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Article

Isolated Distal Deep Vein Thrombosis in the Direct Oral Anticoagulant (DOAC) Era – Should Our Management Change?

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Abstract: Objectives: There remains no consensus management for isolated distal deep vein thrombosis (IDDVT), with current data inconclusive and dating back to the warfarin era. In the current direct oral anticoagulant (DOAC) era, optimal management of IDDVT needs to be re-assessed. **Methods:** A retrospective evaluation of patients treated with therapeutic anticoagulation for IDDVT in the DOAC era (2013-2016) was compared with historically published data from the warfarin era (2011-2012). **Results:** 247 patients were evaluated, 103 from the DOAC era and 122 from the warfarin era. There were less provoked events in the DOAC cohort (45.6% vs 66.7%, p=<0.01). Overall rate of major bleeding was 1.6% with 1.0% in the DOAC era and 2.1% in the warfarin era (p=0.50). There was no difference in rates of VTE progression on treatment 5.8% vs 4.9% respectively (p=0.91). Overall risk of VTE recurrence post cessation was 5.3% (1.86 per 100 person years) with no difference between groups (5.8% vs 4.9%, p=0.74). **Conclusions:** Our data shows IDDVT is not always benign, with risk of extension despite treatment and long-term risk of VTE-recurrence. Therapeutic anticoagulation with DOAC in these patients was associated with a major bleeding rate of 1.0% in the DOAC cohort. Further clinical trials into the optimal IDDVT management in the DOAC era are necessary.

Keywords: Venous thrombosis, Anticoagulants, Haemorrhage, Isolated distal deep vein thrombosis, Direct oral anticoagulants

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1. Introduction

Isolated distal deep vein thrombosis (IDDVT), defined as thrombosis limited to unilateral infra-popliteal veins, is a common condition, accounting for between 31-56% of all leg deep vein thrombosis (DVT)[1]. IDDVT has typically been considered a "minor" venous thromboembolism (VTE) and lacks a consensus approach with management ranging from observation to therapeutic anticoagulation[2]. However, IDDVT is not always benign with a risk of propagation to the proximal system of 8-15%[3] without treatment, including the risk of pulmonary embolus 0-6%[4]. Additionally, long-term complications can occur including post thrombotic syndrome, reported in around 10%[4] of events and VTE recurrence with rates reported at 7.6%[5], comparable to proximal VTE[6].

A literature review by Masuda et al found no study of sufficient quality to determine optimal IDDVT treatment, hence concluding both anticoagulation and imaging surveillance would remain as acceptable standards of care[4]. The majority of current evidence is based on warfarin era data where delivery of anticoagulation was difficult and associated with a higher risk of bleeding relative to the direct oral anticoagulant (DOAC) era[7, 8]. Furthermore DOACs are associated with increased patient acceptability in comparison

to warfarin[9, 10]. Adherence rates for DOACs are significantly higher[11, 12] along with more stable pharmacokinetics than warfarin of which in one large population study only 41% of patients were within therapeutic range ≥65% of the time[13]. Additionally, the seminal trials such as XALIA, EINSTEIN-DVT and AMPLIFY have suggested DOACs are as efficacious as warfarin at preventing VTE recurrence and extension with an equivalent or better rate of bleeding complications[14-16].

To evaluate the safety and efficacy of IDDVT in the DOAC era, we retrospectively reviewed consecutive patients diagnosed with IDDVT and treated with DOAC in our institution and compared them with a previously collected cohort of patients during the warfarin era[6].

2. Methods

A retrospective evaluation of patients continued or commenced on DOACs for IDDVT between September 2013 and September 2016 at The Northern Hospital, a tertiary hospital in Melbourne, Australia was performed. Relevant patients were identified using 'iGuidance', a DOAC prescription stewardship program in which prescribers must obtain approval when prescribing DOACs for all inpatients, discharges and outpatients. Our local hospital protocol is to treat all IDDVT patients with therapeutic anticoagulation in the absence of contraindications. The agent of choice is a DOAC if the patient does not breach any criteria for use, with a treatment duration of 6 weeks to 3 months at clinician discretion. This project was approved by the Northern Health Governance Office as a Quality Improvement project (ALR23.2017).

Medical records were retrospectively reviewed including patient demographics and safety data. Primary endpoints included major bleeding, thrombosis progression and recurrent VTE. IDDVT was defined as an isolated infrapopliteal DVT including isolated muscular vein thrombosis. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis – Scientific and Standardisation Committee (ISTH-SCC) as events scoring 3 or greater on the bleeding assessment tool[17]. VTE progression was defined as extension or increased size of thrombus on repeat imaging within 30 days from the index event. Recurrent thrombosis was defined as a recurrence in the same area following documented resolution or at a new site following the initial event. Patients who had not re-presented to our medical service or had documentation of an event in their medical records were assumed not to have experienced a complication. Follow up duration was defined based on last documented record of interaction with the health service. We compared our data to our previously published retrospective database of IDDVT presentations during the warfarin era between July 2011 and December 2012[6]. Of note, we excluded the patients who were not treated with therapeutic anticoagulation or who had active malignancy to enable accurate comparison to our DOAC cohort.

3. Statistical Analysis

Descriptive statistics including counts and percentage frequencies, mean or median range are provided as appropriate to summarise patient characteristics and outcomes. The differences in categorical variables including baseline characteristics and risk factors were evaluated using the chi-squared test. Time to event analysis was conducted with endpoint of VTE recurrence post anticoagulation cessation. Mortality was treated as a competing risk and patients lost to follow up before recurrent thrombosis or death were censored at date of last follow up. A two-tailed p-value of less than 0.05 was considered to be statistically significant. Statistical analysis was performed using IBM SPSS Statistics 27 and Microsoft Excel 2016.

4. Results

4.1. Baseline Demographics and Treatment Duration

4.1.1. DOAC Era

One hundred-five patients with IDDVT (49 males, 56 females) with median age 53 years (range 22-85) were identified using the iGuidance approval system. Two patients with active malignancy were excluded. The majority of patients had good renal function with 94% having an estimated glomerular filtration rate (eGFR) >60 ml/min/1.73m^2. 45.6% (n=47) of patients had a provoked event including 51.0% (n=24) who had a surgical procedure in the previous 8 weeks. Nineteen (18.4%) patients had previous VTE while three (2.9%) had a history of major bleeding. No patients were known to have antiphospholipid syndrome.

The vast majority of patients, 94.2% (n= 97), received rivaroxaban 15mg twice a day for the first three weeks followed by 20mg daily. The remaining 5.8% (n=6) were on apixaban 10mg twice a day for one week followed by 5mg twice daily. The duration of therapeutic DOAC therapy was available for 97.1% (n=102) patients. Of the patients who had limited duration of therapeutic DOAC treatment the median duration was 3 months for both the provoked (range <1-9) and unprovoked (range <1-10). Fifteen patients (14.6%) went on to long-term anticoagulation, including six on prophylactic apixaban, due to a combination of reasons including history of recurrent VTE requiring long term anticoagulation (n=5), subsequent diagnosis of atrial fibrillation (n=1) and recurrence/extension of thrombus during initial therapy (n=2). The median follow-up was 40 months (range 20-70 months), three patients were lost to follow up.

4.1.2. Warfarin Era

Our historical warfarin era data identified 164 patients with IDDVT. For the purposes of comparison, only the 144 patients who received therapeutic anticoagulation with a vitamin K antagonist (n=131) or low molecular weight heparin (LMWH) (n=13) were included in our analysis (Table 1). Genders were equally represented with 52.8% (n=76) males in the warfarin cohort with a trend towards being older (median age of 62 years, range 25-95; p=0.06). 66.7% (n=96) patients had provoked events including 36.5% (n=35) who had surgery in the prior 8 weeks. 18.1% of patients had a prior history of VTE. Duration of treatment was available for 82.6% (n=119) of patients. In the provoked cohort 8.3% (n=8) had long term anticoagulation for recurrent VTE or atrial fibrillation. The median duration of warfarin for provoked IDDVT patients who had short term anticoagulation was 3 months (range <1-12) the same as the DOAC era. The unprovoked warfarin cohort had a longer median treatment duration than the DOAC cohort at 5 months (range 1-12) p=<0.01. 20.4% (n=10) of the unprovoked patients went on to long term warfarin.

Table 1. Outline of baseline demographics of DOAC and Warfarin era cohorts

	Total Population (n=247)	DOAC Era (n=103)	Warfarin Era (n=144)	p-value
Male gender	50.6% (n=125)	47.6% (n=49)	52.8% (n=76)	0.42
Median age years (range)	56 (22-95)	53 (22-85)	62 (25-95)	0.06
Past history of VTE	18.2% (n=45)	18.4% (n=19)	18.1% (n=26)	0.94
Provoked events	57.9 (n=143)	45.6% (n=47)	66.7% (n=96)	<0.01
Anticoagulant prescribed:				
Rivaroxaban		94.2% (n=97)		
Apixaban		5.8% (n=6)		
Warfarin			91.0% (n=131)	
Enoxaparin			9.0% (n=13)	
Limited treatment duration (months):				
Provoked	3 (<1-12)	3 (<1-9)	3 (<1-12)	
Unprovoked	3 (<1-12)	3 (<1-10)	5 (1-12)	<0.01
Long term treatment:				
Provoked	5.6% (n=8)	0% (n=0)	8.3% (n=8)	0.04
Unprovoked	11.5% (n=12)	3.6% (n=2)	20.8% (n=10)	<0.01
Median follow-up months (range)	27 (2-70)	53 (20-70)	22 (2-31)	<0.01

4.1.3. Comparison of outcomes for patients treated during DOACs era and warfarin era

Table 2 shows the overall major bleeding rate of both datasets was 1.6%, while the VTE progression on treatment rate was 4.0%. Recurrent VTE post anticoagulation cessation occurred in 5.3% (1.86 per 100 person years) of patients.

Table 2. Comparison of complication rates between DOAC and warfarin era cohorts

	Total Population (n=247)	DOAC Era (n=103)	Warfarin Era (n=144)	p-value
Major bleeding on anticoagulation (ISTH-SCC Grade 3-4[17])	1.6% (n=4)	1.0% (n=1)	2.1% (n=3)	0.50
VTE progression while on anticoagulation:				
Total	4.0% (n=10)	3.9% (n=4)	4.2% (n=6)	0.91
PE	1.2% (n=3)	1.9% (n=2)	0.7% (n=1)	0.38
Types of recurrent VTE post treatment cessation:				
Total	5.3% (n=13)	5.8% (n=6)	4.9% (n=7)	0.74
PE	2.4% (n=6)	2.9% (n=3)	2.1% (n=3)	0.67
DVT	2.8% (n=7)	2.9% (n=3)	2.8% (n=4)	0.95
Subsequent Malignancy	0.8% (n=2)	1.0% (n=1)	0.7% (n=1)	0.81
All-cause mortality	3.2% (n=8)	1.9% (n=2)	4.2% (n=6)	0.33

4.1.3.1. Major Bleeding

In the DOAC era there was one episode (1.0%) of major bleeding in a patient who initially presented with an unprovoked medial gastrocnemius IDDVT and was com-

menced on rivaroxaban. The patient re-presented 6 weeks post diagnosis and was concurrently found to have a spontaneous intramuscular haematoma and a symptomatic proximal DVT of the contralateral leg. Of note they did not have prior imaging of the contralateral leg and the possibility of an initial diagnosis of bilateral DVT cannot be excluded.

In the warfarin era there were a total of three episodes of major bleeding (2.1%) including two patients who had traumatic bleeding episodes while on long term anticoagulation (12 and 19 months respectively). Only one patient had a spontaneous gastrointestinal bleed within 1 week of anticoagulation initiation while on concurrent bridging enoxaparin.

4.1.3.2. VTE Progression/Recurrence

In the DOAC cohort, four patients (3.9%) were found to have thrombus extension during their treatment phase, all while taking rivaroxaban 20mg daily. The one patient with extension following unprovoked IDDVT is outlined above while the remaining three patients had provoked events. One presented with worsening symptoms within two weeks of treatment and had confirmed proximal DVT extension while one was found to have PE following representation after two weeks with worsening dyspnoea. The third patient developed PE in the context of having their anticoagulation withheld temporarily for a surgical procedure. In the warfarin era cohort, six episodes of VTE extension on anticoagulation were captured including one episode of PE, all cases except one occurred despite therapeutic range INR.

Six DOAC era patients (5.8%, 1.33 per 100 person years) had recurrent VTE following cessation of treatment including three patients with PE. There were seven episodes (4.9%, 2.82 per 100 person years) captured in the warfarin cohort including three episodes of PE. Overall, this represented a 5.3%, 1.86 per 100 person years risk of post anticoagulation cessation VTE recurrence.

4.1.3.3. Subsequent Malignancy

One patient from the DOAC cohort was subsequently diagnosed with a malignant Leydig cell tumour within 12 months of initial presentation with unprovoked IDDVT. Similarly, one patient with an unprovoked IDDVT during the warfarin era was subsequently diagnosed with a gastrointestinal stromal tumour.

4.1.3.4. All-cause Mortality

There were two episodes (1.9%) of all-cause mortality captured in the DOAC era and six (4.2%) in the warfarin era, none of which were due to VTE or bleeding complications.

5. Discussion

This study provides, to the best of our knowledge, the first overview on the evolution of IDDVT management in Australia as we moved from the warfarin to DOAC era. The recommended treatment of IDDVT remains heterogeneous as few studies have examined IDDVT in detail, often with differing study protocols and discordant results[4]. The CACTUS trial compared low molecular weight heparin treatment for 6 weeks to placebo in IDDVT and found treatment was not superior in reducing thrombus extension or PE but was associated with increased bleeding risk[18]. The TICT study treated IDDVT patients with therapeutic low molecular weight heparin twice daily for one week followed by a daily (half) dose for three weeks. They reported a 2.9% rate of progression to proximal veins on treatment and 2.9% VTE recurrence rate post treatment within three months while no major bleeding complications were captured[19]. This paucity of high-quality evidence and conflicting results has led to considerable variation in management guidelines ranging from no anticoagulation with serial ultrasound monitoring to treatment for 3 months with therapeutic anticoagulation (Table 3).

Table 3. Comparison of major guideline and key studies recommendations

	Provoked	Unprovoked	Comments
THANZ Guidelines 2019 [20]	6 weeks of therapeutic anticoagulation	3 months of therapeutic anticoagulation (also if persisting risk factors)	Serial ultrasound over 2 weeks is reasonable, especially if the patient has bleeding risk factors
CHEST Guidelines[21]	Surgically provoked or non-surgical transient provoking factor – 3 months of anticoagulation	3 months minimum of anticoagulation	
NICE Guidelines[22]	No treatment recommendation specifically for IDDVT		If suspected DVT and negative proximal ultrasound scan and positive D-dimer test repeat proximal imaging in 6-8 days
European Society of Cardiology[23]	4-6 weeks full or low dose anticoagulation or venous ultrasound surveillance	3 months of anticoagulation (also if high risk including previous VTE events, age >50 years, persistent hampered mobilisation, presence of predisposing diseases)	
ASH Guidelines[24]	No treatment recommendation specifically for IDDVT		Diagnosis of VTE guidelines states that either whole leg or proximal leg ultrasound is appropriate (serial imaging if intermediate or high risk of DVT)[25]

Whilst IDDVT was historically considered a minor VTE, we have previously shown that IDDVT is not always as benign as previously thought. Our study's risk of VTE recurrence rate post cessation was substantial at 5.3% (1.86 per 100 person years) overall, sitting in the mid-range of published recurrence rates varying from 2.7%[26] to 11%[27]. Risk of VTE progression on therapeutic anticoagulation was 4.0% overall, concordant with the literature with reported rates of 1.1%[28] and 3.2%[29]. In addition, the higher reported rates of progression of untreated IDDVT patients between 3-15%[2] in other studies, raises the question of whether routine anticoagulation of patients without contraindications should be considered in the DOAC era. However, this needs to be balanced with the bleeding risk associated with anticoagulation such as the CACTUS study data where IDDVT treatment with nadroparin led to increased bleeding risk without reduction in proximal vein extension[18].

Our local practice of routinely administering therapeutic anticoagulation (in the absence of contraindications such as high bleeding risk) for between 6 weeks to 3 months appears to have a low bleeding risk overall of 1.6% and effectively treat the underlying DVT in the majority of the patients. Our DOAC-era bleeding rate of 1.0% was comparable to other studies such as the sub-analysis of the XALIA trial finding a major bleeding rate of 0.9%[28] for anticoagulated IDDVT patients and the real world-data from the RIETE registry with a major bleeding rate of 2.8% in treated IDDVT[26]. Complication rates in the DOAC group were comparable to the historic warfarin group including rates of major bleeding on anticoagulation (1.0% vs 2.1%, p=0.50), VTE progression while on anticoagulation (3.9% vs 4.2%, p=0.91) and recurrent VTE post treatment cessation (5.8% vs 4/9%, p=0.74). Given the added convenience of DOAC and ability to safely deliver this drug as an outpatient[30], further large cohort studies are warranted to inform clinical guidelines regarding the risk-benefit of routine anticoagulation for IDDVT.

5.1. Limitations

We acknowledge the limitations of our study including its retrospective nature, restricted study numbers and that patients may have re-presented to other institutions resulting in underreporting of complications rates. Furthermore, the DOAC cohort evaluation was restricted to patients treated with therapeutic doses of DOAC which may be affected by treatment selection bias and did not capture patients who were not anticoagulated or who were anticoagulated with alternate agents. This is a reflection of our local hospital protocol to treat all patients with IDDVT in the absence of a contraindication but limits the studies depth and generalisability to untreated patients or those managed with other agents.

6. Conclusion

Despite its prevalence, the optimal approach to IDDVT remains unclear with wide variations from diagnosis to treatment. In this real-world study we found IDDVT is not always a benign entity with significant risks of extension and VTE recurrence. We report overall major bleeding rates of 1.6% in therapeutically anticoagulated patients without a significant difference between the DOAC and warfarin era cohorts. In comparison, rates of VTE progression were 4% and post treatment VTE recurrence 5.3% (1.86 per 100 person years). This raises the question of whether our management strategies for IDDVT should change in the DOAC era and ongoing prospective research with larger cohorts is required to further assess the safety and efficacy of routine therapeutic anticoagulation with DOAC in patients with IDDVT without contraindications.

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