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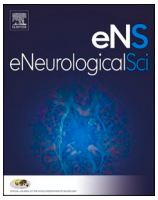

Warfarin versus factor Xa inhibitors in the long-term treatment of cerebral venous sinus thrombosis a single-center retrospective analysis

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ABSTRACT

Long-term anticoagulation in the treatment of Cerebral Venous Sinus Thrombosis (CVST) has revolved around the use of warfarin. The relatively recent introduction of Direct Oral Anticoagulants (DOACs), such as Factor Xa inhibitors, in treating CVSTs promises to offer numerous patient benefits. We aimed to examine the efficacy of Factor Xa inhibitors in comparison to warfarin in the long-term treatment of CVSTs. A single-center retrospective analysis was conducted in which 49 eligible patients having presented with a first-time CVST were identified. Long-term anticoagulation was achieved with Warfarin (n = 23) or Factor Xa Inhibitors (n = 26; Apixaban or Rivaroxaban). Outcomes of interest were improvements in patient functional status, modified Ranking Scores (mRS), and radiographic improvement/resolution in sinus thromboses. Secondary comparisons included complication rates, particularly recurring venous thrombotic events. Patient mRS scores by 7-to-18-month follow-up all fell within the extremely favorable range of 0–1 regardless of the long-term anticoagulant (P-value = 0.3591). Proportion of patients with radiographic improvement/resolution of thrombosed sinuses trended towards being higher in the Factor Xa Inhibitor group at the <12-month period, 69.2%, compared to 33.3% with Warfarin (*P*-value = 0.0548). By the >12-month follow-up period, Warfarin and Factor Xa inhibitor groups had similar rates of radiographic sinus improvement – 76.9% versus 71.4%, respectively (*P*-value = 0.6298). No statistically significant differences were documented between groups regarding complications. Factor Xa inhibitors are equally as effective as Warfarin in the long-term treatment of CVSTs, whether it be restoring patient functional status, sinus thrombus burden reduction, or minimizing bleeding complications whilst preventing recurrent venous thrombosis.

1. Introduction

Cerebral venous sinus thrombosis (CVST) occurs secondary to thrombus formation, and potential occlusion, within the dural venous sinuses and/or accompanying venous structures such as the internal jugular vein or cerebral veins [1]. The annual incidence of CVSTs in the United States has been estimated to be between 2 and 5 cases per million people – only accounting for 0.5–1% of all strokes [2,3]. Despite its relatively low incidence rate, CVSTs still presents a major burden to the healthcare system as well as to the patients affected by them - considering that death or permanent neurological deficits are not uncommon sequelae [4].

Ultimate treatment of CVSTs has traditionally been guided by lessons learned in the treatment of Deep Vein Thromboses (DVTs). With this being said, mechanical thrombectomy, when indicated, and acute anticoagulation with Heparin and/or Low Molecular Weight Heparin (LMWH) have been the mainstays of acute treatment on an inpatient basis [5]. Long-term treatment subsequently relies on the use of further anticoagulation, usually Warfarin, for a period of 3 to 6 months in the case of a provoked CVST (e.g. secondary to recent infection), 6 to 12 months if the CVST was unprovoked, or indefinitely if a patient has a recurrent hypercoagulability risk [5,6].

Warfarin has been the mainstay long-term treatment of CVSTs; however, it comes with the requirement for regular INR checks and major issues with non-compliance [7]. Additionally, Warfarin use may also present itself with dietary and pharmacologic interactions, thereby further limiting its use [8,9]. Of note, LMWHs have also been used in the context of long-term CVST treatment, but their use remains limited to primarily pregnant patients or patients whose INRs have been historically difficult to stabilize [10,11]. LMWH use presents itself with its own unique downsides, the primary of which is that it must be introduced subcutaneously [12]. With this being said, utilizing the newer

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generation of anticoagulants - DOACs - in the long-term treatment of CVSTs has been of great interest as they avoid many of the pitfalls discussed above associated with classic treatment regimens [13].

The primary DOAC that has been examined in the context of CVST treatment has been the direct thrombin inhibitor Dabigatran. Results published as part of the open-label randomized control RE-SPECT trial by Ferro et al. showed that Dabigatran was just as safe as Warfarin and prevented recurrent CVSTs to the same extent [14]. On the other hand, looking at the Factor Xa inhibitor class of DOACs, there have been no randomized controlled trials published comparing them either to standard therapy or even to DOACs amongst themselves in the context of CVSTs [15]. Of note, we are aware of two ongoing trials aiming to address the above gap – *Study of Rivaroxaban for Cerebral Venous Thrombosis (*SECRET, NCT03178864) and *Rivaroxaban* versus *Warfarin in CVT Treatment* (RWCVT, NCT04569279).

With the above in mind, we performed a retrospective single-center analysis aimed at examining patient outcomes, recanalization rates, and frequency of complications between Warfarin and Factor Xa inhibitors in the treatment of CVSTs. We also included data from Enoxaparin use for completeness' sake although long-term Enoxaparin use was rare at our institution. In conducting the above, we hope to contribute to the growing body of case-reports, case-series, and single/multi-center retrospective analyses examining the role of DOACs in the treatment of CVSTs [15].

2. Methods

2.1. Data collection

An initial Electronic Medical Record (EMR) query was performed based on the ICD-10 codes I67.6 (non-pyogenic thrombosis of the intracranial venous system) and I63.6 (cerebral infarction due to cerebral venous sinus thrombosis, non-pyogenic) to capture patients that presented to Indiana University Health (IUH) for treatment of CVST. In particular, patients presenting between the dates of 01/01/2015 and 12/31/2020 were included in our study. Our initial query yielded 120 patients fitting either of the ICD-10 codes between the aforementioned dates (Fig. 1). Exclusion criteria were as follows: patients <18 years old at presentation, patients actively on anticoagulation prior to presentation, patients with no documented follow-up after hospital discharge, and patients with inadequate EMR data to ensure accurate calculation of the duration of anticoagulation. Based on the above exclusion criteria, we had 53 patients eligible for inclusion in our analysis (Fig. 1). A single person was on Dabigatran as long-term anticoagulation, and they were not included as part of our analysis due to the inability to perform meaningful statistical analyses on this group. Data for the three patients that died during their hospital admission can be found in Supplemental Table 1. Data compilation and analysis documented above was performed in accordance with an approved Institutional Review Board protocol (IRB# 11889) with all patient data collected and safely stored within REDCap – *Research Electronic Data Capture* [16,17].

2.2. Data analysis

Prior to analysis of our collected data, we grouped eligible patients based on the long-term anticoagulation regimen they were prescribed (i.e. Warfarin, Factor Xa Inhibitors, or Enoxaparin) – whether this occurred following hospital admission or on a strictly outpatient basis. In certain circumstances, patients did switch anticoagulation regimens from their original designation and thus any analyses performed on these patients ensured to only capture the data from the first anticoagulant utilized. Dosing of any of the anticoagulants in our study was done strictly based on physician judgment in accordance with established dosing protocols.

Our primary outcome of interest in the treatment of presenting patients was the resolution of any symptoms and a return to pre-presentation levels of functionality and independence in their

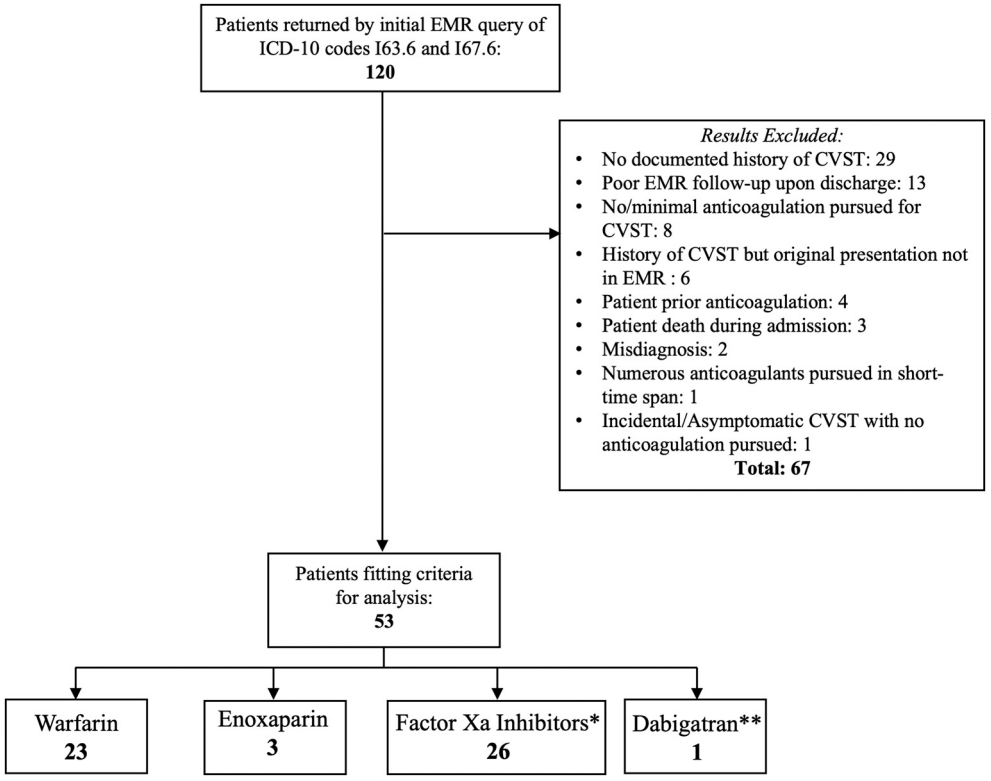

Fig. 1. Depiction of EMR query patient breakdown. *Factor Xa inhibitor breakdown was as follows: 19 patients on Apixaban and 7 on Rivaroxaban. Patients on Apixaban or Rivaroxaban were grouped and analyzed together. **There was one patient on Dabigatran that fit our analysis criteria however they were excluded due to no meaningful statistical analyses would be able to be conducted.

activities of daily living. With this being said, we utilized the Modified Rankin Scale (mRS) as a grounds for assessing the degree of functional impairment a patient's symptoms might be causing them, whether this be at patient presentation, discharge, or during any of the follow-up periods [18]. Scores were retrospectively calculated based on in-depth chart analysis taking into consideration aspects such as documented patient history as well as performed physical exams. Secondary outcomes primarily revolved around any potential complications during the treatment period and included the following categories: major bleeding events, minor bleeding events, thrombotic Events (ex. CVST recurrence or DVT(s)), and non-bleeding complications (ex. seizures). The definition of *major bleeding events* was based on the established definition utilized by the International Society on Thrombosis and Hemostasis who define major bleeding as fatal bleeding; or symptomatic bleeding in a critical region/organ (ex. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), bleeding causing a drop in hemoglobin level by ≥2-g/dL; and/or bleeding leading to transfusion of ≥2 units of blood [19,20]. Bleeding events not fitting within the outlined criteria above were classified as *minor bleeding events* and included complications such as self-limiting epistaxis and bruising.

In-line with our aim to understand how radiographic resolution of the CVSTs might compare between the treatment groups, we also gathered patient radiology data from their admission and follow-ups – when available in the latter case. Summary statistics regarding the number and location of involved dural venous sinuses, at presentation, was drawn based on confirmed involvement as dictated by radiology utilizing either Head CT without contrast, Head CT-Venography, Head MRI, or Head MRV protocols. Determination of radiographic thrombus resolution/improvement was done based on available outpatient radiology and strictly looked at the presence of any sign of improvement/resolution of the thrombus since initial presentation, not necessarily the degree of change.

All statistical analyses were performed in Microsoft Excel. ANOVA tests were utilized for all comparisons between the three anticoagulant groups, followed by Tukey's Test for pair-wise analysis if ANOVA did indicate any significance. In the context of our paper, all p-values <0.05 were taken to be significant.

3. Results

3.1. Cerebral venous sinus thrombosis patient presentation

The average age at presentation for our cohorts was 53.2, 42.5, and 49.2 years of age for the Warfarin, Enoxaparin, and Factor Xa inhibitor groups respectively (Table 1; P-value = 0.482). Both the Warfarin and Enoxaparin groups had a greater percentage of patients that identified as female, while the Factor Xa inhibitor group was composed of an even split between male and female patients (Table 1; P-value = 0.381). The aforementioned trend is not entirely unexpected, particularly in the case of the Enoxaparin group, as LMWHs are a common long-term anticoagulant used in patients that are pregnant.

In terms of the most common symptoms at presentation, headaches, nausea/vomiting, and new-onset seizure activity topped the list in all three of the cohorts. Additional patient presentations also included symptoms such as weakness/hemiparesis, changes in vision, or altered mental status as well. Of note, the Factor Xa inhibitor group had the greatest proportion, 11.5%, of patients that were asymptomatic at presentation – thus having their CVST be an incidental finding on radiology (Table 1; P-value = 0.213). Although no statistical significance was seen between majority of the symptoms at presentation, we did see a significantly greater proportion of patients in the Enoxaparin group presenting with either aphasia or dysarthria compared to the other two groups (Table 1; P-value = 0.042). The range of mRS scores at presentation was consistent between groups and spanned almost the entire spectrum - from completely asymptomatic (mRS of 0) to severely disabling (mRS of

Table 1
Patient characteristics grouped based on long-term anticoagulation regimen.

	Warfarin (n = 23)	Enoxaparin (n = 3)	Factor Xa Inhibitors (n = 26)	P-values
Demographics				
Age (years)	53.2	42.5	49.2	*0.482*
Males	30.4%	33.3%	50.0%	*0.381*
Females	69.6%	66.7%	50.0%	–
Patient Presentation				
Asymptomatic	0.0%	0.0%	11.5%	*0.213*
Headache	69.6%	100.0%	68.0%	*0.527*
Seizure(s)	26.1%	0.0%	32.0%	*0.507*
Vertigo and/or Dizziness	4.3%	0.0%	4.0%	*0.939*
Changes in Vision	13.0%	33.3%	16.0%	*0.675*
Nausea and/or Vomiting	34.8%	0.0%	20.0%	*0.301*
Neck and/or Jaw Pain	4.3%	0.0%	20.0%	*0.203*
Altered Mental Status	13.0%	0.0%	8.0%	*0.719*
Aphasia and/or Dysarthria	17.4%	33.3%	0.0%	***0.042***
Numbness or Paresthesia	4.3%	33.3%	4.0%	*0.116*
Facial Droop	4.3%	0.0%	4.0%	*0.939*
Paresis and/or Weakness	26.1%	33.3%	4.0%	*0.071*
Changes in Mood	4.3%	0.0%	0.0%	*0.542*
Concurrent Infarct(s)	43.5%	0.0%	26.9%	*0.226*
Concurrent Hemorrhage	30.4%	33.3%	23.1%	*0.827*
mRS at Presentation	2.78	2.33	2.38	*0.550*
CVST Risk Factors				
Traumatic Head Injury	4.3%	0.0%	7.7%	*0.810*
Estrogen-Based Contraception	17.4%	66.7%	15.4%	*0.101*
Malignancy	8.7%	0.0%	15.4%	*0.637*
Recent Intracranial Op.	4.3%	0.0%	7.7%	*0.810*
Post-Partum or Puerperium Period	4.3%	0.0%	0.0%	*0.542*
Family History of Hypercoagulability	4.3%	0.0%	0.0%	*0.542*
Personal History of Hypercoagulability	17.4%	33.3%	30.8%	*0.542*
Dehydration	4.3%	0.0%	7.7%	*0.810*
Systemic or Localized Infection	4.3%	0.0%	7.7%	*0.810*
Acute Treatment				
Thrombectomy Performed	4.3%	0.0%	3.8%	*0.938*
Average Duration of Hospital Stay (days)	7.3	8.3	5.7	*0.434*
Patients Presenting on an Outpatient Basis	8.7%	0.0%	19.2%	*0.709*
Acute Anticoagulation				
Heparin	18.2%	0.0%	46.2%	*0.053*
Heparin with Enoxaparin Bridge	52.2%	33.3%	7.7%	***0.002***
Low-Molecular Weight Heparin	17.4%	66.7%	15.4%	*0.101*
No Acute Anticoagulation	8.7%	n/a	30.8%	*0.057*
Average Duration of Acute Anticoagulation (days)	5.67	n/a	5.65	*0.993*
Long-Term Anticoagulation				
Average Duration of Long-Term Anticoagulation (days)	648.77	298.67	357.22	*0.117*
Patients on Indefinite Anticoagulation	40.9%	0.0%	30.8%	*0.668*

Significance bold for the p-value < 0.05

5). Despite the great variability in patients presenting with CVSTs, average mRS scores at presentation ranged between 2.33 in the Enoxaparin group and 2.78 in the Warfarin group with the Factor Xa inhibitor group having an average of 2.38 (Table 1; P-value = 0.550).

Although CVST risk factors were not able to be identified in all patients presented in our study, the greatest majority either had a personal history of hypercoagulability, whether newly diagnosed after presentation or prior to presentation (Table 1). Most commonly, a personal history of hypercoagulability entailed being hetero/homozygous for mutations in Methylenetetrahydrofolate reductase (MTHFR) or having a Factor V Leiden mutation. Second to the genetic predispositions to hypercoagulability, estrogen-based contraceptives were the next most common risk factor predisposing patients, particularly women, to CVSTs (Table 1). No statistically significant differences were noted between any of the long-term anticoagulation groups and any particular CVST risk factors. Of note, we did see a non-statistically significant greater percentage of the population in the enoxaparin group having had exposure to estrogen-based contraceptives however this appears to be an artifact secondary to lack of therapeutic INR achievement and therefore physician choice to simply remain on enoxaparin for treatment.

Radiology conducted upon patient presentation on average identified CVSTs involving 2 (Enoxaparin) to 3.6 (Factor Xa inhibitors) venous structures - particularly dural venous sinuses, cortical/cerebral veins, and/or the internal jugular vein(s) (Fig. 2A, P-value = 0.1531). In further analyzing which distinct dural venous sinuses might be involved, we noted no statistically significant differences amongst the three groups, with an equal spread of sinus involvement (Fig. 2B). Involvement of a venous structure was defined as the presence of a radiologically identifiable thrombus, whether occlusive or non-occlusive, within any of the venous structures identified in Fig. 2B. Secondary to thrombus formation, concurrent venous infarcts and/or parenchymal hemorrhages were also noted in certain instances, however no statistically significant difference was seen in the presenting rates between the groups (Table 1). Concurrent venous infarct rates for the Warfarin group were around 43.5% versus 26.9% in the Factor Xa inhibitor group (P-value = 0.23).

3.2. Acute treatment

Acute treatment of presenting patients primarily revolved around the use of anticoagulation, with only a select few patients requiring thrombectomies as part of treatment (Table 1). Of note, two of the patients excluded in our study, due to their death during hospitalization for their CVST, had required a thrombectomy simply due to the significant extent of their presenting thrombi. Two decompressive craniotomies were also performed however both patients were excluded from analysis due to their eventual death during hospitalization. Comparing the choice of acute anticoagulation between our three cohorts, we see the emergence of expected significant/near-significant trends (Table 1). For example, patients eventually transitioned to Warfarin had a higher likelihood of being acutely anticoagulated with a Heparin-Enoxaparin bridge (Table 1; P-value = 0.002). Bridging to Warfarin was usually accomplished over the course of a few days as INRs began to be within therapeutic ranges. On the other hand, Heparin alone, or even no acute anticoagulant (i.e. immediate use of long-term medication), was preferentially utilized in patients prescribed Factor Xa inhibitors (Table 1; P-value = 0.053 and 0.057, respectively). Duration of acute anticoagulation and hospital stays between the three groups were statistically similar, with acute anticoagulation lasting an average of 5.7 days before transition to long-term anticoagulation (Table 1; P-value = 0.993).

By patient discharge, in the case of patients not treated entirely on an outpatient basis, mRS scores had significantly improved regardless of the acute anticoagulation utilized – with a favorable mRS score range from 0.7 to 1.0 (Fig. 3; P-value = 0.221).

3.3. Long-term treatment & follow-up

Long-term anticoagulation duration was pursued, on average, for 298 days (Enoxaparin), 357 days (factor Xa inhibitors), and 648 days (Warfarin) – no statistically significant difference between long-term anticoagulant duration (Table 1; P-value = 0.117). As anticipated, no patients originally prescribed Enoxaparin were on it indefinitely, in contrast to both the Factor Xa inhibitors and Warfarin, each with 30.8 and 40.9%, respectively, of patients on them indefinitely (Table 1; P-value = 0.668). Follow-up mRS scores had a notable downward trend in all groups from the day of discharge till the most distant date of follow-up (i.e. 7 to 18 months) tracked however there was no documented statistical significance when comparing any of the mRS scores to the respective score at day of discharge (Fig. 3). In cases where patients did not experience full symptom resolution by the last follow-up period, common residual CVST symptoms included lingering headaches, residual seizures, and/or complaints of permanent changes in vision.

Tracking radiographic improvement of patient thrombi, we see that both Enoxaparin and Factor Xa inhibitors have slightly higher rates, although not statistically significant, of radiographic improvement

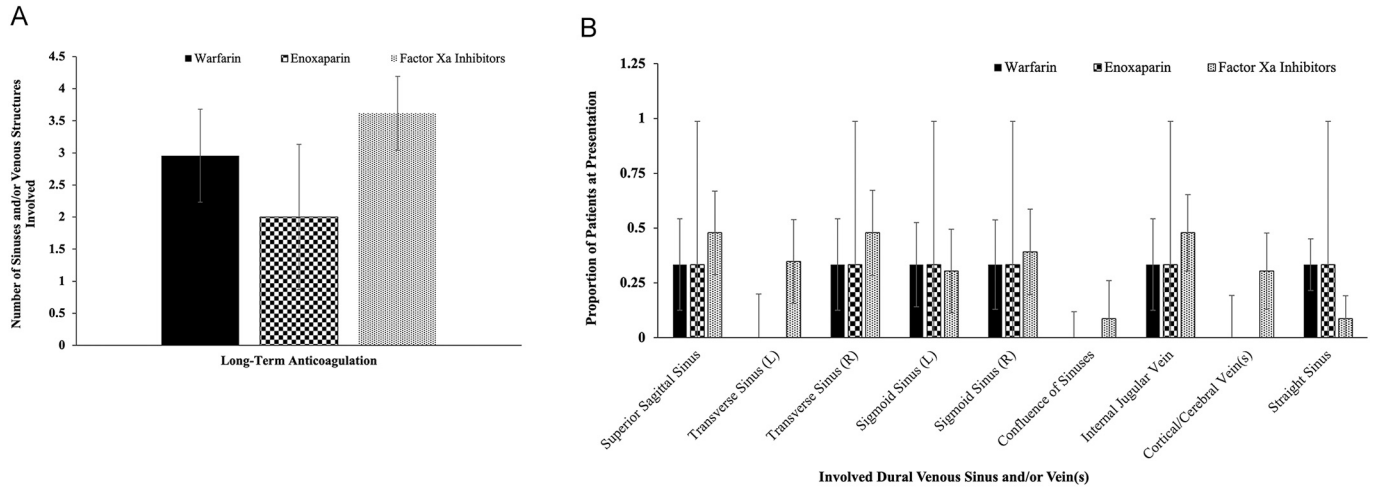

Fig. 2. Radiographic quantification of dural venous sinus and venous structure involvement. (A) Summation of structures containing thrombus – whether occlusive or non-occlusive. (B) Subdivision of venous structures of interest for our analysis. Error bars plotted represent 95% confidence intervals. No identified statistical significance between or within groups.

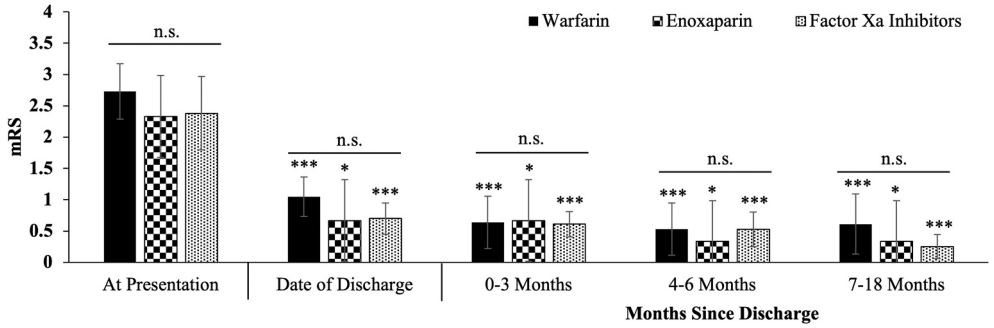

Fig. 3. Graphical representation of patient mRS scores at various points in CVST course. Horizontal bars with n.s. denote no statistically significant differences within groups. Asterisks denote statistical significance when comparing respective group to their original presentation. * Denotes P-value <0.05. *** Denotes P-value <0.001. Error bars plotted represent 95% confidence intervals.

within a year since presentation – 100.0% and 69.0% respectively compared to 33.3% in the Warfarin group (Fig. 4; P-value = 0.0548). Following the initial 12-month period, we then appreciate a roughly two-fold rise, 33.3% to 71.0%, in the proportion of patients taking Warfarin that undergo radiographic improvement – approximating the 76.9% seen with factor Xa inhibitors at the same time point (Fig. 4; P-value = 0.1211).

3.4. Long-term anticoagulation complications

Looking at the composite rate of overall complications amongst anticoagulant groups, Enoxaparin arises as an immediate outlier with a 100.0% complication rate (Fig. 5, P-value <0.05). Upon further subdivision of the complications experienced by patients on long-term anticoagulation, we see that it is the increased rate of switching to alternative anticoagulants that makes Enoxaparin appear as if it has a higher rate of complications (P-value <0.05). The aforesaid makes sense when considering that Enoxaparin generally is not ideal for prolonged anticoagulation due to the inconvenience associated with its administration.

Further analysis of the main complications patients experienced whilst on long-term anticoagulation showed that most complications, 70.0% between all groups, consisted of Minor Bleeding events which primarily involved epistaxis and bruising with other isolated cases of events such as microscopic hematuria (Fig. 5). No major bleeding events were seen in the Factor Xa inhibitor group compared to one event in the Warfarin group - acute blood loss anemia requiring transfusion of three units of blood; and one event in the Enoxaparin group - acute subarachnoid hemorrhage three days after hospital discharge (Fig. 5; P-value = 0.2483). A total of two thrombotic events were recorded, one in the Factor Xa inhibitor group – CVST recurrence, and the other in the Warfarin group – ischemic stroke (Fig. 5; P-value = 0.6224). It is important to mention that in the case of the CVST recurrence, medication non-compliance was suspected to be responsible.

4. Discussion

Current long-term treatment guidelines in the realm of CVSTs have thus far been guided by approaches utilized in the treatment of DVTs. In other words, heavy reliance on warfarin has remained a major theme unless particular contraindications exist leading to the use of unfractionated heparins – for example in the case of pregnant patients. The relatively recent acceptance of DOACs, in particular Factor Xa inhibitors, has led to newfound interest in the possible utilization of this class of drugs to hopefully replace the reliance on warfarin for long-term treatment. Numerous case reports, case series, and observational studies have been published examining treatment outcomes in utilizing factor Xa inhibitors versus warfarin, however, a sparsity of data still exists as no randomized control trial has been published yet unlike in the case of examining warfarin versus dabigatran for CVST treatment [14]. Data sparsity is particularly notable when looking at dural venous sinus recanalization rates which we also present here.

In comparing the data across the board, we are able to show that Factor Xa inhibitors are equally as effective as Warfarin in the long-term treatment of CVSTs. More specifically, Factor Xa inhibitors maintained an overall lower average mRS over all periods of follow-up in

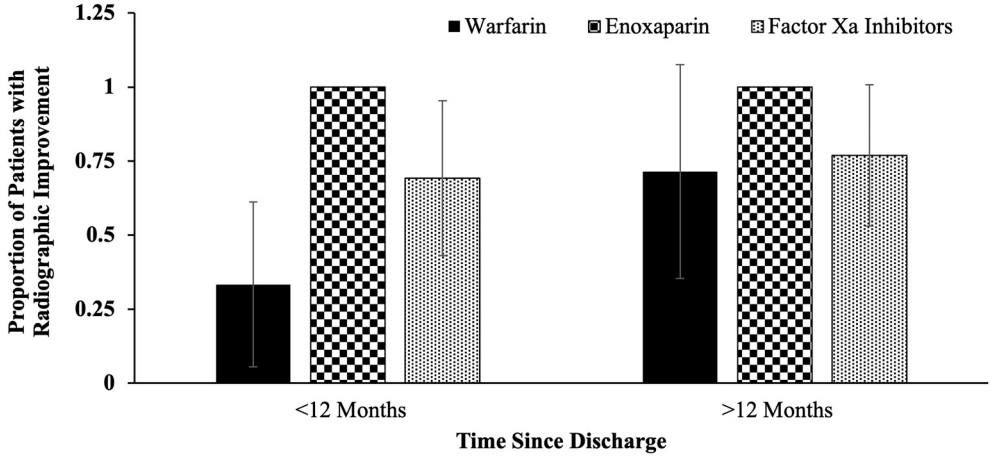

Fig. 4. Proportion of patients having had radiographic improvement with regards to overall thrombus burden in designated time frame since hospital discharge. Radiographic improvement was defined as any reduction in thrombus size or number of sinuses containing thrombus. No statically significant differences seen within or between groups. Error bars plotted represent 95% confidence intervals.

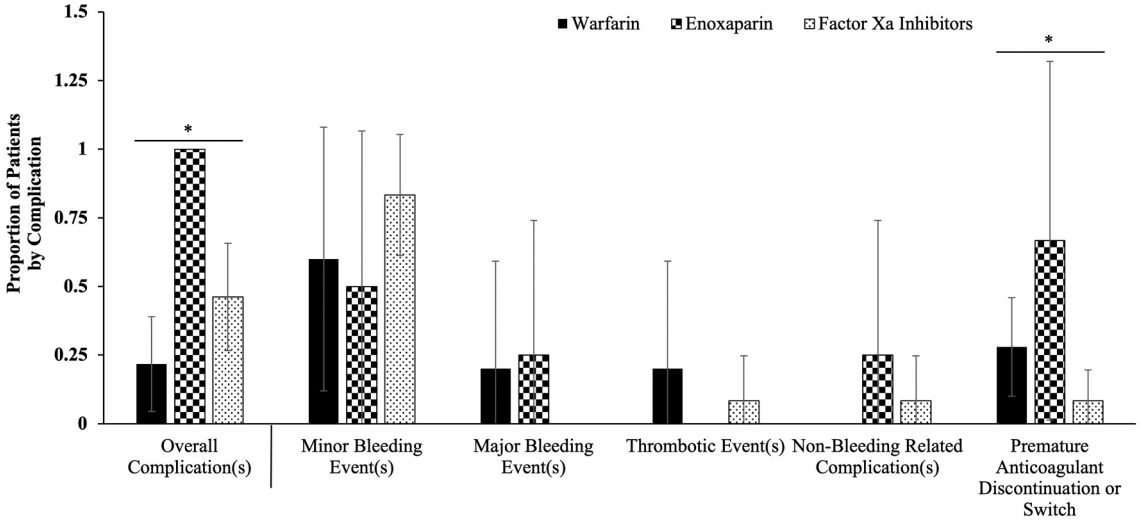

Fig. 5. Proportion of patients grouped based by complications during long-term anticoagulation treatment. Definitions of *minor* and *major* bleeding events based on established definition from International Society on Thrombosis and Hemostasis (see Methods). * Denotes P-value <0.05. Error bars plotted represent 95% confidence intervals.

comparison to the Warfarin group – although no statistical significance was documented. This slight trend towards better outcomes in the Factor Xa inhibitor group, without statistical significance, was also mirrored in the meta-analysis published by Bose et al. where 93% of patients utilizing DOACs achieved a mRS score of between 0 and 2 compared to just 85% in the standard therapy group [15]. Similar conclusions were also drawn by Lee et al [21].

In-line with improved patient functional status, patients taking Factor Xa inhibitors also had notably greater radiographic improvement rates at the ≤12-month time-point compared to Warfarin treatment groups. However, as with the mRS data, no statistical significance was able to be shown. By the >12-month time-period, rates of recanalization relatively equalized between the two groups, perhaps suggesting a greater therapeutic recanalization response much earlier on when utilizing Factor Xa inhibitors compared to Warfarin - a phenomenon priorly only documented in literature surrounding DVT treatment [22,23]. However, it is important to note, the above data does not necessarily suggest improved patient outcomes. Sinus recanalization rates have not been shown to necessarily influence overall clinical outcomes in CVST treatment thus making patient mRS scores a better representation of patient treatment outcomes [24].

Equally as important as patient outcomes, complication rates during treatment are also an extremely important outcome that needs to be accounted for. With this being said, no statistically significant difference was documented for any particular complication between the Warfarin and Factor Xa inhibitor groups, a conclusion drawn by other studies as well [21]. However, of note, patients on Factor Xa inhibitors did exhibit more reports of minor bleeding complications while patients on Warfarin had a slightly higher degree of major bleeding complications. This non- statistically significant predilection for major bleeding events in patients on Warfarin has also been priorly documented [21,25]. Lastly, patients on Warfarin were noted to have a slightly increased risk of recurring venous thrombosis, 20%, compared to Factor Xa inhibitors at 8.3%. However, the aforementioned difference appears to be less so related to the anticoagulants themselves and more so with potential compliance issues that arise as a result of the therapeutic regimens [25].

Bearing in mind the relative outcome similarity between the Warfarin and Factor Xa inhibitor groups, one could easily argue that Factor Xa inhibitors are superior to Warfarin in the treatment of CVSTs as they avoid the numerous pitfalls of being on Warfarin, while also providing the benefit of having a reversal agent – Andexanet Alfa [26]. Pitfalls generally associated with Warfarin treatment was actually manifested in our data by means of higher rates of medication non-compliance and adopting of Factor Xa inhibitors in patients originally prescribed Warfarin. Of note, the generally high cost of Factor Xa inhibitors, compared to Warfarin, does prove a barrier in the treatment of certain patients who might not be compliant in the face of financial difficulties [27]. Although price reduction is to be anticipated with the surfacing of generic Factor Xa inhibitor equivalents within the next five years.

Although our data does appear to align with numerous other publications, it is important to mention that the small sample size and retrospective nature of our study does present some limitations in terms of the conclusions being drawn. Additionally, we were not able to draw conclusions regarding treatment efficacy and patient outcomes as they pertain to each Factor Xa inhibitor individually as they were examined under the umbrella of Factor Xa inhibitors. Warfarin compliance was additionally hard to assess as outpatient INR documentation is infrequently found in patient charts. Lastly, specific anticoagulation recommendations in subsets of patients, e.g. those with underlying malignancies, is difficult to make given that so few of our patients had predisposing malignancies. The lack of certainty regarding CVST treatment selection in patients with malignancies is also present in our population as the use of Factor Xa inhibitors and Warfarin were both documented. No patients received long-term Heparin/Enoxaparin, as has also been documented in the literature, for treatment of CVSTs secondary to underlying malignancy [28]. With this being said, future publication of currently ongoing randomized control trials should be able to address the issue and provide stronger evidence for the utilization of Factor Xa inhibitors in the realm of CVSTs.

5. Conclusion

In conclusion, our work outlined above acts to further support the role of Factor Xa inhibitors in the long-term management of patients presenting with CVSTs. We have been able to show, in-line with priorly published studies, that Factor Xa inhibitors are at least equally as effective as Warfarin in improving patient outcomes, minimizing complications associated with anticoagulant therapies, and promoting sinus recanalization [15,21,29–32]. More importantly, we have been the first to suggest that utilizing Factor Xa inhibitors for CVST treatment could potentially lead to better sinus recanalization rates at the <12-month time-period compared to Warfarin. The above conclusions, coupled with the overall improved ease of Factor Xa inhibitor regimens on patients,

proves a recipe for greater compliance in patients requiring long-term anticoagulation. We hope that the eventual publication of randomized controlled trials will show similar results to our study and shift ultimate long-term treatment guidelines for CVSTs.

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CRediT authorship contribution statement

Alexei Christodoulides: Data Curation, Formal Analysis, Methodology, Writing - original draft. **Bradley N. Bohnstedt:** Supervision, Validation, Writing - review.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ensci.2022.100412.

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