given this, the purpose of this study was to describe the management of acute VTE amongst patients discharged from hospitals within the Edmonton, Alberta and Regina, Saskatchewan areas as well as rural Alberta. Specifically, we sought to determine the anticoagulant therapy provided at hospital discharge for acute VTE and secondarily, to examine factors which may have influenced the therapy prescribed.

METHODS

Setting and Patients

A retrospective chart review was conducted at the 4 largest hospitals in Edmonton, Alberta (University of Alberta Hospital, Royal Alexandra Hospital, Misericordia Hospital, Grey Nuns Hospital), 3 rural hospitals in Alberta (Wetaskiwin Hospital, Westlock Healthcare Centre and Athabasca Healthcare Centre) and the 2 hospitals in Regina, Saskatchewan (Regina General Hospital and Pasqua Hospital). These areas were selected based on a collaboration of local investigators. All patients with a discharge diagnosis of deep vein thrombosis (DVT) (ICD-10 code I82 + sub-indices) or pulmonary embolism (PE) (ICD-10 code I26 + sub-indices) between April 1, 2014 and March 31, 2015 were screened. Atypical clot locations (e.g., axillary/subclavian veins, portal vein) were not included given their lack of enrollment in the large scale non-inferiority trials of the DOACs.[6-11] Patients were also excluded if they had another

indication for therapeutic anticoagulation, were not discharged alive, had an anticipated lifespan < 3 months (documentation of palliation or prognosis), were < 18 years of age, were discharged directly from the emergency department or were pregnant or breastfeeding.

Outcomes

Primarily, we sought to determine the proportion of patients discharged from hospital with acute VTE that were prescribed a traditional therapy (parenteral anticoagulant ± warfarin) or a DOAC. Secondarily, we sought to compare differences in management between those in the Edmonton area, Regina area and rural Alberta. Use of DOACs for PE versus DVT was compared, as well as whether clot burden influenced anticoagulant selection. DVT was classified as proximal (at or above the popliteal vein) or distal in the leg. For PE, the validated simplified Pulmonary Embolism Severity Indices (sPESI) of either 0 or ≥ 1 was used, calculated at the time of presentation of the PE.[12,13]

When prescribed, the use of DOACs was assessed for concordance with dosing regimens with Health Canada approved product monographs as per prescriptions in hospital and at the point of discharge.[1-4] DOAC dosing was considered concordant if therapy was provided with either a parenteral anticoagulant or the appropriate up front (larger dose) of rivaroxaban (15mg BID) or apixaban (10mg BID) for the appropriate duration (3 and 1 week, respectively). We also assessed the difference in length of hospital stay in patients prescribed a DOAC versus a traditional therapy, and with whom follow-up was to occur after discharge.

Notably, these data represent a detailed evaluation specific to patients hospitalized with acute VTE. Our audit also encompassed the cohort of patients discharged directly from emergency departments from all institutions. As per our pre-planned analysis, there are 2 other manuscripts under review; one detailing the emergency department cohort (see Supplementary file 1) and the other comparing (in aggregate amongst the urban settings) patents discharged directly from the emergency department versus those hospitalized (see Supplementary file 2).[14,15]

Data sources and analysis

All data elements were extracted from the hospital –based charts by trained data abstractors (2 for Alberta-based sites and 1 for Regina-sites) and directly entered into the research electronic data capture (REDCap). As this was a retrospective chart review, missing data elements (such as weight) were identified and reported, accordingly.

Data analysis was performed at the Epidemiology Coordinating and Research (EPICORE) Centre. Data were collated and reported based on location, namely Edmonton area, Regina area and rural Alberta. Patients' characteristics were compared between sites using mean (SD) or median (IQR) as appropriate for the continuous data and proportions (%) for categorical data. Chi-square test was used to compare discharge therapies between sites and different groups. Statistical analysis was carried out on SAS version 9.4. Health Research Ethics Board approval was received through the University of Alberta (Pro00056384) for all Alberta sites, and via the Regina Qu'Appelle Health Region (REB 15-65) for the Regina sites.

RESULTS

A total of 958 charts were screened with 695 (72.5%) included (Figure 1). The most common reasons for exclusion were lack of an acute VTE diagnosis (39.9%) and another indication for therapeutic anticoagulation (23.6%). Overall, those included had an average age ($\pm$SD) of 63.3 $\pm$ 17.3 years, a median body weight of 85.5Kg and only a minority (3.5%) had a creatinine clearance (CrCl) <30mL/min (Table 1). The majority of patients had PE (82.9%), particularly in the urban centres of Edmonton (84.4%) and Regina (80.8%), while the diagnosis of PE was lower in rural Alberta (63.3%). Based on the sPESI score, the majority with PE in Edmonton (66.5%) and Regina (58.8%) had a PESI score $\geq$ 1, while rural Alberta was nearly half the patients (47.4%). The majority of patients admitted for DVT had a proximal clot; Edmonton (87.1%), rural Alberta (81.8%), Regina (69.6%). Of note, full leg ultrasounds were utilized in Regina while only above the knee ultrasounds were utilized in both Edmonton and rural Alberta.

The majority of patients (70.2%) were discharged from hospital on a traditional therapy (parenteral anticoagulant +/- warfarin), with 28.3% receiving a DOAC (Table 2). Notably, Regina had the highest rate of a warfarin-based regimen (60.8%), with less warfarin used in Edmonton (40.5%) and rural Alberta (30%). Use of DOACs was most common in rural Alberta (57.9%), followed by Edmonton (28.3%) and Regina (23.3%).

There was no difference in proportionate use of a DOAC for PE compared to DVT (28.0% and 30.3%, respectively; P=0.61). Patients having a sPESI score of 0 were more likely to be prescribed a DOAC relative to those with a score $\geq$ 1 (33.3% and 24.3%, respectively; P<0.0001). Only a small portion of patients in our study had distal DVTs (N=13) compared with proximal DVTs (N=99), and DOAC use was not significantly different for distal DVTs (50%) compared to proximal DVTs (27.6%) (P=0.14).

Amongst the 197 patients prescribed a DOAC, the majority (97.5%) received rivaroxaban, with a minority of patients receiving apixaban (N=3 [1.5%]) and dabigatran (N=2 [1.0%]). DOAC dosing for the acute treatment of VTE was consistent with product monographs in 85.8% of patients. The majority of inconsistent dosing with rivaroxaban was attributable to not having a full 3 weeks of therapy of higher dose (rivaroxaban 15mg BID) prior to implementing the lower maintenance dose of 20mg daily (N=25/28). Only a minority of patients had renal dysfunction with a CrCl < 30mL/min (N=23 [3.5%]). DOAC use declined with worsening renal function with 31.1% (161/517), 19.0% (23/121), and 4.4% (1/23) prescribed a DOAC with a CrCl >50, 30-50 and <30mL/min, respectively (P<0.0001).

Combining all sites, median (IQR) length of stay was shortest amongst those prescribed a DOAC (4 days [2.0, 9.0]) and longest for those transitioning from LMWH to warfarin therapy (7 days [4.0, 12.0]) (P<0.0001) (Table 3). At discharge, amongst the urban sites follow-up was to occur most commonly with a VTE clinic/specialist (47.5% for Edmonton and 52.5% with Regina) whereas rural Alberta referred most to family doctors (66.7%) (Table 2).

DISCUSSION

Amongst all sites, the majority (70.2%) of patients presenting with acute VTE were prescribed traditional therapies (parenteral anticoagulant +/- warfarin) at hospital discharge, and 28.3% received a DOAC. Rural Alberta had the greatest uptake of the DOACs (50%), followed by the Edmonton area (28.3%) and Regina area (23.3%). Uptake of DOACs in rural Alberta is likely attributable to many factors, including more limited laboratory availability for routine coagulation testing, primary care physicians providing care within the hospital and hospital pharmacists who were comfortable with data pertaining to the use of DOACs in this population. While we found no difference in the use of DOACs for PE relative to DVT, DOACs were used more in patients with lower risk PE and normal renal function. When prescribed, the majority of DOAC use (85.8%) was concordant with Canadian product labeling.

Our overall rate of DOAC use for acute VTE (28.3%) is similar to that reported amongst 328 patients discharged from Florence, Italy hospitals following acute PE (32.5%) during 2014 and 2015.[16] These investigators assessed a time interval that partially overlapped with ours, and report an increase in DOAC use from 2014 (23.2%) to 2015 (40.1%). A single site evaluation of therapy for an incident VTE presentation amongst 256 patients in Montreal, Quebec Canada in 2013 found similar overall trends to our study with most patients being treated with warfarin (54.7%) followed by LMWH alone (27.7%) and rivaroxaban (17.6%).[17] Unlike our study, those in the Quebec evaluation with DVT (N=94) were more likely than those with PE (N=162) to receive rivaroxaban (28.7% and 11.1%, respectively). In terms of clinical presentation of PE, a single site evaluation of 39 patients with PE being discharged from hospital on a DOAC showed more use amongst those defined as low risk (83%), with overall DOAC use still being high for those at intermediate-low risk (40%), intermediate-high risk (68%) and high risk (40%).[16] Our study found similar results in that more patients with a sPESI score of 0 (33.3%) received DOACs, however DOACs were still used amongst those with a score of $\geq$ 1 (24.3%).

Concordance with dosing for acute VTE in our study (85.8%) was similar to that reported in an audit assessing the appropriateness of DOAC prescribing amongst 39 VTE patients in Australia (84.6%)[18]

and lower than that reported in a non-interventional study assessing the use of the appropriate initial dosing of rivaroxaban (93.7%).[19] Unlike our study wherein the majority of patients not receiving DOAC dosing per the product monographs due to not receiving the appropriate up front rivaroxaban 15mg BID, the non-interventional study reported that only 73% of patients went onto step down to rivaroxaban 20mg daily.[19] Unfortunately, we were not able to identify therapy changes beyond that planned at hospital discharge within our study.

Given that initial therapy with an injectable anticoagulant is not required for both rivaroxaban and apixaban and that routine coagulation monitoring is not performed with all of the DOACs, care delivery with a DOACs compared to traditional therapy with a parenteral anticoagulant ± warfarin should be simplified. Data from the North American cohort of patients enrolled in landmark trials reports a significantly shorter length of stay for those receiving rivaroxaban (3.0 days [3.0-5.0]) compared to traditional therapy (4.0 days [3.0-6.0]; P=0.0004).[20] A single site evaluation in Quebec, Canada affirmed the clinical trial data, and reported median length of stay to be shorter with rivaroxaban use (3.5 days) relative to LMWH alone or warfarin therapy (6 days).[17] Similarly, a single American institution identified those discharged on rivaroxaban compared to warfarin had shorter hospital stays (3.5 and 7 days, respectively; P<0.001).[21] These data are consistent with ours, as patients receiving a DOAC had a shorter median length of stay (Table 3).

STRENGTHS AND LIMITATIONS

We present data herein reflective of the largest cohort of patients with acute VTE being discharged following hospitalization. For all sites, we reviewed all medical records with a discharge diagnosis of deep vein thrombosis (DVT) (ICD-10 code I82 + sub-indices) or pulmonary embolism (PE) (ICD-10 code I26 + sub-indices) over the span of a full year (April 2014 to March 2015). In doing so, different sample sizes were identified from each area, with rural Alberta and Regina having fewer patients (N=30 and N=120, respectively) than the Edmonton area (N=545). Despite the differences in

sample sizes, these data reflect local practices given the geographic populations and catchment areas (Edmonton: 1,328,290 plus catchment of ~500,000; Regina: 230,020 plus catchment of 500,000; rural Alberta 3 sites: 30,065) and that an entire year was assessed.[22-26] The timing of our audit is reflective of the early uptake of DOACs for the acute treatment of VTE given only rivaroxaban had Health Canada approval throughout the entire time interval audited. Despite this, we identified reasonable uptake of the DOACs (28.3%), with use that complied with product monograph labeling in the vast majority (85.8%). This data can serve as a marker for future analyses wherein usage can be compared to assess the uptake of this therapeutic approach over time as guidelines more aggressively incorporate the utilization of DOACs in this population and clinicians become more comfortable with their use.

Our design (retrospective medical record review) was selected to allow us to accurately select patients with acute VTE to ascertain practice patterns. Given the diverse geography and volume of records to review, 3 data abstractors were necessary. A master key defining eligibility, data points to collect and how to code variables in REDCap was used. Within REDCap, restrictions for variables were programmed to minimize data entry error. Prior to finishing data collection at each site, quality assurance reports were performed to ensure accuracy of data. As this was a record review, we were limited only to information available in the hospital-based chart. Given this, some data elements were not documented (e.g., weight, serum creatinine), leaving us to report data for those available. Moreover, our design did not enable us to collect data following hospital discharge, limiting us from determining if patients got their prescriptions filled or had complications following discharge.

CONCLUSION

In summary, we report the management of a large cohort of acute VTE patients being discharged from hospitals within Canada. Over a time interval early in the approval process for DOACs for the acute treatment of VTE, we report a modest update of DOACs (28.3%) that were, overall, dosed correctly for the majority of patients (85.8%). Variation in therapies used was evident with the most

common regimen being warfarin-based in Regina (60.7%) and Edmonton (40.5%) and a DOAC in rural Alberta (50.5%). Use of rivaroxaban was proportionately higher for less severe clots, and those prescribed a DOAC had a shorted length of stay relative to those given traditional therapies. As time evolves, it is anticipated use of DOACs will increase for the management of VTE. Practitioners and health delivery systems should continue to consider the opportunity provided by the DOACs to simplify and shorten hospital based care as further data emerges to support their place in therapy. Future evaluations should occur to assess temporal changes, ongoing appropriateness of care delivery and the impact that DOACs may have on healthcare system resource allocation.

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AUTHOR CONTRIBUTIONS

TJB contributed to the design of the work, the acquisition, analysis and interpretation of the data. TJB drafted the original manuscript, approved the final version to be published and is accountable for all aspects of the work related to accuracy or integrity. BR contributed to the design of the work, the interpretation of the data and critically revised the manuscript. BR approved the final version to be published and is accountable for all aspects of the work related to accuracy or integrity. JB contributed to the acquisition and interpretation of the data, critically revised the manuscript and approved the final version to be published. JB is accountable for all aspects of the work related to accuracy or integrity. WS contributed to the design, acquisition and interpretation of the data, critically revised the manuscript and approved the final version to be published. WS is also accountable for the accuracy and integrity of this work.

Figure 1: Patient Flow

Table 1: Baseline Characteristics

	Total	Edmonton	Rural Alberta	Regina
Screened (N)	958	736	41	181
Included (N, %)	695 (72.5%)	545 (74.0%)	30 (73.2%)	120 (66.3%)
Male (N, %)	350 (50.4%)	282 (51.7%)	16 (53.3%)	52 (43.3%)
Mean age (mean ± SD)	63.3 ± 17.3	63.8 ± 17.2	64.2 ± 16.9	60.4 ± 17.6
Weight Documented (N, %)[a]	680 (97.8%)	534 (98.0%)	28 (93.3%)	118 (98.3%)
Weight, Kg (Median, IQR)	85.5 (70.0, 106.0)	84.5 (70.0, 106.0)	84.3 (71.0, 98.3)	90.5 (70.0, 110.0)
CrCl Documented (N, %) [a]	661 (95.0%)	515 (94.5%)	29 (96.7%)	117 (97.5%)
< 30 mL/min	23 (3.5%)	20 (3.9%)	1 (3.5%)	2 (1.7%)
30-49 mL/min	121 (18.3%)	96 (18.6%)	3 (10.3%)	22 (18.8%)
> 50 mL/min	517 (78.2%)	399 (77.5%)	25 (86.2%)	93 (79.5%)
VTE				
DVT	119 (17.1%)	85 (15.6%)	11 (36.6%)	23 (19.2%)
Distal	13 (10.9%)	7 (8.2%)	0	6 (26.1%)
Proximal[b]	99 (83.2%)	74 (87.1%)	9 (81.8%)	16 (69.6%)
Not documented	7 (5.9%)	4 (4.7%)	2 (18.2%)	1 (4.3%)
PE and PE + DVT [c]	576 (82.9%)	460 (84.4%)	19 (63.3%)	97 (80.8%)
PE – Simplified PESI Score:[d]	567 (98.4%)	451 (98.0%)	19 (100%)	97 (100%)
0 point	201 (35.4%)	151 (33.5%)	10 (52.6%)	40 (41.2%)
≥ 1 points	366 (64.6%)	300 (66.5%)	9 (47.4%)	57 (58.8%)
History of:				
Cancer	158 (22.7%)	119 (21.8%)	10 (33.3%)	29 (24.2%)
Pulmonary disease	143 (20.6%)	114 (20.9%)	6 (20.0%)	23 (19.2%)
Prior VTE	100 (14.4%)	81 (14.9%)	6 (20.0%)	13 (10.8%)
Recent surgery	32 (4.6%)	23 (4.2%)	0	9 (7.5%)
Length of Stay (median, IQR)	6.0 (3.0, 11.0)	6.0 (3.0, 11.0)	5.5 (3.0, 13.0)	6.0 (3.0, 9.0)

CrCl=Creatinine Clearance; SD=Standard Deviation; IQR=Interquartile Range; PE=Pulmonary Embolism; DVT=Deep Vein Thrombosis; PESI= Pulmonary Embolism Severity Index; LOS=Length of Stay

[a]not all patients had weight and serum creatinine documented in the chart

[b]Combined popliteal, femoral, common femoral, and iliac

[c]combined PE with PE+DVT and report it all as PE

[d]PESI score could not be calculated in 9 patients due to missing variable(s)

Table 2: Therapy at Discharge and Follow-Up Plan for Hospitalized Cohort

	Total	Edmonton	Rural Alberta	Regina	P Value
VTE (All Combined)					<0.0001
Parenteral AC alone	185 (26.6%)	160 (29.4%)	6 (20.0%)	19 (15.8%)	
Parenteral AC + warfarin	145 (20.9%)	83 (15.2%)	4 (13.3%)	58 (48.3%)	
Warfarin	158 (22.7%)	138 (25.3%)	5 (16.7%)	15 (12.5%)	
DOAC	197 (28.3%)	154 (28.3%)	15 (50.0%)	28 (23.3%)	
Rivaroxaban	192 (97.5%)	151 (98.1%)	14 (93.3%)	27 (96.4%)	
Dabigatran	2 (1.0%)	0	1 (6.7%)	1 (3.6%)	
Apixaban	3 (1.5%)	3 (2.0%)	0	0	
Not Documented	10 (1.4%)	10 (1.8%)	0	0	
PE and PE+DVT					<0.0001
Parenteral AC alone	146 (25.3%)	129 (28.0%)	5 (26.3%)	12 (12.4%)	
Parenteral AC + warfarin	129 (22.4%)	77 (16.7%)	1 (5.3%)	51 (52.6%)	
Warfarin	132 (22.9%)	119 (25.8%)	2 (10.5%)	11 (11.3%)	
DOAC	161 (28.0%)	127 (27.6%)	11 (57.9%)	23 (23.7%)	
Rivaroxaban	156 (96.9%)	124 (97.6%)	10 (90.9%)	22 (95.6%)	
Dabigatran	2 (1.2%)	0	1 (9.1%)	1 (4.4%)	
Apixaban	3 (1.9%)	3 (2.4)	0	0	
Not Documented	8 (1.4%)	8 (1.7%)	0	0	
DVT alone					0.045
Parenteral AC alone	39 (32.8%)	31 (36.5%)	1 (9.1%)	7 (30.4%)	
Parenteral AC + warfarin	16 (13.4%)	6 (7.1%)	3 (2.7%)	7 (30.4%)	
Warfarin	26 (21.8%)	19 (22.4%)	3 (27.3%)	4 (17.4%)	
DOAC	36 (30.3%)	27 (31.8%)	4 (36.4%)	5 (21.7%)	
Rivaroxaban	36 (100%)	27 (100.0%)	4 (100.0%)	5 (100.0%)	
Dabigatran	0	0	0	0	
Apixaban	0	0	0	0	
Not Documented	2 (1.7%)	2 (2.4%)	0	0	
Follow-Up					
Family Doctor	358 (51.5%)	276 (50.6%)	20 (66.7%)	62 (51.7%)	
VTE Clinic	202 (29.1%)	201 (36.9%)	1 (3.3%)	0	
Specialist	124 (17.8%)	58 (10.6%)	3 (10.0%)	63 (52.5%)	
Anticoagulation Clinic	34 (4.9%)	10 (1.8%)	0	24 (20.0%)	

Return to ED	10 (1.4%)	8 (1.5%)	2 (6.7%)	0	
Other	101 (14.5%)	90 (16.5%)	6 (20.0%)	5 (4.2%)	
Not documented	41 (5.9%)	33 (6.1%)	2 (6.7%)	6 (5.0%)	

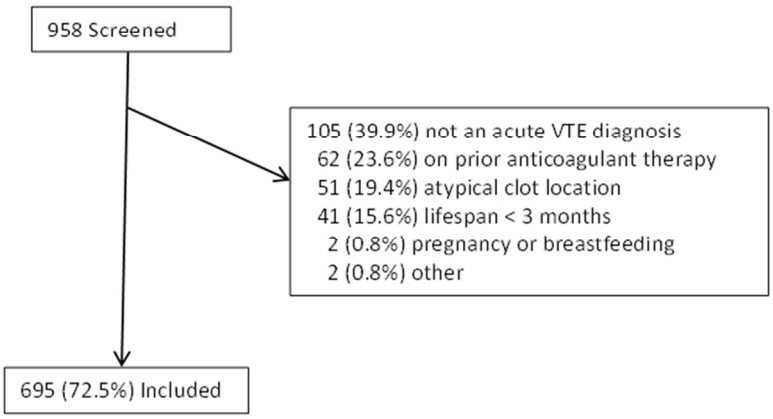
VTE=Venous Thromboembolism; PE=Pulmonary Embolism; DVT=Deep Vein Thrombosis; DOAC=Direct Oral Anticoagulant; AC=Anticoagulant; ED=Emergency Department

Table 3: Length of Stay in Days (Median, IQR) Based on Therapy

Therapy	All	Edmonton	Rural Alberta	Regina
DOAC	4 (2.0, 9.0)	4 (2.0, 8.0)	6 (2.0, 19.0)	4.5 (2.0, 8.5)
Parenteral Alone	5 (3.0, 10.0)	5 (2.0, 9.0)	15 (5.0, 21.0)	6 (4.0, 10.0)
Parenteral + Warfarin / Warfarin alone	7 (4.0, 12.0)	8 (4.0, 14.0)	4 (2.0, 6.0)	7 (4.0, 9.0)
P Value	<0.0001	<0.0001	0.091	0.223

DOAC=Direct Oral Anticoagulant

Figure 1: Patient Flow



214x110mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	NA-full year of data
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, Figure 1
		(b) Give reasons for non-participation at each stage	8, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Management of Acute Venous Thromboembolism Amongst a Cohort of Patients Discharged from Urban and Rural Hospitals

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Management of Acute Venous Thromboembolism Amongst a Cohort of Patients Discharged from Urban and Rural Hospitals

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ABSTRACT:

Objective: To determine anticoagulant therapy at hospital discharge for patients with acute venous thromboembolism (VTE) and secondarily, to describe factors affecting choice of therapy.

Design: A retrospective chart review.

Setting: Canadian hospitals in Edmonton, Alberta (N=4), Regina, Saskatchewan (N=2) and rural Alberta (N=3) from April 2014 to March 2015.

Participants: All patients discharged with an acute VTE were screened. Those with atypical clots, another indication for anticoagulation, pregnancy/breastfeeding or lifespan < 3 months were excluded.

Interventions: None.

Primary and secondary outcomes: Primarily, we identified the proportion of patients discharged from hospital with acute VTE that were prescribed either traditional therapy (parenteral anticoagulant + warfarin) or a direct acting oral anticoagulant (DOAC). Secondarily, management based on setting, therapy choice based on DVT versus PE, clot burden and renal function was compared. DOAC dosing was assessed (when prescribed), length of hospital stay based on therapy was compared, and planned follow-up in the community was described.

Results: Amongst the 695 patients included, most were discharged following a diagnosis of PE (82.9%) on traditional therapy (parenteral anticoagulant +/- warfarin) (70.2%) with follow-up by either a family doctor (51.5%) or specialist/clinic (46.9%) post-discharge. Regional variation was most evident between urban and rural sites. Of those prescribed a DOAC (28.3%), the majority were dosed appropriately (85.8%). DOAC use did not differ between those with DVT and PE, was proportionately higher for less severe clots, and declined with worsening renal function. Patients prescribed DOACs vs traditional therapy had shorter length of stays (4 versus 7 days, respectively).

Conclusions: Uptake of DOAC therapy for acute VTE was modest and may have been influenced by the timing of the audit in relation to the approval of these agents for this indication. Future audits should occur to assess temporal changes and ongoing appropriateness of care delivery.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study consists of a large cohort of patients discharged with acute DVT or PE from 2 urban areas and 3 rural sites throughout an entire year, thereby providing a good reflection of practice patterns.
- All patient charts were reviewed for inclusion, thereby enabling accurate data capture of the acute VTE population.
- Although this audit occurred early in the licensing of DOACs for VTE, these data offer a benchmark for future usage as guidelines more aggressively incorporate the utilization of DOACs in this population.
- Given our study design, we were not able to collect data for patients following discharge from hospital, thereby prohibiting the assessment of patient outcomes.

FUNDING STATEMENT

Funding was received from Pfizer Canada (via Dr. Bungard) in the form of an unrestricted grant. The sponsor had no role in the protocol design, study conduct, analysis/interpretation of the findings or decision to publish.

COMPETING INTEREST STATEMENT

TJB has received honoraria for an advisory board for BMS-Pfizer and Boehringer Ingelheim, as well as honoraria for speaking from Bayer. TJB has received unrestricted grants from Pfizer, Bayer and Leo Pharma. BR has served on advisory boards, given sponsored lectures using his own slides and received travel expense remuneration for Bayer, Baxter, Beohringer-Ingelheim, CSL-Behring, Pfizer, Sanofi, Servier and Shire. In lieu of honoraria for these activities, the companies have given financial contributions to the University of Alberta. BR reports grants from Novo Nordisk, CSL-Behring and Baxter, all outside of this submitted work. JB has received speaker honoraria from Boehringer Ingleheim in the

past two years. WS has received honoraria from Bayer, Pfizer, Bristol Myers Squibb and Boehringer Ingleheim. He has served as a consultant or on an Advisory Board for Bayer and Pfizer/Bristol Myers Squibb and he has received an unrestricted research grant from Pfizer.

INTRODUCTION

After over half a century of vitamin K antagonists as the only available oral anticoagulant therapy, several direct oral anticoagulants (DOACs) have been approved within the past 5 years for the acute treatment of venous thromboembolism (VTE).[1-4] Large scale trials have reported non-inferiority for efficacy and similar (or improved) rates of major bleeding with the DOACs relative to traditional therapy .[5-10] Moreover, the DOACs (rivaroxaban, dabigatran, apixaban and edoxaban) offer advantages over the traditional therapy of an injectable anticoagulant (typically low molecular weight heparin [LMWH]) overlapped with warfarin.[11] Unlike warfarin therapy, all DOACs have standardized dosing regimens that lack the need for routine coagulation monitoring and offer a therapeutic effect within hours of administration. Rivaroxaban and apixaban do not require initial therapy with an injectable anticoagulant, further streamlining care delivery.

While guidelines in 2012[12] recommended the management of deep vein thrombosis (DVT) on an outpatient basis, only more recent guidelines (2016)[13] suggest the management of those with a low risk pulmonary embolism (PE) at home or following a short length of stay in hospital. With both changing recommendations for managing DVT/PE alongside the emergence of new and more streamlined anticoagulant options, patterns of practices for managing VTE amongst those discharged from hospital across both urban and rural sites has not been well characterized in the literature. As such, amongst a cohort of patients discharged from hospital with acute VTE, we hypothesized a modest early adoption of DOACs across both urban and rural sites in preference to traditional therapies, with DOAC uptake anticipated to be most prevalent in those with less severe clots.

METHODS

Data Sources

For each institution, medical records were retrieved and reviewed by trained data abstractors (2 for Alberta-based sites and 1 for Regina-sites). All data elements (demographics, DVT vs PE,

anticoagulant prescribed at discharge and follow-up plan in the community) were extracted as per the documentation in the hospital-based and directly entered into the research electronic data capture (REDCap) program. As this was a retrospective chart review, missing data elements (such as weight) were identified and reported, accordingly.

Study Setting

Reflective of a collaboration of local investigators, this retrospective chart review was conducted at the 4 largest hospitals in Edmonton, Alberta (University of Alberta Hospital, Royal Alexandra Hospital, Misericordia Hospital, Grey Nuns Hospital), 3 rural hospitals in Alberta (Wetaskiwin Hospital, Westlock Healthcare Centre and Athabasca Healthcare Centre) and the 2 hospitals in Regina, Saskatchewan (Regina General Hospital and Pasqua Hospital). Given that Alberta and Saskatchewan are 2 neighboring provinces in Canada having different health authorities with different geographic distributions, data for the urban sites of Edmonton and Regina were kept separate and compared, accordingly.

Patient Population

All patients with a discharge diagnosis of deep vein thrombosis (DVT) (ICD-10 code I82 + sub-indices) or pulmonary embolism (PE) (ICD-10 code I26 + sub-indices) between April 1, 2014 and March 31, 2015 were screened. Atypical clot locations (e.g., axillary/subclavian veins, portal vein) were not included given their lack of enrollment in the large scale non-inferiority trials of the DOACs.[5-10] Patients were also excluded if they had another indication for therapeutic anticoagulation (e.g., mechanical heart valve, atrial fibrillation), were not discharged alive, had an anticipated lifespan < 3 months (documentation of palliation or prognosis), were < 18 years of age, were discharged directly from the emergency department or were pregnant or breastfeeding.

Outcomes

Primarily, we sought to determine the proportion of patients discharged from hospital with acute VTE that were prescribed a traditional therapy (parenteral anticoagulant ± warfarin) or a DOAC.

Secondarily, we sought to compare differences in management between those in the Edmonton area, Regina area and rural Alberta. Use of DOACs for PE versus DVT was compared, as well as whether clot burden influenced anticoagulant selection. DVT was classified as proximal (at or above the popliteal vein) or distal in the leg. For PE, the validated simplified Pulmonary Embolism Severity Indices (sPESI) of either 0 or $\geq$ 1 was used, calculated at the time of presentation of the PE.[14,15]

When prescribed, the use of DOACs was assessed for concordance with dosing regimens with Health Canada approved product monographs as per prescriptions received both in hospital and as planned at the point of discharge.[1-4] DOAC dosing was considered concordant if therapy was provided with either a parenteral anticoagulant or the appropriate up front (larger dose) of rivaroxaban (15mg BID) or apixaban (10mg BID) for the appropriate duration (3 and 1 week, respectively). We also assessed the difference in length of hospital stay in patients prescribed a DOAC versus a traditional therapy, and with whom follow-up was to occur after discharge.

Notably, these data represent a detailed evaluation specific to patients hospitalized with acute VTE. Our audit also encompassed the cohort of patients discharged directly from emergency departments from all institutions. As per our pre-planned analysis, there are 2 other manuscripts under review; one detailing the emergency department cohort and the other comparing (in aggregate amongst the urban settings) patents discharged directly from the emergency department versus those hospitalized.[16,17]

Patient and Public Involvement Statement

Patients and or the public were not involved in this study.

Analysis

Data analysis was performed at the Epidemiology Coordinating and Research (EPICORE) Centre. All data is contained within REDCap, University of Alberta, and are available to the principal investigator (TJB). No data sharing agreement is in place. Data were collated and reported based on location, namely

Edmonton area, Regina area and rural Alberta. Patients' characteristics were compared between sites using mean (SD) or median (IQR) as appropriate for the continuous data and proportions (%) for categorical data. Chi-square test was used to compare discharge therapies between sites and different groups. Statistical analysis was carried out on SAS version 9.4. Health Research Ethics Board approval was received through the University of Alberta (Pro00056384) for all Alberta sites, and via the Regina Qu'Appelle Health Region (REB 15-65) for the Regina sites.

RESULTS

A total of 958 charts were screened with 695 (72.5%) included (Figure 1). The most common reasons for exclusion were lack of an acute VTE diagnosis (39.9%) and another indication for therapeutic anticoagulation (23.6%). Overall, those included had an average age (±SD) of 63.3 ± 17.3 years, a median body weight of 85.5Kg and only a minority (3.5%) had a creatinine clearance (CrCl) <30mL/min (Table 1). The majority of patients had PE (82.9%), particularly in the urban centres of Edmonton (84.4%) and Regina (80.8%), while the diagnosis of PE was lower in rural Alberta (63.3%). Based on the sPESI score, the majority with PE in Edmonton (66.5%) and Regina (58.8%) had a PESI score ≥ 1, while rural Alberta was nearly half the patients (47.4%). The majority of patients admitted for DVT had a proximal clot; Edmonton (87.1%), rural Alberta (81.8%), Regina (69.6%). Of note, full leg ultrasounds were utilized in Regina while only above the knee ultrasounds were utilized in both Edmonton and rural Alberta.

The majority of patients (70.2%) were discharged from hospital on a traditional therapy (parenteral anticoagulant +/- warfarin), with 28.3% receiving a DOAC (Table 2). Notably, Regina had the highest rate of a warfarin-based regimen (60.8%), with less warfarin used in Edmonton (40.5%) and rural Alberta (30%). Use of DOACs was most common in rural Alberta (57.9%), followed by Edmonton (28.3%) and Regina (23.3%).

There was no difference in proportionate use of a DOAC for PE compared to DVT (28.0% and 30.3%, respectively; P=0.61). Patients having a sPESI score of 0 were more likely to be prescribed a

DOAC relative to those with a score ≥ 1 (33.3% and 24.3%, respectively; P<0.0001). Only a small portion of patients in our study had distal DVTs (N=13) compared with proximal DVTs (N=99), and DOAC use was not significantly different for distal DVTs (50%) compared to proximal DVTs (27.6%) (P=0.14).

Amongst the 197 patients prescribed a DOAC, the majority (97.5%) received rivaroxaban, with a minority of patients receiving apixaban (N=3 [1.5%]) and dabigatran (N=2 [1.0%]). DOAC dosing for the acute treatment of VTE was consistent with product monographs in 85.8% of patients. The majority of inconsistent dosing with rivaroxaban was attributable to not having a full 3 weeks of therapy of higher dose (rivaroxaban 15mg BID) prior to implementing the lower maintenance dose of 20mg daily (N=25/28). Only a minority of patients had renal dysfunction with a CrCl < 30mL/min (N=23 [3.5%]). DOAC use declined with worsening renal function with 31.1% (161/517), 19.0% (23/121), and 4.4% (1/23) prescribed a DOAC with a CrCl >50, 30-50 and <30mL/min, respectively (P<0.0001).

Combining all sites, median (IQR) length of stay was shortest amongst those prescribed a DOAC (4 days [2.0, 9.0]) and longest for those transitioning from LMWH to warfarin therapy (7 days [4.0, 12.0]) (P<0.0001) (Table 3). At discharge, amongst the urban sites follow-up was to occur most commonly with a VTE clinic/specialist (47.5% for Edmonton and 52.5% with Regina) whereas rural Alberta referred most to family doctors (66.7%) (Table 2).

DISCUSSION

Amongst all sites, the majority (70.2%) of patients presenting with acute VTE were prescribed traditional therapies (parenteral anticoagulant +/- warfarin) at hospital discharge, and 28.3% received a DOAC. Rural Alberta had the greatest uptake of the DOACs (50%), followed by the Edmonton area (28.3%) and Regina area (23.3%). Uptake of DOACs in rural Alberta is likely attributable to many factors, including more limited laboratory availability for routine coagulation testing, primary care physicians providing care within the hospital and hospital pharmacists who were comfortable with data pertaining to the use of DOACs in this population. While we found no difference in the use of DOACs for PE relative

to DVT, DOACs were used more in patients with lower risk PE and normal renal function. When prescribed, the majority of DOAC use (85.8%) was concordant with Canadian product labeling.

Our overall rate of DOAC use for acute VTE (28.3%) is similar to that reported amongst 328 patients discharged from Florence, Italy hospitals following acute PE (32.5%) during 2014 and 2015.[18] These investigators assessed a time interval that partially overlapped with ours, and report an increase in DOAC use from 2014 (23.2%) to 2015 (40.1%). A single site evaluation of therapy for an incident VTE presentation amongst 256 patients in Montreal, Quebec Canada in 2013 found similar overall trends to our study with most patients being treated with warfarin (54.7%) followed by LMWH alone (27.7%) and rivaroxaban (17.6%).[19] Unlike our study, those in the Quebec evaluation with DVT (N=94) were more likely than those with PE (N=162) to receive rivaroxaban (28.7% and 11.1%, respectively). In terms of clinical presentation of PE, a single site evaluation of 39 patients with PE being discharged from hospital on a DOAC showed more use amongst those defined as low risk (83%), with overall DOAC use still being high for those at intermediate-low risk (40%), intermediate-high risk (68%) and high risk (40%).[18] Our study found similar results in that more patients with a sPESI score of 0 (33.3%) received DOACs, however DOACs were still used amongst those with a score of $\geq$ 1 (24.3%).

Concordance with dosing for acute VTE in our study (85.8%) was similar to that reported in an audit assessing the appropriateness of DOAC prescribing amongst 39 VTE patients in Australia (84.6%)[20] and lower than that reported in a non-interventional study assessing the use of the appropriate initial dosing of rivaroxaban (93.7%).[21] Unlike our study wherein the majority of patients not receiving DOAC dosing per the product monographs due to not receiving the appropriate up front rivaroxaban 15mg BID, the non-interventional study reported that only 73% of patients went onto step down to rivaroxaban 20mg daily.[21] Unfortunately, we were not able to identify therapy changes beyond that planned at hospital discharge within our study.

Given that initial therapy with an injectable anticoagulant is not required for both rivaroxaban and apixaban and that routine coagulation monitoring is not performed with all of the DOACs, care delivery with a DOACs compared to traditional therapy with a parenteral anticoagulant ± warfarin should be simplified. Data from the North American cohort of patients enrolled in landmark trials reports a significantly shorter length of stay for those receiving rivaroxaban (3.0 days [3.0-5.0]) compared to traditional therapy (4.0 days [3.0-6.0]; P=0.0004).[22] A single site evaluation in Quebec, Canada affirmed the clinical trial data, and reported median length of stay to be shorter with rivaroxaban use (3.5 days) relative to LMWH alone or warfarin therapy (6 days).[19] Similarly, a single American institution identified those discharged on rivaroxaban compared to warfarin had shorter hospital stays (3.5 and 7 days, respectively; P<0.001).[23] While we did not set out to discern other factors that may have impacted length of hospital stay, our data is consistent with these,[19,22,23] as patients receiving a DOAC had a shorter median length of stay (Table 3).

STRENGTHS AND LIMITATIONS

Herein we present a large cohort of patients with acute VTE being discharged following hospitalization. For all sites, we reviewed all medical records with a discharge diagnosis of deep vein thrombosis (DVT) (ICD-10 code I82 + sub-indices) or pulmonary embolism (PE) (ICD-10 code I26 + sub-indices) over the span of a full year (April 2014 to March 2015). In doing so, different sample sizes were identified from each area, with rural Alberta and Regina having fewer patients (N=30 and N=120, respectively) than the Edmonton area (N=545). Despite the differences in sample sizes, these data reflect local practices given the geographic populations and catchment areas (Edmonton: 1,328,290 plus catchment of ~500,000; Regina: 230,020 plus catchment of 500,000; rural Alberta 3 sites: 30,065) and that an entire year was assessed.[24-28] The timing of our audit is reflective of the early uptake of DOACs for the acute treatment of VTE given only rivaroxaban had Health Canada approval throughout the entire time interval audited and that prescribing patterns may have changed beyond the timing of the

audit (March 2015). Despite this, we identified reasonable uptake of the DOACs (28.3%), with use that complied with product monograph labeling in the vast majority (85.8%). This data can serve as a marker for future analyses wherein usage can be compared to assess the uptake of this therapeutic approach over time as guidelines more aggressively incorporate the utilization of DOACs in this population and clinicians become more comfortable with their use.

Our design (retrospective medical record review) was selected to allow us to accurately select patients with acute VTE to ascertain practice patterns. Given the diverse geography and volume of records to review, 3 data abstractors were necessary. A master key defining eligibility, data points to collect and how to code variables in REDCap was used. Within REDCap, restrictions for variables were programmed to minimize data entry error. Prior to finishing data collection at each site, quality assurance reports were performed to ensure accuracy of data. As this was a record review, we were limited only to information available in the hospital-based chart. Given this, some data elements were not documented (e.g., weight, serum creatinine), leaving us to report data for those available. Moreover, our design did not enable us to collect data following hospital discharge, limiting us from determining if patients got their prescriptions filled or had complications following discharge.

CONCLUSION

In summary, we report the management of a large cohort of acute VTE patients being discharged from hospitals within Canada. Over a time interval early in the approval process for DOACs for the acute treatment of VTE, we report a modest update of DOACs (28.3%) that were, overall, dosed correctly for the majority of patients (85.8%). Variation in therapies used was evident with the most common regimen being warfarin-based in Regina (60.7%) and Edmonton (40.5%) and a DOAC in rural Alberta (50.5%). Use of rivaroxaban was proportionately higher for less severe clots, and those prescribed a DOAC had a shorted length of stay relative to those given traditional therapies. As time evolves, it is anticipated use of DOACs will increase for the management of VTE. Practitioners and health

delivery systems should continue to consider the opportunity provided by the DOACs to simplify and shorten hospital based care as further data emerges to support their place in therapy. Future evaluations should occur to assess temporal changes, ongoing appropriateness of care delivery and the impact that DOACs may have on healthcare system resource allocation.

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DATA SHARING AGREEMENT

There is no data sharing agreement – this is included in the original research article.

AUTHOR CONTRIBUTIONS

TJB contributed to the design of the work, the acquisition, analysis and interpretation of the data. TJB drafted the original manuscript, approved the final version to be published and is accountable for all aspects of the work related to accuracy or integrity. BR contributed to the design of the work, the interpretation of the data and critically revised the manuscript. BR approved the final version to be published and is accountable for all aspects of the work related to accuracy or integrity. JB contributed to the acquisition and interpretation of the data, critically revised the manuscript and approved the final version to be published. JB is accountable for all aspects of the work related to accuracy or integrity. WS contributed to the design, acquisition and interpretation of the data, critically revised the manuscript and approved the final version to be published. WS is also accountable for the accuracy and integrity of this work.

Figure 1: Patient Flow

Table 1: Baseline Characteristics

	Total	Edmonton	Rural Alberta	Regina
Screened (N)	958	736	41	181
Included (N, %)	695 (72.5%)	545 (74.0%)	30 (73.2%)	120 (66.3%)
Male (N, %)	350 (50.4%)	282 (51.7%)	16 (53.3%)	52 (43.3%)
Mean age (mean ± SD)	63.3 ± 17.3	63.8 ± 17.2	64.2 ± 16.9	60.4 ± 17.6
Weight Documented (N, %)[a]	680 (97.8%)	534 (98.0%)	28 (93.3%)	118 (98.3%)
Weight, Kg (Median, IQR)	85.5 (70.0, 106.0)	84.5 (70.0, 106.0)	84.3 (71.0, 98.3)	90.5 (70.0, 110.0)
CrCl Documented (N, %) [a]	661 (95.0%)	515 (94.5%)	29 (96.7%)	117 (97.5%)
< 30 mL/min	23 (3.5%)	20 (3.9%)	1 (3.5%)	2 (1.7%)
30-49 mL/min	121 (18.3%)	96 (18.6%)	3 (10.3%)	22 (18.8%)
> 50 mL/min	517 (78.2%)	399 (77.5%)	25 (86.2%)	93 (79.5%)
VTE				
DVT	119 (17.1%)	85 (15.6%)	11 (36.6%)	23 (19.2%)
Distal	13 (10.9%)	7 (8.2%)	0	6 (26.1%)
Proximal[b]	99 (83.2%)	74 (87.1%)	9 (81.8%)	16 (69.6%)
Not documented	7 (5.9%)	4 (4.7%)	2 (18.2%)	1 (4.3%)
PE and PE + DVT [c]	576 (82.9%)	460 (84.4%)	19 (63.3%)	97 (80.8%)
PE – Simplified PESI Score:[d]	567 (98.4%)	451 (98.0%)	19 (100%)	97 (100%)
0 point	201 (35.4%)	151 (33.5%)	10 (52.6%)	40 (41.2%)
≥ 1 points	366 (64.6%)	300 (66.5%)	9 (47.4%)	57 (58.8%)
History of:				
Cancer	158 (22.7%)	119 (21.8%)	10 (33.3%)	29 (24.2%)
Pulmonary disease	143 (20.6%)	114 (20.9%)	6 (20.0%)	23 (19.2%)
Prior VTE	100 (14.4%)	81 (14.9%)	6 (20.0%)	13 (10.8%)
Recent surgery	32 (4.6%)	23 (4.2%)	0	9 (7.5%)
Length of Stay (median, IQR)	6.0 (3.0, 11.0)	6.0 (3.0, 11.0)	5.5 (3.0, 13.0)	6.0 (3.0, 9.0)

CrCl=Creatinine Clearance; SD=Standard Deviation; IQR=Interquartile Range; PE=Pulmonary Embolism; DVT=Deep Vein Thrombosis; PESI= Pulmonary Embolism Severity Index; LOS=Length of Stay

[a]not all patients had weight and serum creatinine documented in the chart

[b]Combined popliteal, femoral, common femoral, and iliac

[c]combined PE with PE+DVT and report it all as PE

[d]PESI score could not be calculated in 9 patients due to missing variable(s)

Table 2: Therapy at Discharge and Follow-Up Plan for Hospitalized Cohort

	Total	Edmonton	Rural Alberta	Regina	P Value
VTE (All Combined)					<0.0001
Parenteral AC alone	185 (26.6%)	160 (29.4%)	6 (20.0%)	19 (15.8%)	
Parenteral AC + warfarin	145 (20.9%)	83 (15.2%)	4 (13.3%)	58 (48.3%)	
Warfarin	158 (22.7%)	138 (25.3%)	5 (16.7%)	15 (12.5%)	
DOAC	197 (28.3%)	154 (28.3%)	15 (50.0%)	28 (23.3%)	
Rivaroxaban	192 (97.5%)	151 (98.1%)	14 (93.3%)	27 (96.4%)	
Dabigatran	2 (1.0%)	0	1 (6.7%)	1 (3.6%)	
Apixaban	3 (1.5%)	3 (2.0%)	0	0	
Not Documented	10 (1.4%)	10 (1.8%)	0	0	
PE and PE+DVT					<0.0001
Parenteral AC alone	146 (25.3%)	129 (28.0%)	5 (26.3%)	12 (12.4%)	
Parenteral AC + warfarin	129 (22.4%)	77 (16.7%)	1 (5.3%)	51 (52.6%)	
Warfarin	132 (22.9%)	119 (25.8%)	2 (10.5%)	11 (11.3%)	
DOAC	161 (28.0%)	127 (27.6%)	11 (57.9%)	23 (23.7%)	
Rivaroxaban	156 (96.9%)	124 (97.6%)	10 (90.9%)	22 (95.6%)	
Dabigatran	2 (1.2%)	0	1 (9.1%)	1 (4.4%)	
Apixaban	3 (1.9%)	3 (2.4)	0	0	
Not Documented	8 (1.4%)	8 (1.7%)	0	0	
DVT alone					0.045
Parenteral AC alone	39 (32.8%)	31 (36.5%)	1 (9.1%)	7 (30.4%)	
Parenteral AC + warfarin	16 (13.4%)	6 (7.1%)	3 (2.7%)	7 (30.4%)	
Warfarin	26 (21.8%)	19 (22.4%)	3 (27.3%)	4 (17.4%)	
DOAC	36 (30.3%)	27 (31.8%)	4 (36.4%)	5 (21.7%)	
Rivaroxaban	36 (100%)	27 (100.0%)	4 (100.0%)	5 (100.0%)	
Dabigatran	0	0	0	0	
Apixaban	0	0	0	0	
Not Documented	2 (1.7%)	2 (2.4%)	0	0	
Follow-Up					
Family Doctor	358 (51.5%)	276 (50.6%)	20 (66.7%)	62 (51.7%)	
VTE Clinic	202 (29.1%)	201 (36.9%)	1 (3.3%)	0	
Specialist	124 (17.8%)	58 (10.6%)	3 (10.0%)	63 (52.5%)	
Anticoagulation Clinic	34 (4.9%)	10 (1.8%)	0	24 (20.0%)	

Return to ED	10 (1.4%)	8 (1.5%)	2 (6.7%)	0	
Other	101 (14.5%)	90 (16.5%)	6 (20.0%)	5 (4.2%)	
Not documented	41 (5.9%)	33 (6.1%)	2 (6.7%)	6 (5.0%)	

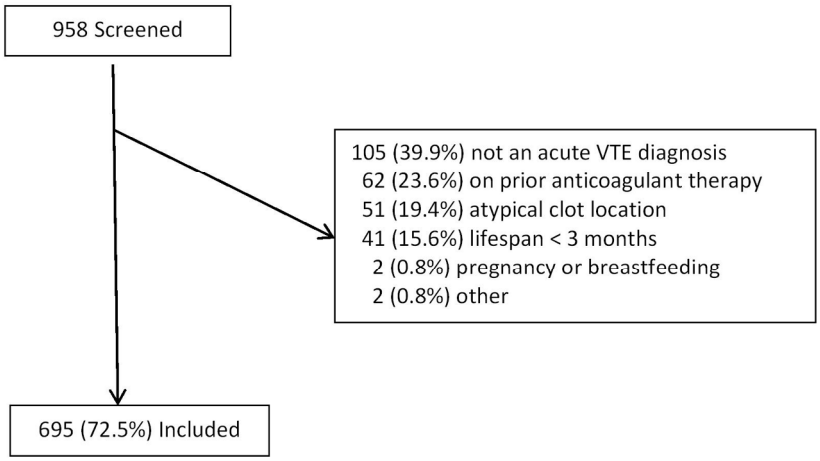
VTE=Venous Thromboembolism; PE=Pulmonary Embolism; DVT=Deep Vein Thrombosis; DOAC=Direct Oral Anticoagulant; AC=Anticoagulant; ED=Emergency Department

Table 3: Length of Stay in Days (Median, IQR) Based on Therapy

Therapy	All	Edmonton	Rural Alberta	Regina
DOAC	4 (2.0, 9.0)	4 (2.0, 8.0)	6 (2.0, 19.0)	4.5 (2.0, 8.5)
Parenteral Alone	5 (3.0, 10.0)	5 (2.0, 9.0)	15 (5.0, 21.0)	6 (4.0, 10.0)
Parenteral + Warfarin / Warfarin alone	7 (4.0, 12.0)	8 (4.0, 14.0)	4 (2.0, 6.0)	7 (4.0, 9.0)
P Value	<0.0001	<0.0001	0.091	0.223

DOAC=Direct Oral Anticoagulant

Figure 1: Patient Flow



165x95mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	NA-full year of data
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, Figure 1
		(b) Give reasons for non-participation at each stage	8, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Anticoagulant Therapies for Acute Venous Thromboembolism Amongst a Cohort of Patients Discharged from Canadian Urban and Rural Hospitals

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Anticoagulant Therapies for Acute Venous Thromboembolism Amongst a Cohort of Patients Discharged from Canadian Urban and Rural Hospitals

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ABSTRACT:

Objective: To determine anticoagulant therapy at hospital discharge for patients with acute venous thromboembolism (VTE) and secondarily, to describe factors affecting choice of therapy.

Design: A retrospective chart review.

Setting: Canadian hospitals in Edmonton, Alberta (N=4), Regina, Saskatchewan (N=2) and rural Alberta (N=3) from April 2014 to March 2015.

Participants: All patients discharged with an acute VTE were screened. Those with atypical clots, another indication for anticoagulation, pregnancy/breastfeeding or lifespan < 3 months were excluded.

Interventions: None.

Primary and secondary outcomes: Primarily, we identified the proportion of patients discharged from hospital with acute VTE that were prescribed either traditional therapy (parenteral anticoagulant + warfarin) or a direct acting oral anticoagulant (DOAC). Secondarily, management based on setting, therapy choice based on DVT versus PE, clot burden and renal function was compared. DOAC dosing was assessed (when prescribed), length of hospital stay based on therapy was compared, and planned follow-up in the community was described.

Results: Amongst the 695 patients included, most were discharged following a diagnosis of PE (82.9%) on traditional therapy (parenteral anticoagulant +/- warfarin) (70.2%) with follow-up by either a family doctor (51.5%) or specialist/clinic (46.9%) post-discharge. Regional variation was most evident between urban and rural sites. Of those prescribed a DOAC (28.3%), the majority were dosed appropriately (85.8%). DOAC use did not differ between those with DVT and PE, was proportionately higher for less severe clots, and declined with worsening renal function. Patients prescribed DOACs vs traditional therapy had shorter length of stays (4 versus 7 days, respectively).

Conclusions: Uptake of DOAC therapy for acute VTE was modest and may have been influenced by the timing of the audit in relation to the approval of these agents for this indication. Future audits should occur to assess temporal changes and ongoing appropriateness of care delivery.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study consists of a large cohort of patients discharged with acute DVT or PE from 2 urban areas and 3 rural sites throughout an entire year, thereby providing a good reflection of practice patterns.
- All patient charts were reviewed for inclusion, thereby enabling accurate data capture of the acute VTE population.
- Although this audit occurred early in the licensing of DOACs for VTE, these data offer a benchmark for future usage as guidelines more aggressively incorporate the utilization of DOACs in this population.
- Given our study design, we were not able to collect data for patients following discharge from hospital, thereby prohibiting the assessment of patient outcomes.

FUNDING STATEMENT

Funding was received from Pfizer Canada (via Dr. Bungard) in the form of an unrestricted grant. The sponsor had no role in the protocol design, study conduct, analysis/interpretation of the findings or decision to publish.

COMPETING INTEREST STATEMENT

TJB has received honoraria for an advisory board for BMS-Pfizer and Boehringer Ingelheim, as well as honoraria for speaking from Bayer. TJB has received unrestricted grants from Pfizer, Bayer and Leo Pharma. BR has served on advisory boards, given sponsored lectures using his own slides and received travel expense remuneration for Bayer, Baxter, Beohringer-Ingelheim, CSL-Behring, Pfizer, Sanofi, Servier and Shire. In lieu of honoraria for these activities, the companies have given financial contributions to the University of Alberta. BR reports grants from Novo Nordisk, CSL-Behring and Baxter, all outside of this submitted work. JB has received speaker honoraria from Boehringer Ingleheim in the

past two years. WS has received honoraria from Bayer, Pfizer, Bristol Myers Squibb and Boehringer Ingleheim. He has served as a consultant or on an Advisory Board for Bayer and Pfizer/Bristol Myers Squibb and he has received an unrestricted research grant from Pfizer.

INTRODUCTION

After over half a century of vitamin K antagonists as the only available oral anticoagulant therapy, several direct oral anticoagulants (DOACs) have been approved within the past 5 years for the acute treatment of venous thromboembolism (VTE).[1-4] Large scale trials have reported non-inferiority for efficacy and similar (or improved) rates of major bleeding with the DOACs relative to traditional therapy .[5-10] Moreover, the DOACs (rivaroxaban, dabigatran, apixaban and edoxaban) offer advantages over the traditional therapy of an injectable anticoagulant (typically low molecular weight heparin [LMWH]) overlapped with warfarin.[11] Unlike warfarin therapy, all DOACs have standardized dosing regimens that lack the need for routine coagulation monitoring and offer a therapeutic effect within hours of administration. Rivaroxaban and apixaban do not require initial therapy with an injectable anticoagulant, further streamlining care delivery.

While guidelines in 2012[12] recommended the management of deep vein thrombosis (DVT) on an outpatient basis, only more recent guidelines (2016)[13] suggest the management of those with a low risk pulmonary embolism (PE) at home or following a short length of stay in hospital. With both changing recommendations for managing DVT/PE alongside the emergence of new and more streamlined anticoagulant options, patterns of practices for managing VTE amongst those discharged from hospital across both urban and rural sites has not been well characterized in the literature. As such, amongst a cohort of patients discharged from hospital with acute VTE, we hypothesized a modest early adoption of DOACs across both urban and rural sites in preference to traditional therapies, with DOAC uptake anticipated to be most prevalent in those with less severe clots.

METHODS

Data Sources

For each institution, medical records were retrieved and reviewed by trained data abstractors (2 for Alberta-based sites and 1 for Regina-sites). All data elements (demographics, DVT vs PE,

anticoagulant prescribed at discharge and follow-up plan in the community) were extracted as per the documentation in the hospital-based record and directly entered into the research electronic data capture (REDCap) program. As this was a retrospective chart review, missing data elements (such as weight) were identified and reported, accordingly.

Study Setting

Reflective of a collaboration of local investigators, this retrospective chart review was conducted at the 4 largest hospitals in Edmonton, Alberta (University of Alberta Hospital, Royal Alexandra Hospital, Misericordia Hospital, Grey Nuns Hospital), 3 rural hospitals in Alberta (Wetaskiwin Hospital, Westlock Healthcare Centre and Athabasca Healthcare Centre) and the 2 hospitals in Regina, Saskatchewan (Regina General Hospital and Pasqua Hospital). Given that Alberta and Saskatchewan are 2 neighboring provinces in Canada having different health authorities with different geographic distributions, data for the urban sites of Edmonton and Regina were kept separate and compared, accordingly.

Patient Population

All patients with a discharge diagnosis of deep vein thrombosis (DVT) (ICD-10 code I82 + sub-indices) or pulmonary embolism (PE) (ICD-10 code I26 + sub-indices) between April 1, 2014 and March 31, 2015 were screened. Atypical clot locations (e.g., axillary/subclavian veins, portal vein) were not included given their lack of enrollment in the large scale non-inferiority trials of the DOACs.[5-10] Patients were also excluded if they had another indication for therapeutic anticoagulation (e.g., mechanical heart valve, atrial fibrillation), were not discharged alive, had an anticipated lifespan < 3 months (documentation of palliation or prognosis), were < 18 years of age, were discharged directly from the emergency department or were pregnant or breastfeeding.

Outcomes

Primarily, we sought to determine the proportion of patients discharged from hospital with acute VTE that were prescribed a traditional therapy (parenteral anticoagulant ± warfarin) or a DOAC.

Secondarily, we sought to compare differences in management between those in the Edmonton area, Regina area and rural Alberta. Use of DOACs for PE versus DVT was compared, as well as whether clot burden influenced anticoagulant selection. DVT was classified as proximal (at or above the popliteal vein including the trifurcation area) or distal in the leg. For PE, the validated simplified Pulmonary Embolism Severity Indices (sPESI) of either 0 or $\geq$ 1 was used, calculated at the time of presentation of the PE.[14,15]

When prescribed, the use of DOACs was assessed for concordance with dosing regimens with Health Canada approved product monographs as per prescriptions received both in hospital and as planned at the point of discharge.[1-4] DOAC dosing was considered concordant if therapy was provided with either a parenteral anticoagulant or the appropriate up front (larger dose) of rivaroxaban (15mg BID) or apixaban (10mg BID) for the appropriate duration (3 and 1 week, respectively). We also assessed the difference in length of hospital stay in patients prescribed a DOAC versus a traditional therapy, and with whom follow-up was to occur after discharge.

Notably, these data represent a detailed evaluation specific to patients hospitalized with acute VTE. Our audit also encompassed the cohort of patients discharged directly from emergency departments from all institutions. As per our pre-planned analysis, there are 2 other manuscripts under review; one detailing the emergency department cohort and the other comparing (in aggregate amongst the urban settings) patents discharged directly from the emergency department versus those hospitalized.[16,17]

Patient and Public Involvement Statement

Patients and or the public were not involved in this study.

Analysis

Data analysis was performed at the Epidemiology Coordinating and Research (EPICORE) Centre. All data is contained within REDCap, University of Alberta, and are available to the principal investigator (TJB). No data sharing agreement is in place. Data were collated and reported based on location, namely

Edmonton area, Regina area and rural Alberta. Patients' characteristics were compared between sites using mean (SD) or median (IQR) as appropriate for the continuous data and proportions (%) for categorical data. Chi-square test was used to compare discharge therapies between sites and different groups. Statistical analysis was carried out on SAS version 9.4. Health Research Ethics Board approval was received through the University of Alberta (Pro00056384) for all Alberta sites, and via the Regina Qu'Appelle Health Region (REB 15-65) for the Regina sites.

RESULTS

A total of 958 charts were screened with 695 (72.5%) included (Figure 1). The most common reasons for exclusion were lack of an acute VTE diagnosis (39.9%) and another indication for therapeutic anticoagulation (23.6%). Overall, those included had an average age (±SD) of 63.3 ± 17.3 years, a median body weight of 85.5Kg and only a minority (3.5%) had a creatinine clearance (CrCl) <30mL/min (Table 1). The majority of patients had PE (82.9%), particularly in the urban centres of Edmonton (84.4%) and Regina (80.8%), while the diagnosis of PE was lower in rural Alberta (63.3%). Based on the sPESI score, the majority with PE in Edmonton (66.5%) and Regina (58.8%) had a PESI score ≥ 1, while rural Alberta was nearly half the patients (47.4%). The majority of patients admitted for DVT had a proximal clot; Edmonton (87.1%), rural Alberta (81.8%), Regina (69.6%). Of note, full leg ultrasounds were utilized in Regina while only above the knee ultrasounds were utilized in both Edmonton and rural Alberta.

The majority of patients (70.2%) were discharged from hospital on a traditional therapy (parenteral anticoagulant +/- warfarin), with 28.3% receiving a DOAC (Table 2). Notably, Regina had the highest rate of a warfarin-based regimen (60.8%), with less warfarin used in Edmonton (40.5%) and rural Alberta (30%) (P<0.0001). Use of DOACs was most common in rural Alberta (57.9%), followed by Edmonton (28.3%) and Regina (23.3%) (P<0.0001).

There was no difference in proportionate use of a DOAC for PE compared to DVT (28.0% and 30.3%, respectively; P=0.61). Patients having a sPESI score of 0 were more likely to be prescribed a

DOAC relative to those with a score ≥ 1 (33.3% and 24.3%, respectively; P<0.0001). Only a small portion of patients in our study had distal DVTs (N=13) compared with proximal DVTs (N=99), leaving too few to perform statistical comparisons.

Amongst the 197 patients prescribed a DOAC, the majority (97.5%) received rivaroxaban, with a minority of patients receiving apixaban (N=3 [1.5%]) and dabigatran (N=2 [1.0%]). DOAC dosing for the acute treatment of VTE was consistent with product monographs in 85.8% of patients. The majority of inconsistent dosing with rivaroxaban was attributable to not having a full 3 weeks of therapy of higher dose (rivaroxaban 15mg BID) prior to implementing the lower maintenance dose of 20mg daily (N=25/28). Amongst these 25 patients, 5 had < 7 days of rivarxoban 15mg BID and 10 patients completed both 7-14 and 14-20 days of this regimen. Only a minority of patients had renal dysfunction with a CrCl < 30mL/min (N=23 [3.5%]). DOAC use declined with worsening renal function with 31.1% (161/517), 19.0% (23/121), and 4.4% (1/23) prescribed a DOAC with a CrCl >50, 30-50 and <30mL/min, respectively (P<0.0001).

Combining all sites, median (IQR) length of stay was shortest amongst those prescribed a DOAC (4 days [2.0, 9.0]) and longest for those transitioning from LMWH to warfarin therapy (7 days [4.0, 12.0]) (P<0.0001) (Table 3). At discharge, amongst the urban sites follow-up was to occur most commonly with a VTE clinic/specialist (47.5% for Edmonton and 52.5% with Regina) whereas rural Alberta referred most to family doctors (66.7%) (Table 2).

DISCUSSION

Amongst all sites, the majority (70.2%) of patients presenting with acute VTE were prescribed traditional therapies (parenteral anticoagulant +/- warfarin) at hospital discharge, and 28.3% received a DOAC. Rural Alberta had the greatest uptake of the DOACs (50%), followed by the Edmonton area (28.3%) and Regina area (23.3%). Uptake of DOACs in rural Alberta is likely attributable to many factors, including more limited laboratory availability for routine coagulation testing, primary care physicians

providing care within the hospital and hospital pharmacists who were comfortable with data pertaining to the use of DOACs in this population. While we found no difference in the use of DOACs for PE relative to DVT, DOACs were used more in patients with lower risk PE and normal renal function. When prescribed, the majority of DOAC use (85.8%) was concordant with Canadian product labeling.

Our overall rate of DOAC use for acute VTE (28.3%) is similar to that reported amongst 328 patients discharged from Florence, Italy hospitals following acute PE (32.5%) during 2014 and 2015.[18] These investigators assessed a time interval that partially overlapped with ours, and report an increase in DOAC use from 2014 (23.2%) to 2015 (40.1%). A single site evaluation of therapy for an incident VTE presentation amongst 256 patients in Montreal, Quebec Canada in 2013 found similar overall trends to our study with most patients being treated with warfarin (54.7%) followed by LMWH alone (27.7%) and rivaroxaban (17.6%).[19] Unlike our study, those in the Quebec evaluation with DVT (N=94) were more likely than those with PE (N=162) to receive rivaroxaban (28.7% and 11.1%, respectively). In terms of clinical presentation of PE, a single site evaluation of 39 patients with PE being discharged from hospital on a DOAC showed more use amongst those defined as low risk (83%), with overall DOAC use still being high for those at intermediate-low risk (40%), intermediate-high risk (68%) and high risk (40%).[18] Our study found similar results in that more patients with a sPESI score of 0 (33.3%) received DOACs, however DOACs were still used amongst those with a score of $\geq$ 1 (24.3%).

Concordance with dosing for acute VTE in our study (85.8%) was similar to that reported in an audit assessing the appropriateness of DOAC prescribing amongst 39 VTE patients in Australia (84.6%)[20] and lower than that reported in a non-interventional study assessing the use of the appropriate initial dosing of rivaroxaban (93.7%).[21] Unlike our study wherein the majority of patients not receiving DOAC dosing per the product monographs due to not receiving the appropriate up front rivaroxaban 15mg BID, the non-interventional study reported that only 73% of patients went onto step down to

rivaroxaban 20mg daily.[21] Unfortunately, we were not able to identify therapy changes beyond that planned at hospital discharge within our study.

Given that initial therapy with an injectable anticoagulant is not required for both rivaroxaban and apixaban and that routine coagulation monitoring is not performed with all of the DOACs, care delivery with a DOACs compared to traditional therapy with a parenteral anticoagulant ± warfarin should be simplified. Data from the North American cohort of patients enrolled in landmark trials reports a significantly shorter length of stay for those receiving rivaroxaban (3.0 days [3.0-5.0]) compared to traditional therapy (4.0 days [3.0-6.0]; P=0.0004).[22] A single site evaluation in Quebec, Canada affirmed the clinical trial data, and reported median length of stay to be shorter with rivaroxaban use (3.5 days) relative to LMWH alone or warfarin therapy (6 days).[19] Similarly, a single American institution identified those discharged on rivaroxaban compared to warfarin had shorter hospital stays (3.5 and 7 days, respectively; P<0.001).[23] Our study also identified a shorter length of stay amongst patients receiving a DOAC, consistent with these data (Table 3).[19,22,23] Our results, however, may have been confounded by those having more severe thrombosis receiving traditional therapies.

STRENGTHS AND LIMITATIONS

Herein we present a large cohort of patients with acute VTE being discharged following hospitalization. For all sites, we reviewed all medical records with a discharge diagnosis of deep vein thrombosis (DVT) (ICD-10 code I82 + sub-indices) or pulmonary embolism (PE) (ICD-10 code I26 + sub-indices) over the span of a full year (April 2014 to March 2015). In doing so, different sample sizes were identified from each area, with rural Alberta and Regina having fewer patients (N=30 and N=120, respectively) than the Edmonton area (N=545). Despite the differences in sample sizes, these data reflect local practices given the geographic populations and catchment areas (Edmonton: 1,328,290 plus catchment of ~500,000; Regina: 230,020 plus catchment of 500,000; rural Alberta 3 sites: 30,065) and that an entire year was assessed.[24-28] The timing of our audit is reflective of the early uptake of DOACs

for the acute treatment of VTE given only rivaroxaban had Health Canada approval throughout the entire time interval audited. Provincial remuneration was only starting to occur, only being in place for rivaroxaban for the duration of the audit year for DVT in both provinces and for PE in June 2014 for Saskatchewan (beyond the audit year for PE in Alberta). Given the timing of approval and remuneration, prescribing patterns may have changed beyond the timing of this audit (March 2015). Despite this, we identified reasonable uptake of the DOACs (28.3%), with use that complied with product monograph labeling in the vast majority (85.8%). This data can serve as a marker for future analyses wherein usage can be compared to assess the uptake of this therapeutic approach over time as guidelines more aggressively incorporate the utilization of DOACs in this population and clinicians become more comfortable with their use.

Our design (retrospective medical record review) was selected to allow us to accurately select patients with acute VTE to ascertain practice patterns. Given the diverse geography and volume of records to review, 3 data abstractors were necessary. A master key defining eligibility, data points to collect and how to code variables in REDCap was used. Within REDCap, restrictions for variables were programmed to minimize data entry error. Prior to finishing data collection at each site, quality assurance reports were performed to ensure accuracy of data. As this was a record review, we were limited only to information available in the hospital-based chart. Given this, some data elements were not documented (e.g., weight, serum creatinine), leaving us to report data for those available. Moreover, our design did not enable us to collect data following hospital discharge, limiting us from determining if patients got their prescriptions filled or had complications following discharge.

CONCLUSION

In summary, we report the management of a large cohort of acute VTE patients being discharged from hospitals within Canada. Over a time interval early in the approval process for DOACs for the acute treatment of VTE, we report a modest update of DOACs (28.3%) that were, overall, dosed

correctly for the majority of patients (85.8%). Variation in therapies used was evident with the most common regimen being warfarin-based in Regina (60.7%) and Edmonton (40.5%) and a DOAC in rural Alberta (50.5%) (P<0.0001). Use of rivaroxaban was proportionately higher for less severe clots, and those prescribed a DOAC had a shorted length of stay relative to those given traditional therapies. As time evolves, it is anticipated use of DOACs will increase for the management of VTE. Practitioners and health delivery systems should continue to consider the opportunity provided by the DOACs to simplify and shorten hospital based care as further data emerges to support their place in therapy. Future evaluations should occur to assess temporal changes, ongoing appropriateness of care delivery and the impact that DOACs may have on healthcare system resource allocation.

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DATA SHARING AGREEMENT

There is no data sharing agreement – this is included in the original research article.

AUTHOR CONTRIBUTIONS

TJB contributed to the design of the work, the acquisition, analysis and interpretation of the data. TJB drafted the original manuscript, approved the final version to be published and is accountable for all aspects of the work related to accuracy or integrity. BR contributed to the design of the work, the interpretation of the data and critically revised the manuscript. BR approved the final version to be published and is accountable for all aspects of the work related to accuracy or integrity. JB contributed to the acquisition and interpretation of the data, critically revised the manuscript and approved the final version to be published. JB is accountable for all aspects of the work related to accuracy or integrity. WS contributed to the design, acquisition and interpretation of the data, critically revised the manuscript and approved the final version to be published. WS is also accountable for the accuracy and integrity of this work.

Figure 1: Patient Flow

Table 1: Baseline Characteristics

	Total	Edmonton	Rural Alberta	Regina
Screened (N)	958	736	41	181
Included (N, %)	695 (72.5%)	545 (74.0%)	30 (73.2%)	120 (66.3%)
Male (N, %)	350 (50.4%)	282 (51.7%)	16 (53.3%)	52 (43.3%)
Mean age (mean ± SD)	63.3 ± 17.3	63.8 ± 17.2	64.2 ± 16.9	60.4 ± 17.6
Weight Documented (N, %)[a]	680 (97.8%)	534 (98.0%)	28 (93.3%)	118 (98.3%)
Weight, Kg (Median, IQR)	85.5 (70.0, 106.0)	84.5 (70.0, 106.0)	84.3 (71.0, 98.3)	90.5 (70.0, 110.0)
CrCl Documented (N, %) [a]	661 (95.0%)	515 (94.5%)	29 (96.7%)	117 (97.5%)
< 30 mL/min	23 (3.5%)	20 (3.9%)	1 (3.5%)	2 (1.7%)
30-49 mL/min	121 (18.3%)	96 (18.6%)	3 (10.3%)	22 (18.8%)
> 50 mL/min	517 (78.2%)	399 (77.5%)	25 (86.2%)	93 (79.5%)
VTE				
DVT	119 (17.1%)	85 (15.6%)	11 (36.6%)	23 (19.2%)
Distal	13 (10.9%)	7 (8.2%)	0	6 (26.1%)
Proximal[b]	99 (83.2%)	74 (87.1%)	9 (81.8%)	16 (69.6%)
Not documented	7 (5.9%)	4 (4.7%)	2 (18.2%)	1 (4.3%)
PE and PE + DVT [c]	576 (82.9%)	460 (84.4%)	19 (63.3%)	97 (80.8%)
PE – Simplified PESI Score:[d]	567 (98.4%)	451 (98.0%)	19 (100%)	97 (100%)
0 point	201 (35.4%)	151 (33.5%)	10 (52.6%)	40 (41.2%)
≥ 1 points	366 (64.6%)	300 (66.5%)	9 (47.4%)	57 (58.8%)
History of:				
Cancer	158 (22.7%)	119 (21.8%)	10 (33.3%)	29 (24.2%)
Pulmonary disease	143 (20.6%)	114 (20.9%)	6 (20.0%)	23 (19.2%)
Prior VTE	100 (14.4%)	81 (14.9%)	6 (20.0%)	13 (10.8%)
Recent surgery	32 (4.6%)	23 (4.2%)	0	9 (7.5%)
Length of Stay (median, IQR)	6.0 (3.0, 11.0)	6.0 (3.0, 11.0)	5.5 (3.0, 13.0)	6.0 (3.0, 9.0)

CrCl=Creatinine Clearance; SD=Standard Deviation; IQR=Interquartile Range; PE=Pulmonary Embolism; DVT=Deep Vein Thrombosis; PESI= Pulmonary Embolism Severity Index; LOS=Length of Stay

[a]not all patients had weight and serum creatinine documented in the chart

[b]Combined popliteal, femoral, common femoral, and iliac

[c]combined PE with PE+DVT and report it all as PE

[d]PESI score could not be calculated in 9 patients due to missing variable(s)

Table 2: Therapy at Discharge and Follow-Up Plan for Hospitalized Cohort

	Total	Edmonton	Rural Alberta	Regina	P Value
VTE (All Combined)					<0.0001*
Parenteral AC alone	185 (26.6%)	160 (29.4%)	6 (20.0%)	19 (15.8%)	
Parenteral AC + warfarin	145 (20.9%)	83 (15.2%)	4 (13.3%)	58 (48.3%)	
Warfarin	158 (22.7%)	138 (25.3%)	5 (16.7%)	15 (12.5%)	
DOAC	197 (28.3%)	154 (28.3%)	15 (50.0%)	28 (23.3%)	
Rivaroxaban	192 (97.5%)	151 (98.1%)	14 (93.3%)	27 (96.4%)	
Dabigatran	2 (1.0%)	0	1 (6.7%)	1 (3.6%)	
Apixaban	3 (1.5%)	3 (2.0%)	0	0	
Not Documented	10 (1.4%)	10 (1.8%)	0	0	
PE and PE+DVT					<0.0001*
Parenteral AC alone	146 (25.3%)	129 (28.0%)	5 (26.3%)	12 (12.4%)	
Parenteral AC + warfarin	129 (22.4%)	77 (16.7%)	1 (5.3%)	51 (52.6%)	
Warfarin	132 (22.9%)	119 (25.8%)	2 (10.5%)	11 (11.3%)	
DOAC	161 (28.0%)	127 (27.6%)	11 (57.9%)	23 (23.7%)	
Rivaroxaban	156 (96.9%)	124 (97.6%)	10 (90.9%)	22 (95.6%)	
Dabigatran	2 (1.2%)	0	1 (9.1%)	1 (4.4%)	
Apixaban	3 (1.9%)	3 (2.4)	0	0	
Not Documented	8 (1.4%)	8 (1.7%)	0	0	
DVT alone					0.045*
Parenteral AC alone	39 (32.8%)	31 (36.5%)	1 (9.1%)	7 (30.4%)	
Parenteral AC + warfarin	16 (13.4%)	6 (7.1%)	3 (2.7%)	7 (30.4%)	
Warfarin	26 (21.8%)	19 (22.4%)	3 (27.3%)	4 (17.4%)	
DOAC	36 (30.3%)	27 (31.8%)	4 (36.4%)	5 (21.7%)	
Rivaroxaban	36 (100%)	27 (100.0%)	4 (100.0%)	5 (100.0%)	
Dabigatran	0	0	0	0	
Apixaban	0	0	0	0	
Not Documented	2 (1.7%)	2 (2.4%)	0	0	
Follow-Up					
Family Doctor	358 (51.5%)	276 (50.6%)	20 (66.7%)	62 (51.7%)	P=0.23
VTE Clinic	202 (29.1%)	201 (36.9%)	1 (3.3%)	0	P<0.001
Specialist	124 (17.8%)	58 (10.6%)	3 (10.0%)	63 (52.5%)	P<0.001
Anticoagulation Clinic	34 (4.9%)	10 (1.8%)	0	24 (20.0%)	P<0.001

Return to ED	10 (1.4%)	8 (1.5%)	2 (6.7%)	0	P=0.045
Other	101 (14.5%)	90 (16.5%)	6 (20.0%)	5 (4.2%)	
Not documented	41 (5.9%)	33 (6.1%)	2 (6.7%)	6 (5.0%)	

VTE=Venous Thromboembolism; PE=Pulmonary Embolism; DVT=Deep Vein Thrombosis; DOAC=Direct Oral Anticoagulant; AC=Anticoagulant; ED=Emergency Department

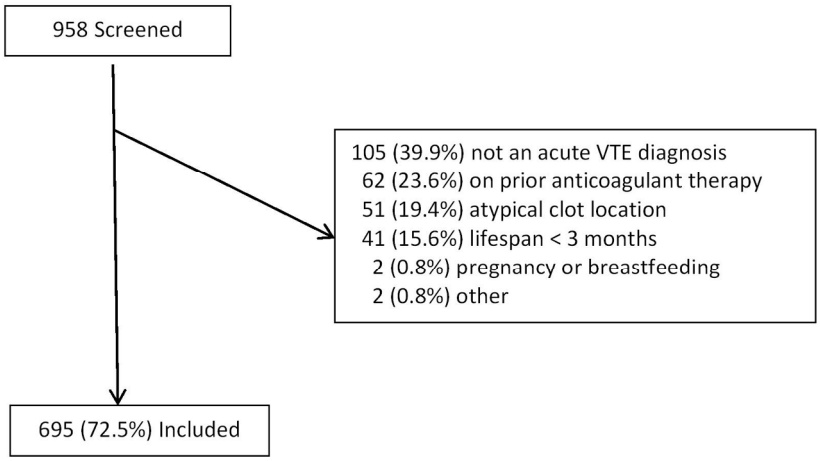
*P value compares therapies (categorized as parenteral anticoagulant alone, parenteral anticoagulant with warfarin, warfarin or a direct acting anticoagulant) used across the 3 settings

Table 3: Length of Stay in Days (Median, IQR) Based on Therapy

Therapy	All	Edmonton	Rural Alberta	Regina
DOAC	4 (2.0, 9.0)	4 (2.0, 8.0)	6 (2.0, 19.0)	4.5 (2.0, 8.5)
Parenteral Alone	5 (3.0, 10.0)	5 (2.0, 9.0)	15 (5.0, 21.0)	6 (4.0, 10.0)
Parenteral + Warfarin / Warfarin alone	7 (4.0, 12.0)	8 (4.0, 14.0)	4 (2.0, 6.0)	7 (4.0, 9.0)
P Value	<0.0001	<0.0001	0.091	0.223

DOAC=Direct Oral Anticoagulant

Figure 1: Patient Flow



165x95mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	NA-full year of data
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, Figure 1
		(b) Give reasons for non-participation at each stage	8, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.