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Original Article

Real-World Data on Characteristics and Management of Community Patients Receiving Anticoagulation Therapy Who Presented with Acute Bleeding to the Emergency Department at a Regional Australian Hospital: A Prospective Observational Study

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Abstract. ***Objective:*** **To study patients receiving anticoagulants with or without antiplatelet therapy presenting at a regional Australian hospital with bleeding. The main aims are to explore: (1) patients' characteristics and management provided; (2) association between the type of anticoagulant and antiplatelet agent used and the requirement of reversal; (3) and the length of hospital stay (LoS) in conjunction with bleeding episode and management.**
Methods: **A prospective cross-sectional review of medical records of all patients who presented at a tertiary referral centre with bleeding while receiving anticoagulation therapy between January 2016 and June 2018. Data included: patients, demographics, investigations (kidney and liver function tests, coagulation profile, FBC), LoS, bleeding site, type of and reason for anticoagulation therapy, and management provided. Data analysis included descriptive statistics, χ^2 association, and regression models.**
Results: **Among the 144 eligible patients, 75 (52.1%) were male, and the mean age was 76 years (*SD*=11.1). Gastrointestinal tract bleeding was the most common (*n*=48, 33.3%), followed by epistaxis (*n*=32, 22.2%). Atrial fibrillation was the commonest reason for anticoagulation therapy (*n*=65, 45.1%). Warfarin was commonly used (*n*=74, 51.4%), followed by aspirin (*n*=29, 20.1%), rivaroxaban (*n*=26, 18.1%), and apixaban (*n*=12, 8.3%). The majority had increased blood urea nitrogen (*n*=67, 46.5%), while 58 (40.3%) had an elevated serum creatinine level, and 59 (41.0%) had a mild reduction in eGFR. Thirty-five of the warfarinised patients (47.3%) had an INR above their condition's target range despite normal liver function. Severe anaemia (Hb<80g/L) was reported in 88 patients (61.1%). DOACs were associated with a reduced likelihood of receiving reversal (*B*= -1.7, *P*=<.001), and with a shorter LoS (*B*= -4.1, P=.046) when compared with warfarin, LMWH, and antiplatelet therapy.**
Conclusion: **Warfarin use was common among patients who presented with acute bleeding, and the INR in many warfarinised patients exceeded the target for their condition. DOACs were associated with a reduced likelihood of receiving reversal and a shorter LoS than warfarin, LMWH, which might support a broader application of DOACs into community practice.**

Keywords: Anticoagulation; Antiplatelets; Bleeding; Reversal; DOAC; Length of Hospital stay; Outcome.

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Introduction. One in every 20 patients will suffer from venous thromboembolism (VTE), either in the form of DVT alone or in combination with PE.[1] VTE is associated with high morbidity and mortality rates and significantly harms the quality of life. Furthermore, it has negative financial consequences. All of this highlights the need for proper prevention[2] and treatment. VTE management requires a challenging risk assessment,[2] and measures which may be pharmacological, mechanical, surgical, or a combination.[3] Pharmacological anticoagulation therapy is most common and includes anticoagulants[4] and antiplatelet agents.[5] Anticoagulants are classified into vitamin K antagonists (such as warfarin), unfractionated heparin, low molecular weight heparin (LMWH, e.g., enoxaparin), and the novel direct oral anticoagulants (DOACs), including rivaroxaban, apixaban, and dabigatran.[4] Anticoagulants work by targeting steps in the coagulation cascade.[4] DOACs achieve an equivalent anticoagulant effect to classical anticoagulants (warfarin, heparin, and its derivatives) with equal or reduced bleeding risk.[6-8] While more specific,[9] the DOACs are more costly than warfarin, which may hinder widespread use in the community, even though they do not need a specific monitoring test.[10] Balancing the benefits of anticoagulants against the associated risks is a concern for clinical practice and requires further real-world evidence to support decision-making.

The rate of major bleeding resulting from receiving anticoagulants in Australia is high (seven out of every 100 patients per year),[11] suggesting the need for pragmatic, evidence-based guidelines for their use. While the DOACs have relatively low bleeding risk when compared with warfarin,[8,12,13] clinicians do not tend to use DOACs because they are difficult to monitor and no standard reversal agent is available.[14,15]

The treatment of patients presenting with bleeding while receiving anticoagulants with or without antiplatelet agents is based on many factors, such as the source of bleeding, hemodynamic stability of the patient, and the severity of blood loss.[16] In major bleeding, the management provided might include interventions such as reversing the effect of a therapeutic agent, a surgical achievement of homeostasis, or a combination of both.[17,18] Since reversal is indicated for severe and life-threatening haemorrhage among such patients,[19] it might be acceptable to consider reversal-receiving as an indicator of a severe bleeding episode. There are currently limited studies of the real-world association between pharmacological anticoagulation therapy and reversal being implemented in severe and life-threatening bleeding events. Further, patients who receive a reversal of anticoagulant therapy often require hospitalisation and recommencement of anticoagulation therapy. This decision could be challenging, given the lack of evidence-based guidelines in the selection of therapy.[20,21]

LoS is used extensively in the literature to indicate the severity of a condition and the efficacy and cost of treatment.[22] Moreover, LoS is used as an outcome measure for health services,[23] including quality improvement.[24] It is worth noting that the use of LoS as an outcome measure should be taken into account for other individual factors as an indicator of both bleeding severity and management cost.[24] Currently, only a few studies have explored the LoS associated with bleeding events among patients receiving anticoagulation therapy in Australia.

The aim of this study was to explore the gap between VTE assessment and management guidelines on the one hand and clinical practice on the other. This purpose was achieved by investigating patients receiving anticoagulants with or without antiplatelet agents who presented with an acute bleeding episode at a regional tertiary referral hospital, Launceston General Hospital Emergency Department (LGH-ED). This exploration included the patients' characteristics, organ function in correlation with their bleeding presentation and the management provided, type of anticoagulation therapy, the severity of bleeding, and LoS. Translating the findings into real-world clinical practice might bridge the knowledge–practice gap in this field.

Methods.

Ethics approval. The project was approved by the Human Research Ethics Committee, the University of Tasmania (H0016734). Because this study was a clinical audit where patient management was not affected, and patients were not actively participating, consent was not required from patients; thus, the Ethics Committee agreed to waive the consent requirement for this low-risk audit.

Data sampling. Data sampling was limited to patients who presented to the LGH-ED with acute bleeding and at the same time were receiving anticoagulation therapeutic agent(s). The LGH is a tertiary regional referral centre in Northern Tasmania, and it has the only

Emergency Department within a 100-kilometer radius in the region. The LGH has an electronic/digital medical record (DMR) for all patients presenting to the Emergency Department. Thus, we conducted an electronic search for all patients who presented with bleeding in the period between January 2016 and June 2018. The Pharmacy Department then checked the records at the LGH to determine whether those patients were receiving anticoagulation-therapeutic agent(s) in the form of an anticoagulant with or without antiplatelet agents. Accordingly, only records that satisfied our selection criteria – presentation with acute bleeding while receiving anticoagulation therapeutic agent in the form of DOACs plus/minus antiplatelet agents – were included in the analysis.

Data collection. Data were extracted from the LGH patients' DMR. The LGH electronic patient file and computerised records provided basic demographics such as age, gender, ethnic group, and language. Further, the system data provided information about the bleeding episode, including the source of bleeding, admission/discharge details, management provided, and LoS in days. The DMR offers data about the indications for administering anticoagulation therapeutic agent(s) and their doses and results of routine blood tests carried out on admission for each patient presenting with bleeding. These tests included full blood count (FBC), renal function (blood urea nitrogen, serum creatinine, eGFR), liver function (ALT, AST albumin, bilirubin), bleeding and coagulation profile (INR, APTT, PT, platelet count), and intervention provided.

Table 1. Characteristics of patients receiving anticoagulation therapy who presented to the LGH-ED with acute bleeding during the study period between January 2016 and June 2018.

		Count	Percent
Gender			
	Female	69	(47.9%)
	Male	75	(52.1%)
Site of bleeding			
	CNS	3	(2.1%)
	GIT	48	(33.3%)
	Epistaxis	32	(22.2%)
	Haematuria	14	(9.7%)
	Skin	9	(6.3%)
	Mucous membrane	2	(1.4%)
	Internal	6	(4.2%)
	Others	22	15.3%)
Reason for anticoagulation therapy			
	AF	65	(45.1%)
	valvular	7	(4.9%)
	PE/VTE	19	(13.2%)
	Stroke	3	(2.1%)
	Prophylactic	27	(18.8%)
Anticoagulation therapeutic agent(s)		Multiple Response Count	Response %
	Warfarin	74	(51.4%)
	Rivaroxaban	26	(18.1%)
	Apixaban	12	(8.3%)
	Dabigatran	8	(5.6%)
	Clexane	11	(7.6%)
	Clopidogrel	12	(8.3%)
	Aspirin	29	(20.1%)
	Other anticoagulants	1	(.7%)
		Mean	(*SD*)
Age		76	(11.1)
Lab investigations on admission			
	Creatinine µmol/L	105	(57.7)
	Urea mmol/L	10.66	(8.3)
	eGFR mL/min	60	(22.3)
	AST U/L	25	(18.6)
	ALT U/L	22	(27.6)
	Bili µmol/L	13	(12.0)
	Hb g/L	117	(26.2)
	Platelet /mL	274	(302.1)
	INR	2.2	(3.5)
	aPTT (sec)	38	(14.0)
	PT (sec)	15.14	(5.4)
Length of stay (days)		5	(5.0)

Data analysis. Data were analysed using SPSS V26.1.[25] The values of laboratory tests were categorised after adjusting for gender, as per the reference intervals published by the Royal College of Pathologists of Australasia or the World Health Organization.[26] The anticoagulation therapeutic agent(s) were re-categorised based on the mechanism of action (antiplatelet or anticoagulants). Participants' characteristics, count, and valid percentages (for non-missing values) were calculated for categorical variables, and means with standard deviation (*SD*) were calculated for continuous variables. The association between the reason for administering anticoagulation therapeutic agent(s) and the medication used was evaluated by a multinomial logistic regression. A Firth logistic regression model was used to overcome the small sample size to explore the association between the type of anticoagulation therapeutic agent(s) and receiving reversal. Finally, an adjusted linear regression model was used to explore the association between the type of anticoagulation therapeutic agent(s) used and LoS.

Results.

Participant characteristics. Among the 1501 patients presenting to the ED at the LGH in the period between January 2016 and June 2018 with a diagnosis of acute bleeding, only 144 (14.4%) were identified by the Pharmacy Department as receiving anticoagulation therapeutic agent(s) in the form of anticoagulants or antiplatelet agents and therefore were eligible for inclusion in our study. Just over half of patients were males *n*=75 (52.1%), and the mean age was 76 years (*SD*=11.1). Gastrointestinal tract (GIT) bleeding was the most common site of bleeding in 48 patients (33.3%), followed by epistaxis (*n*=32, 22.2%), while haematuria was present in 14 patients (9.7%). The most common reason for administering anticoagulation therapeutic agent(s) was atrial fibrillation (AF) (*n*=65, 45.1%), while PE/VTE treatment was documented in 19 patients (13.2%), and other reasons for anticoagulation therapy were also given (*n*=27, 18.8%). In a multiple response descriptive analysis for the type of anticoagulation therapeutic agent(s) used among the patients presented with acute bleeding, warfarin was the most common (*n*=74, 51.4%), followed by aspirin, which was used by 29 patients (20.1%), then rivaroxaban (*n*=26, 18.1%). Patients' characteristics are detailed in **Table 1**.

According to a multinomial logistic regression model for the type of anticoagulation therapeutic agent(s) used and the reason for administration, DOACs were more likely to be used with AF patients (*OR*=9.6, *P*=.016) than warfarin (*OR*=6.1, *P*=.044). Also, for DVT/PE treatment, LMWH was significantly used (OR=30.0, P=.003) than DOACs when compared with warfarin.

Patient management.

Laboratory investigations. On patients' presentation at the LGH-ED with acute bleeding, routine laboratory investigations were carried out, including coagulation profile, FBC, and kidney and liver function for all patients. It was found that a majority (*n*=67, 46.5%) had an increased blood urea nitrogen level (>3.0-8.0 mmol/L), while 59 (41.0%) had a mild reduction in eGFR (60–89 mL/min). The liver function test showed that most patients had normal AST (*n*=103, 71.5%), all of them had a normal ALT test (*n*=144, 100%), and normal bilirubin levels (<20 mmol/L) (*n*=131, 91.0%). Among those under the vitamin K antagonist warfarin (*n*=74), many (*n*=35, 47.3%) had their INR above the target range (adjusted for the reason of administration),[27] despite a minority having elevated AST (*n*=14, 18.9%), while all (100%) had normal ALT without a known liver disease. It is worth noting that no data were available on assays used for measuring DOACs activities. Most patients (*n*=112, 77.8%) had a normal platelet count (150-400 $x10^9$/L), but a few (*n*=18, 12.5%) had thrombocytopenia (<150 $x10^9$/L), and among them 13 (72.2%) had severe thrombocytopenia (less than 30 $x10^9$/L). Thrombocythemia (>400 $x10^9$/L) was reported in 14 (9.7%) patients. However, most patients (*n*=88, 61.1%) were found to have severe anaemia (Hb: female <80g/L, male <80g/L), which was based on the PenaRosas, et al.[26] guidelines on haemoglobin concentration for diagnosis and assessment of anaemia severity published by the World Health Organization. Details of laboratory investigations are found in **Table 2**.

Treatment provided. Among those patients who presented with bleeding while receiving anticoagulation therapy, 128 patients (88.9%) were admitted for management, and 81 patients (56.3%) received an intervention. Among those patients who received an intervention, medical management was the most common (*n*=44, 54.3%) followed by surgical intervention (n=28, 34.6%), such as ligation/cautery of the bleeding vessel, while a few received a combined medical and surgical management (n=9, 11.1%). Among those who received reversal (*n*=47), by using multiple response descriptive, vitamin K was the most frequent (*n*=23, 48.9%), while 17 (36.2%) received prothrombin (**Table 3**).

The choice of anticoagulation therapeutic agents on recommencement was similar to the pre-admission agent: warfarin (*OR*=17.5, *P*=<.001), rivaroxaban (*OR*=60.7, *P*=<.001), apixaban (*OR*=22.2, *P*=<.001), clexane (*OR*=8.1, *P*=<.033), clopidogrel (*OR*=61.9, *P*=<.001), and aspirin (*OR*=64.0, *P*=<.001). For more detail, see **Table 4**.

Type of anticoagulation therapeutic agent(s) associated with receiving reversal. Based on a χ^2 association for receiving reversal and the type of anticoagulation therapeutic agent(s), vitamin K antagonist (χ^2 =24.2,

Table 2. Laboratory profile of patients presenting with acute bleeding receiving anticoagulation therapy using lab reference ranges.

		Count	(%)
Blood urea			
	Reduced (<3.0mmol/L)	10	(6.9%)
	Normal (3.0-8.0 mmol/L)	67	(46.5%)
	Increased (>8.0mmol/L)	67	(46.5%)
Serum creatinine on admission			
	Lower than the normal range	8	(5.6%)
	Normal (male 59–104µmol/L, female: 45-84µmol/L)	78	(54.2%)
	Higher than the normal range	58	(40.3%)
eGFR on admission			
	Normal (>90 mL/min)	19	(13.2%)
	Mild reduction (60–89 mL/min)	59	(41.0%)
	Moderate reduction (30–59 mL/min)	49	(34.0%)
	Severe reduction (15–29 mL/min)	8	(5.6%)
	Renal failure (<15 mL/min)	9	(6.3%)
AST on admission			
	Normal AST range (female 6–34 IU/L or male 8–40 IU/L)	103	(71.5%)
	Elevated AST	14	(9.7%)
ALT on admission			
	Normal ALT range <35U.L	144	(100.0%)
	Elevated ALT >35 U/L	0	(0%)
Bill Categories on admission			
	Normal (<20 umol/L)	131	(91.0%)
	Elevated(>20 umol/L)	13	(9.0%)
Anaemia status on admission (based on WHO Hb concentration for anaemia diagnosis and adjusted for gender)			
	Non-anaemia (Hb: Female>120 g/L, male>130g/L)	32	(22.2%)
	Mild anaemia (Hb: female 110–119g/L. male 110–129g/L)	9	(6.3%)
	Moderate anaemia (Hb: female 80–109g/L, male 80–109g/L)	15	(10.4%)
	Severe anaemia (Hb: female <80g/L, male <80mg/L)	88	(61.1%)
Platelet count on admission			
	Normal platelet count (150–400 x10^9 per litre)	112	(77.8%)
	Thrombocytopenia (<150 x10^9 per litre)	18	(12.5%)
	Thrombocythemia (>400 x10^9 per litre)	14	(9.7%)
INR target range adjusted for the administration reason in warfarinised patients[27] (*n*=74)			
	Below target INR range	15	(20.3%)
	At target INR range	23	(31.1%)
	Above target INR range	35	(47.3%)
	INR range in warfarinised patients (*n*=73)		
	< 2.00	15	(20.3%)
	2.00-5.00	40	(54.1%)
	5.01-10.00	18	(24.3%)

Table 3. Management provided to patients.

		Count	(%)
Admitted for management (Yes)		128	(88.9%)
Intervention provided (*n*=81, 56.3%)			
	Medical	44	(54.3%)
	Surgical	28	(34.6%)
	Medical and surgical	9	(11.1%)
Reversal received	Yes	47	(58.0%)
Medication used for reversal		**Multiple response count**	**Multiple response %**
Vitamin K		23	(48.9%)
Prothrombin		17	(36.2%)
Fresh Froze Plasma		11	(23.4%)
Platelet		3	(6.4%)
Other reversal medications		18	(38.3%)
Novoseven		0	(0.0%)
Idrucizamab		0	(0.0%)
Protamine sulphate		0	(0.0%)

Table 4- Bivariate association between the anticoagulant therapeutic agent(s) used before and those recommenced after bleeding event.

VTE therapeutic on presentation	Recommenced anticoagulants Therapeutic agents	OR	P-value	95% CI for OR	
				Lower	Upper
Warfarin	Warfarin	17.5	<0.001	6.3	48.3
Rivaroxaban	Rivaroxaban	60.7	<0.001	14.1	261.3
Apixaban	Apixaban	22.8	<0.001	5.1	101.0
Dabigatran	Dabigatran	8.4	0.999	0.000	-[a]
Clexane	Clexane	8.167	0.033	1.1	56.2
Clopidogrel	Clopidogrel	61.9	<0.001	9.0	422.2
ASA	ASA	64.0	<0.001	16.8	242.6

[a] Not calculated due to observation being <=5; ASA: acetylsalicylic acid; CI: confidence interval; OR: Odds Ratio.

P=<.001) and DOACs (χ^2=12.7, *P*=<.001) were significantly associated with receiving reversal (**Table 5**). Using a Firth logistic regression, DOACs use was associated with a reduced likelihood of receiving reversal compared with vitamin K antagonists (B=-1.7,

Table 5. Bivariate association between receiving reversal and anticoagulation therapeutic agent(s).

Anti VTE therapeutic agent		Reversal received (YES)				
		N	**(%)**	**X^2**	***df***	***P*-value**
Vitamin K antagonists	Yes	39	82.7	24.199	1	<.001
Directly oral anticoagulants	Yes	6	12.7	12.756	1	<.001
LMWH	Yes	2	4.2	1.426	1	0.232[b]
Antiplatelet agents	Yes	12	25.5	0.304	1	0.582
Firth Logistic Regression of receiving reversal						
Coefficients						
			95% *CI* for *B*			
	B estimate	Std. Error	**Lower**	**Upper**	X^2	**Sig.**
Vitamin K antagonists	Ref	-	-	-	-	-
Directly acting oral anticoagulants	-1.712	0.484	-2.728	-0.827	15.618	0.000
LMWH	-1.260	0.786	-2.976	0.102	3.257	0.071
Antiplatelet agents	0.091	0.455	-0.805	0.968	0.041	0.840

P=<.001), as shown in **Table 5**. It is worth noting that idarucizumab is the approved reversal for dabigatran in Australia. We observed the use of other options[19] for reversing the effect of DOACs in some cases, such as prothrombin complex and fresh frozen plasma.

Association between the type of anticoagulation therapeutic agent and LoS due to the acute bleeding event in an adjusted linear regression model. In an adjusted linear regression model for LoS in days, DOACs were associated with a significantly shorter LoS (*B*=-4.1, 95% CI: -8.177, -0.082, *P*=0.046) when compared with vitamin K antagonist (warfarin); additionally, a higher haemoglobin concentration on admission was associated with a shorter LoS (*B*=-0.083, 95% CI: -0.150- -0.016, *P*=0.016) (**Table 6**).

Discussion. This study illustrates the characteristics and profile of patients receiving different anticoagulation therapy – in the form of oral anticoagulants including DOAC and antiplatelet agents – who presented with acute bleeding at a regional tertiary hospital in Tasmania, Australia. The associations between the type of anticoagulation therapeutic agent on the one hand and

Table 6: Linear regression model for LoS in days

				95% *CI* for *B*	
	***B* estimate**	**Std. Error**	***P*-value**	**Lower**	**Upper**
Constant	1.119	17.11	0.948	-33.87	36.11
Age	0.152	0.074	0.051	-0.001	0.304
Gender (male)	3.773	2.150	0.090	-0.624	8.170
Anticoagulation therapeutic agent(s)					
Vitamin K antagonist	Ref	-	-	-	-
Directly acting oral anticoagulants	-4.129	1.979	0.046	-8.177	-0.082
LMWH	-2.180	3.750	0.566	-9.850	5.490
Antiplatelet agents	1.296	1.940	0.509	-2.672	5.263
Intervention required	0.765	1.480	0.609	-2.261	3.792
creatinine µmol/L	-0.017	0.065	0.800	-0.151	0.117
Urea mmol/L	-0.032	0.119	0.788	-0.275	0.210
eGFR mL/min	-0.011	0.110	0.919	-0.237	0.214
AST U/L	-0.010	0.056	0.857	-0.125	0.104
ALT U/L	0.086	0.068	0.214	-0.053	0.225
Bili µmol/L	-0.101	0.093	0.286	-0.292	0.089
Hb g/L	-0.083	0.033	0.016	-0.150	-0.016
Platelet /mL	0.002	0.012	0.878	-0.022	0.026
INR	-4.749	2.806	0.101	-10.489	0.991
APTT (sec)	0.220	0.130	0.101	-0.046	0.486
PT (sec)	0.150	0.212	0.486	-0.284	0.584

ALT: alanine transferase; APTT: artificial partial prothrombin time; AST: aspartate transferase; Bili: bilirubin; eGFR: glomerular filtration rate; INR: international normalizing ratio; PT: prothrombin time; VTE: venous thromboembolism.

the severity of bleeding and receiving reversal agent(s) on the other, in conjunction with LoS, were studied. The study showed that warfarin was a frequent anticoagulation therapeutic agent among patients who presented with bleeding. Additionally, many of those warfarinised patients had INRs above the desired target range for the condition being administered. While conventional coagulation profile tests were requested for most patients, no agent-specific laboratory tests were requested for patients receiving DOACs. When

compared with warfarin, DOACs use was more common in patients with AF. It is worth noting that the Therapeutic Goods Administration (TGA) approves dabigatran in non-valvular AF patients only; rivaroxaban and apixaban are approved for both non-valvular AF and anticoagulation-treatment and prophylaxis. While most patients were admitted for management, many had already received medical management to reverse the effect of the anticoagulation therapeutic agent(s). The reversal agents were less likely to be used with DOACs than warfarin and other anticoagulation therapeutic agents (s). On exploring the association between LoS and individual agents (in an adjusted analysis), the use of DOACs was associated with a shorter LoS than LMWH or antiplatelets compared to warfarin. It is worth mentioning that LoS was longer when the patient had lower haemoglobin concentration on admission.

The study findings might enhance the use of DOACs,[28] which were introduced about ten years ago in Australia and had a steady prescription pattern at the present study time. However, because the study did not weigh the prevalence of these medications' prescription rates, caution should be exercised. Overall, the recommended target INR range was not achieved in many patients who received warfarin and presented with bleeding.[29] This suggests the need for continued educational development on pharmacological anticoagulation therapy and clear guidelines and decision aids for medical professionals. While most patients had global coagulation tests, it is argued that these tests are not reliable in patients receiving DOACs.[30] Some assays are currently available for DOACs, such as ecarin clotting time (ECT) and chromogenic anti-FXa,[18] but they were seldom requested by the ED physicians in this study. This finding might suggest the need to improve medical practitioners' knowledge about more reliable tests for measuring DOACs activity.

The majority (*n*=128, 88.9%) of patients who had bleeding because of anticoagulation therapeutic agents were admitted for management. Thirty-one patients (24%) needed reversal. However, this study was able to identify that patients on DOACs were less likely to receive reversal when compared with those who were on warfarin or LMWH. This finding supports the wider implementation of DOACs[28] when compared with warfarin and other anticoagulation therapeutic agents. The real-world association between receiving reversal in patients who presented with life-threatening bleeding due to anticoagulation therapy is very difficult to obtain using other research designs, considering that prolonged cohort studies require substantial resources. However, the present study arrived at the same inference using a cross-sectional design.

Furthermore, the present study was able to find a significant association between pre-and post-bleeding pharmacological anticoagulation therapeutic agents. In contrast, dabigatran and clexane were less likely to be used on the resumption of pharmacological anticoagulation therapy when compared with other agents. It is worth noting that, in Australia, dabigatran and antiplatelet agents are not indicated for the treatment of VTE. Accordingly, this finding ought to be explored in future research.

Using an adjusted analysis[24] for LoS, it was found that DOACs were associated with a shorter LoS (P=0.046) compared with warfarin, LMWH, and antiplatelets. This finding was consistent with two recent studies.[31,32] These studies have concluded that DOACs were significantly associated with a shorter LoS compared to warfarin.[31,32]

Furthermore, there is evidence that DOACs cost significantly less than warfarin for hospitalisation due to a specific bleeding event with blunt traumatic intracranial hemorrhage.[22] However, what is novel in the current study was the wide variety of the bleeding sites and the wide range of anticoagulation therapeutic agents used for various reasons, such as VTE prophylaxis or treatment, in correlation with coagulation profile and kidney and liver function and management and or interventions that were conducted at the time of presentation. Although it might be argued that upfront costs for warfarin administration are cheaper when compared with DOACs,[10] our finding suggests that DOACs are more cost-effective overall in the long run when compared with warfarin or other agents, considering the reduced likelihood of patients' presentations to ED and receiving reversal and the significantly shorter LoS.

Recent literature showed that DOACs have a better safety profile than warfarin, particularly intracranial and subarachnoid haemorrhage.[33] Moreover, rivaroxaban appears to be better than warfarin in limitation of blood-brain barrier disruption after intracranial haemorrhage.[34] In addition to the VTE prophylaxis effect, DOACs show non-inferior results and superior results compared to warfarin in the management of non-valvular atrial fibrillation and prevention of stroke, especially after the availability of reversal agents such as idarucizumab.[35] In this regard, Coons et al. demonstrated in an extensive study of 1840 patients with morbid obesity (BMI>40 kg/m^2) and VTE that DOACs are more effective and less risky than warfarin.[36] In another study, there was no advantage of warfarin over DOACs as VTE prophylaxis in patients who have cancer or atrial fibrillation.[37]

It is worth noting that in our hands that the use of DOACs in the studied cohort with renal impairment was not associated with excessive bleeding as occurs with warfarin. In comparison to warfarin, the safety of DOACs in case of chronic kidney disease (CKD) was always a concern among clinicians. A recent study by Weber, found that apixaban is safer than warfarin in

CKD.[38] Nonetheless, careful consideration of anticoagulation's desired level and anticoagulant dose to achieve the best possible anticoagulation effect and outcome is warranted.[39] It is worth noting that there are no reliable, up-to-date guidelines for recommending DOACs in different doses in case of impaired renal function.[40] However, in practice, DOACs are considered to have a similar or safer profile compared to warfarin in mild to moderate renal impairment, but this is not the case in severe renal impairment, especially in the renal transplant setting.[41]

This study's main limitation was the small sample size yielded from our perspective cross-sectional sampling of patients during the sampling timeframe. However, the same approaches were used to overcome the small sample size by re-categorising anticoagulation therapeutic agents and using statistical methods such as the Fisher's exact test and Firth logistic regression. It may be worth noting that some studies, such as the one conducted by Lamb et al.[22] in the USA, have investigated a closely-related topic but relied on smaller sample size. On the other hand, the present study has several strengths: it included all patients who had bleeding secondary to anticoagulant with or without antiplatelet agents in an entire regional population in mid and north of Tasmania. The LGH is the only tertiary referral hospital in this area, and any patient with acute bleeding would be referred to it. The study contributes to clinical practice by showing the need for better control and effective monitoring of patients on pharmacological anticoagulation therapeutic agents based on administration.

Additionally, our study contributes to research on health services cost-effectiveness by showing that the use of DOACs is associated with a reduced likelihood of receiving reversal and shorter LoS in the absence of life-threatening bleeding compared with warfarin. Furthermore, this study contributes to clinical decision-making with respect to selecting anticoagulation therapeutic agents by showing that reduced morbidity was associated with the use of DOACs compared with warfarin. This study contributed to translational medical research by obtaining real-world evidence on risk assessment and management in patients receiving anticoagulation therapy who presented with bleeding while considering the available guidelines and practice information.

Conclusions. Despite the limitations of our study, it is suggested that the application of DOACs is associated with fewer bleeding complications compared to warfarin. Further, bleeding in DOACs was shown to be less severe in our cohort study with reduced LoS that encourage DOACs' use, although the costs due to the fact of their pharmacodynamic reversal is not often required.

DOACs were associated with a reduced likelihood of receiving reversal, a shorter LoS, and better overall clinical outcomes. The guidelines should probably address and include better indicators for DOACs bleeding risk, such as ECT and Chromogenic anti-FXa. Therefore, ECT and chromogenic anti-FXa should be better understood and utilised in the context of bleeding associated with DOACs among clinicians, especially in the Emergency Department.

References:

1. Bungard TJ, Ritchie B, Bolt J, Semchuk WM. Anticoagulant therapies for acute venous thromboembolism: a comparison between those discharged directly from the emergency department versus hospital in two Canadian cities. BMJ Open 2018;8(10):e022063. https://doi.org/10.1136/bmjopen-2018-022063 PMid:30385438 PMCid:PMC6224720
2. Noel SE, Millar JA. Current state of medical thromboprophylaxis in Australia. The Australasian Medical Journal 2014;7(2):58-63. https://doi.org/10.4066/AMJ.2014.1915 PMid:24611073 PMCid:PMC3941577
3. Kakkos SK, Warwick D, Nicolaides AN, Stansby GP, Tsolakis IA. Combined (mechanical and pharmacological) modalities for the prevention of venous thromboembolism in joint replacement surgery. The Journal of Bone and Joint Surgery 2012;94(6):729-734. https://doi.org/10.1302/0301-620X.94B6.28128 PMid:22628585
4. Moheimani F, Jackson DE. Venous thromboembolism: Classification, risk factors, diagnosis, and management. ISRN Hematology 2011;2011:e124610. https://doi.org/10.5402/2011/124610 PMid:22084692 PMCid:PMC3196154
5. Watson HG, Chee YL. Aspirin and other antiplatelet drugs in the prevention of venous thromboembolism. Blood Reviews 2008;22(2):107-116. https://doi.org/10.1016/j.blre.2007.11.001 PMid:18226435
6. Harter K, Levine M, Henderson SO. Anticoagulation drug therapy: a review. Western Journal of Emergency Medicine 2015;16(1):11-17. https://doi.org/10.5811/westjem.2014.12.22933 PMid:25671002 PMCid:PMC4307693
7. Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. Cochrane Database of Systematic Reviews 2017;2017(11):CD011373. https://doi.org/10.1002/14651858.CD011373.pub2 PMid:29105079 PMCid:PMC6485997
8. Gomez-Outes A, Terleira-Fernandez AI, Lecumberri R, Suarez-Gea ML, Vargas-Castrillon E. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. Thrombosis Research 2014;134(4):774-782. https://doi.org/10.1016/j.thromres.2014.06.020 PMid:25037495
9. TGA. New oral anticoagulants - apixaban (Eliquis), dabigatran (Pradaxa) and rivaroxaban (Xarelto) Australia: The Australian Government Theraputic Goods Administration; 2015 [Available from: https://www.tga.gov.au/node/705240
10. Ortiz-Cartagena L, Gotay AO, Acevedo J. Cost effectiveness of oral anticoagulation therapy for non-valvular atrial fibrillation patients: Warfarin versus the new oral anticoagulants rivaroxaban, dabigatran and apixaban. Journal of the American College of Cardiology 2018;71(11):A490. https://doi.org/10.1016/S0735-1097(18)31031-3
11. Shoeb M, Fang MC. Assessing bleeding risk in patients taking anticoagulants. Journal of Thrombosis and Thrombolysis 2013;35(3):312-319. https://doi.org/10.1007/s11239-013-0899-7 PMid:23479259 PMCid:PMC3888359

12. Hamidi M, Zeeshan M, Sakran JV, Kulvatunyou N, O'Keeffe T, Northcutt A, Zakaria ER, Tang A, Joseph B. Direct oral anticoagulants vs low-molecular-weight heparin for thromboprophylaxis in nonoperative pelvic fractures. Journal of the American College of Surgeons 2018;228(1):89-97.
https://doi.org/10.1016/j.jamcollsurg.2018.09.023
PMid:30359834
13. Bungard TJ, Ritchie B, Bolt J, Semchuk WM. Management of acute venous thromboembolism among a cohort of patients discharged directly from the emergency department. BMJ Open 2018;8(10):e022064.
https://doi.org/10.1136/bmjopen-2018-022064
PMid:30385439 PMCid:PMC6224769
14. Scheres LJJ, Lijfering WM, Middeldorp S, Cheung YW, Barco S, Cannegieter SC, Coppens M. Measurement of coagulation factors during rivaroxaban and apixaban treatment: results from two crossover trials. Research and Practice in Thrombosis and Haemostasis 2018;2(4):689-695.
https://doi.org/10.1002/rth2.12142
PMid:30349888 PMCid:PMC6178718
15. Ebner M, Birschmann I, Peter A, Hartig F, Spencer C, Kuhn J, Rupp A, Blumenstock G, Zuern CS, Ziemann U, Poli S. Limitations of specific coagulation tests for direct oral anticoagulants: a critical analysis. Journal of the American Heart Association 2018;7(19):e009807.
https://doi.org/10.1161/JAHA.118.009807
PMid:30371316 PMCid:PMC6404908
16. Dhakal P, Rayamajhi S, Verma V, Gundabolu K, Bhatt VR. Reversal of anticoagulation and management of bleeding in patients on anticoagulants. Clinical and Applied Thrombosis/Hemostasis 2017;23(5):410-415.
https://doi.org/10.1177/1076029616675970
PMid:27789605
17. Anderson I, Cifu AS. Management of bleeding in patients taking oral anticoagulants. JAMA Journal of American Medical Association 2018;319(19):2032-2033.
https://doi.org/10.1001/jama.2018.3504
PMid:29800198
18. Eikelboom J, Merli G. Bleeding with direct oral anticoagulants vs warfarin: clinical experience. The American Journal of Emergency Medicine 2016;34(11S):S33-S40.
https://doi.org/10.1016/j.amjmed.2016.06.003
PMid:27586367
19. Almegren M. Reversal of direct oral anticoagulants. Vascular Health and Risk Management 2017;13:287-292.
https://doi.org/10.2147/VHRM.S138890
PMid:28769570 PMCid:PMC5529093
20. Qureshi W, Mittal C, Patsias I, Garikapati K, Kuchipudi A, Cheema G, Elbatta M, Alirhayim Z, Khalid F. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. The American Journal of Cardiology 2014;113(4):662-668.
https://doi.org/10.1016/j.amjcard.2013.10.044
PMid:24355310
21. Witt DM. What to do after the bleed: resuming anticoagulation after major bleeding. American Society of Hematology Education Program 2016;2016(1):620-624.
https://doi.org/10.1182/asheducation-2016.1.620
PMid:27913537 PMCid:PMC6142471
22. Lamb LC, DiFiori M, Comey C, Feeney J. Cost analysis of direct oral anticoagulants compared with warfarin in patients with blunt traumatic intracranial hemorrhages. American Surgeon 2018;84(6):1010-1014.
https://doi.org/10.1177/000313481808400657
23. Sarkies MN, Bowles KA, Skinner EH, Mitchell D, Haas R, Ho M, Salter K, May K, Markham D, O'Brien L, Plumb S, Haines TP. Data collection methods in health services research: hospital length of stay and discharge destination. Applied Clinical Informatics 2015;6(1):96-109.
https://doi.org/10.4338/ACI-2014-10-RA-0097
PMid:25848416 PMCid:PMC4377563
24. Brasel KJ, Lim HJ, Nirula R, Weigelt JA. Length of stay: an appropriate quality measure? Archives of Surgery 2007;142(5):461-465.
https://doi.org/10.1001/archsurg.142.5.461
PMid:17515488
25. IBM SPSS Statistics for Windows [program]. 26.1 version. NY, USA: IBM Corporation, 2020.
26. PenaRosas JP, Cusick S, Lynch S. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. World Health Organization. 2011. Available from: https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf?ua=1
27. Liew J, Mathers S. Guideline for the Prevention of Venous Thromboembolism (VTE) in Adult Hospitalised Patients. Queensland Health. Queensland, Australia, 2018. Available from: https://www.health.qld.gov.au/__data/assets/pdf_file/0031/812938/vte-prevention-guideline.pdf
28. Raschi E, Bianchin M, Ageno W, De Ponti R, De Ponti F. Risk-benefit profile of direct-acting oral anticoagulants in established therapeutic indications: an overview of systematic reviews and observational studies. Drug Safety 2016;39(12):1175-1187.
https://doi.org/10.1007/s40264-016-0464-3
PMid:27696300 PMCid:PMC5107188
29. Wallace R, Anderson MA, See K, Gorelik A, Irving L, Manser R. Venous thromboembolism management practices and knowledge of guidelines: a survey of Australian haematologists and respiratory physicians. Internal Medicine Journal 2017;47(4):436-446.
https://doi.org/10.1111/imj.13382
PMid:28150371
30. Adcock DM, Gosselin R. Direct Oral Anticoagulants (DOACs) in the laboratory: 2015 review. Thrombosis Research 2015;136(1):7-12.
https://doi.org/10.1016/j.thromres.2015.05.001
PMid:25981138
31. Badreldin H. Hospital length of stay in patients initiated on direct oral anticoagulants versus warfarin for venous thromboembolism: a real-world single-center study. Journal of Thrombosis and Thrombolysis 2018;46(1):16-21.
https://doi.org/10.1007/s11239-018-1661-y
PMid:29626281
32. Charlton B, Adeboyeje G, Barron JJ, Grady D, Shin J, Redberg RF. Length of hospitalization and mortality for bleeding during treatment with warfarin, dabigatran, or rivaroxaban. PLoS One 2018;13(3):e0193912.
https://doi.org/10.1371/journal.pone.0193912
PMid:29590141 PMCid:PMC5874024
33. Paravattil B, Elewa H. Approaches to Direct Oral Anticoagulant Selection in Practice. J Cardiovasc Pharmacol Ther 2018:1074248418793137.
https://doi.org/10.1177/1074248418793137
PMid:30092658
34. Sawada S, Ono Y, Egashira Y, Takagi T, Tsuruma K, Shimazawa M, Iwama T, Hara H. In Models of Intracerebral Hemorrhage, Rivaroxaban is Superior to Warfarin to Limit Blood Brain Barrier Disruption and Hematoma Expansion. Curr Neurovasc Res 2017;14(2):96-103.
https://doi.org/10.2174/1567202613666161216150835
PMid:27993122
35. Rawal A, Ardeshna D, Minhas S, Cave B, Ibeguogu U, Khouzam R. Current status of oral anticoagulant reversal strategies: a review. Ann Transl Med 2019;7(17):411.
https://doi.org/10.21037/atm.2019.07.101
PMid:31660310 PMCid:PMC6787376
36. Coons JC, Albert L, Bejjani A, Iasella CJ. Effectiveness and Safety of Direct Oral Anticoagulants versus Warfarin in Obese Patients with Acute Venous Thromboembolism. Pharmacotherapy 2020;40(3):204-210.
https://doi.org/10.1002/phar.2369
PMid:31968126
37. Shah S, Norby FL, Datta YH, Lutsey PL, MacLehose RF, Chen LY, Alonso A. Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. Blood Adv 2018;2(3):200-209.
https://doi.org/10.1182/bloodadvances.2017010694
PMid:29378726 PMCid:PMC5812321
38. Weber J, Olyaei A, Shatzel J. The efficacy and safety of direct oral anticoagulants in patients with chronic renal insufficiency: A review of the literature. Eur J Haematol 2019;102(4):312-318.
https://doi.org/10.1111/ejh.13208
PMid:30592337
39. Shrestha S, Baser O, Kwong WJ. Effect of Renal Function on Dosing of Non-Vitamin K Antagonist Direct Oral Anticoagulants Among Patients With Nonvalvular Atrial Fibrillation. Ann Pharmacother 2018;52(2):147-153.
https://doi.org/10.1177/1060028017728295
PMid:28856898
40. Padrini R. Clinical Pharmacokinetics and Pharmacodynamics of Direct Oral Anticoagulants in Patients with Renal Failure. Eur J Drug Metab Pharmacokinet 2019;44(1):1-12.
https://doi.org/10.1007/s13318-018-0501-y
PMid:30167998
41. Kcükköylü S, Rump LC. DOAC use in patients with chronic kidney disease. Hamostaseologie 2017;37(4):286-294.
https://doi.org/10.5482/HAMO-17-01-0003
PMid:29582930