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Treatment of cerebral venous thrombosis: A review

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Abstract

Cerebral venous thrombosis (CVT) is an uncommon cause of stroke. COVID-19 infection and vaccination have been associated with CVT. Fibrinolysis and mechanical thrombectomy may play an emerging role in management.

A literature review summarizing current evidence on use of antiplatelets, anticoagulants, thrombolysis, and mechanical thrombectomy for the management of CVT and COVID-19 related CVT.

A review of MEDLINE, PubMed, and Cochrane Reviews databases was performed using the search terms *CVT AND 'antiplatelets' aspirin', 'ticagrelor', 'clopidogrel', 'eptifibatide', 'Low-molecular-weight-heparin (LMWH)', 'Unfractionated heparin (UH)', 'warfarin', 'DOACs', 'rivaroxaban', 'apixaban', 'dabigatran', 'fibrinolysis', 'intra-sinus thrombolysis', 'mechanical thrombectomy', 'craniectomy' and 'antiepileptic drug'*.

LMWH and UH are safe and effective for the management of acute CVT. Warfarin may be used in the sub-acute phase but has weak evidence. DOACs are potentially a safe warfarin alternative, but only warfarin is currently recommended in international guidelines. Antiplatelets show little evidence for the prevention or management of CVT, but studies are limited. Vaccine-induced CVT is a newly recognized disease with a different pathophysiology, in which treatment of CVT may be relevant and for which non-heparin anticoagulants are recommended. There is a small body of evidence for using endovascular therapy in complex cases.

Relevance to clinical practice: The safe and effective management of CVT is important to reduce the risk of disability. Warfarin and heparin-based therapies remain the mainstay of treatment for CVT, including COVID-19 infection related CVT.

Conclusion: Heparin should be considered first line in acute CVT. In some cases, warfarin / DOACs may be commenced for secondary prevention. COVID-19 related CVT is treated similarly to non-COVID-19 CVT; however, vaccine-related CVT is treated with a combination of non-heparin anticoagulants, immunotherapy, and steroids. Finally, endovascular therapy should be reserved for complex cases in specialist centers.

Introduction

Cerebral venous thrombosis (CVT) is an uncommon cause of cerebrovascular disease, causing around 0.5% of total stroke cases [1]. It predominantly affects young adults and children [2–4], with women of childbearing age being affected two to three times more commonly than men [4,5]. The risk factors for the development of CVT, as with other types of venous thromboses, are conditions causing a hypercoagulable state, including pregnancy, oral contraceptives, dehydration, prothrombotic conditions, infections, cancer, and chemotherapy [2–7]. Most studies reported a low CVT incidence of 0.3 – 0.5 cases per 100 000 people worldwide [1–5,7,8], but two studies reported an incidence of 1.3 – 1.6 cases per 100 000 [6,9], and a higher incidence in women aged 31-50 years of around 2.8 per 100 000 [6]. An increased CVT incidence is reported amongst COVID-19 infected patients [10–12], as well as in those receiving COVID-19 vaccines [13,14]. A retrospective cohort study reported a high CVT incidence of 4.3 per 100 000 within two weeks of COVID-19 infection (n= 537,913), a slight increased when compared with the incidence in the

general population [10]. Another study reported a CVT crude incidence rate (IR) of 83.3 per 100 000 person-years following COVID-19 infection [11].

The most common presenting symptom is headache, present in 70 to 90% of patients. The headache usually progresses over hours to days and may worsen with coughing or bending over. Some patients may also present with seizures or stroke-like symptoms. Clinical signs include hemiparesis and paresis due to frontoparietal cerebral infarction, confusion and aphasia due to temporal lobe infarction, drowsiness and coma in deep cerebral vein thromboses from thalamic dysfunction, and 3rd-6th cranial nerve palsies in cavernous sinus thrombosis (see Ropper and Klein 2021, for a more detailed review on the anatomy and pathophysiology of CVT and its associated clinical syndromes) [15].

The overall outcome of CVT is good, but 7 – 25% have a moderate to severe disability requiring assistance at the time of discharge (modified Rankin Scale [mRS] 3-5) [2,4,5,7]. The in-hospital mortality rate of CVT varies from 3.3 – 7.7% [2,4,7], whilst the mortality at 6-months is 2.8 – 6.8% [4,5]. The mortality is higher in patients with COVID-19 and CVT, ranging from 12.5 – 25% [13,16,17].

The mainstay of treatment in CVT, alongside reversal of the underlying condition and symptom management, is therapeutic anticoagulation. This is recommended even in patients with a secondary intracranial hemorrhage (ICH) [18,19]. Traditionally, heparin, either unfractionated (UFH) or low molecular weight heparin (LMWH), is recommended for the treatment of acute CVT [18,19]. Usually, these patients are subsequently commenced on oral warfarin for maintenance anticoagulation [18,19]. With the advent of direct oral anticoagulants (DOACs), the treatment options have significantly increased. This review summarizes the current understanding of the available pharmacological and interventional therapies for the management of CVT.

The role of antiplatelets in the treatment of CVT

There is little literature on the role of antiplatelets in the treatment of CVT. There are no randomized controlled trials (RCTs) and few observational studies. The use of antiplatelets in CVT is not recommended in either the European [18] or American International Stroke guidelines [19].

Ferro et al. provide comparisons in efficacy between antiplatelets and other CVT treatments [4]. This prospective observational study examines death or dependence (measured using the mRS) of 624 patients at final follow-up (mean 16 months). Of the included patients, 37 (5.9%) were treated with antiplatelet agents, although the specific antiplatelet type is not specified. Death/dependence was lower in the former group; however, this difference was not significant (66/520 [12.7%] dead/dependent versus 19/104 [18.3%]; HR=0.73; 95% CI, 0.44 to 1.21). Chu et al. conducted a retrospective cohort study which extracted information on treatment and functional status of CVT patients [20]. Of the total 113 participants, the majority received LMWH, 15 received aspirin, and 7 received both LMWH and aspirin. However, the study does not provide any breakdown of outcome by treatment type and does not provide comparisons between treatments. Rim et al. conducted a retrospective analysis of treatments and clinical outcomes in 22 patients with CVT, of which 23% were treated with antiplatelet agents. Again, no breakdown of the specific antiplatelet agent used was given [21].

The role of heparin and low-molecular-weight heparin in the treatment of CVT

Heparin is a naturally occurring anticoagulant. Medicinal forms exist primarily as UFH and LMWH. UFH binds antithrombin and inactivates both thrombin and factor Xa, through an antithrombin-dependent mechanism. LMWH is a heterogenous group of molecules with a lower average molecular weight and more predictable pharmacokinetics which similarly binds

antithrombin, but its factor Xa inhibition is greater than thrombin inhibition. The result of both is the inhibition of factor Xa mediated conversion of prothrombin to thrombin and thereby the conversion of fibrinogen to fibrin to prevent formation of a clot.[22] Figure 1 shows the action of LMWH and other anticoagulant drugs.

Current American Heart Association/American Stroke Association (AHA/ASA) and European Stroke Organization (ESO) guidelines recommend UFH or LMWH in patients with acute CVT [18,19]. This recommendation is primarily based on 2 RCTs (n = 79) and several observational studies. The first trial by Einhaupl et al., (n = 20) was a single center study which examined adjusted dose IV UFH by administering a UFH bolus followed by continuous infusion adjusted to optimum APTT ratios [23]. However, the trial was stopped early after recruitment of 20 of the planned 60 patients due to findings of a benefit in favor of heparin. The other trial (n = 59) was a multi-center study which compared high dose, weight adjusted, subcutaneous LMWH with placebo for 3 weeks, followed by 3 months of oral anticoagulation with warfarin [24]. They found that 13% of patients in the group receiving LMWH followed by oral anticoagulation suffered poor outcome (death or Oxford Stroke Handicap Scale ≥ 3), compared with 21% of patients in the placebo group. A Cochrane review and meta-analysis of both RCTs found a non-statistically significant reduction in poor outcome (death or dependency) in those randomized to UFH or LMWH (13% absolute reduction in risk of death or dependency, 95% CI -30% to 3%) [25]. These studies have since been supported by multiple retrospective and prospective observational studies which show that anticoagulation in acute CVT with UFH or LMWH is safe and associated with better outcomes [4,26–34]. The largest study (n = 624 from 89 centers across 21 countries) in which all patients received anticoagulation, found an 8.3% mortality over 16 months, with 79% of patients having a full recovery (mRS 0-1) [4]. However, in most of these studies [4,27,29–34],

patients were treated with LMWH or UFH followed by warfarin for several months, and therefore, it is difficult to comment specifically on outcomes with LMWH or UFH alone. Furthermore, the Venous Thrombosis Portuguese Collaborative Study Group (VENOPORT) study showed that significantly fewer patients are anticoagulated if presenting with CVT with concurrent ICH [29]. Nevertheless, in circumstances of CVT with hemorrhagic transformation, one observational study found that only 11% of patients with hemorrhagic CVT treated with UFH or LMWH showed a deterioration in clinical course [35]. Therefore, current AHA/ASA and ESO guidelines do not consider CVT associated ICH as a contraindication to anticoagulation with UFH or LMWH [19,36]. Although some clinicians may opt for lower doses of anticoagulation, based on clinical judgement, this is not yet supported by any evidence [19].

Recently, 2 RCTs have compared LMWH with UFH in acute CVT. The first (n = 66) showed a significantly lower hospital mortality in those receiving LMWH (0% compared to UFH 18.8%, p = 0.01) [37]. The second (n = 52) showed no statistically significant difference in mortality for those receiving LMWH (3.8%) or UFH (5.6%, p = 0.99) [38]. However, a large non-randomized cohort study (n = 421) supported the use of LMWH over UFH based on better functional prognosis at 6 months and a lower risk of new ICH (adjusted odds ratio, 0.29; CI 0.07 – 1.3) [39]. Despite the limitations of these studies, current EU guidelines make a weak recommendation for LMWH over UFH [18].

Current data and guidelines support the use of both UFH and LMWH as safe and effective treatment options in acute CVT to improve mortality and functional outcomes. If anticoagulation is given, LMWH may be preferable to UFH given slightly more effective outcomes, lower risk of major hemorrhage and ease of administration.

The role of warfarin in the treatment of CVT

Warfarin is an oral anticoagulant that is currently licensed for use in the prevention and treatment of venous thromboembolism (VTE) (i.e. deep vein thrombosis - DVT- and pulmonary embolism - PE), and for the prophylaxis of cerebral and peripheral embolism arising from atrial fibrillation or cardiac valve replacement [40,41].Warfarin is a vitamin K antagonist (VKA) that competitively inhibits vitamin K epoxide reductase complex 1 (VKORC1), an enzyme essential for the activation of vitamin K. Vitamin K is a co-factor required for the complete functioning of coagulation factors II, VII, IX, and X, and the coagulation regulatory factors protein C and protein S [40,41] after hepatic synthesis.

Warfarin is usually continued for at least 3 months with regular monitoring of INR to ensure it remains within the therapeutic range. This can be problematic in situations where regular monitoring may be difficult, for example in remote locations or in developing countries where INR monitoring equipment may not be readily available [42].

There are no RCTs on secondary prevention of CVT or duration of anticoagulation treatment following treatment with UFH or LMWH. Two double-blind RCTs for warfarin in DVT and PE, show that warfarin therapy is significantly associated with a reduction in recurrent VTE [43,44]. In both studies, longer durations of warfarin (18 months versus the usual recommendation of 6 months) were associated with a reduction in recurrent VTE.

Current AHA/ASA and ESO guidelines recommend commencing warfarin as secondary prevention for CVT following acute treatment with UFH or LMWH [18,19]. Recommended durations of therapy are 3-6 months in provoked CVT and 6-12 months in unprovoked CVT [18,19].

Given the lack of randomized trials, the current AHA/ASA and ESO guidelines are primarily based on several prospective and retrospective observational studies [45], and extrapolated data from trials involving other venous thromboembolism e.g. PE and DVT as described above. However, many of these observational studies did not report on survival outcome by anticoagulation status. [45]. In one study, 12 of the 13 accounted deaths were from causes other than recurrent CVT [45,46]. Furthermore, pooled analysis of these observational studies showed that patients receiving warfarin were at far higher risk of recurrent VTE than those not receiving warfarin [45]. The recent RESPECT-CV trial found that warfarin was safe and effective at preventing recurrent VTEs in patients with CVT and no patients out of 60 developed a VTE at 6 months [47]. However, this was an underpowered open-label trial, and there was significant variability in participants' INRs. The mean time in the therapeutic INR range was only 66%, which is a limitation of warfarin therapy. Furthermore, the absolute risk of recurrent thrombosis following CVT is low (estimated to be 4 per 100 patient-years) [48], except for in patients with risk factors, such as thrombophilia or malignancy [19,36,49–51]. Therefore, some have argued that there is currently a lack of evidence to recommend warfarin therapy for all patients following acute CVT, particularly given the potential risks such as major hemorrhage [45].

Emerging studies are showing a role for direct oral anti-coagulants (DOACs) as safe and effective options for the secondary prevention of CVT [52]. This will be particularly useful for patients with contraindications to warfarin, and those with warfarin failure, including pseudo-failure (poor compliance, incorrect dosing, drug interactions, malabsorption) and true failure (cancer, antiphospholipid syndrome, polycythemia) [53]. However, at present, international guidelines do not recommend DOACs for CVT.[19,36]

The role of Direct Oral Anticoagulants in the treatment of CVT

Direct Oral Anticoagulants (DOACs), sometimes referred to as non-vitamin K or novel oral anticoagulants (NOACs) have increasingly been used to treat VTE in the past decade. Four are currently being marketed. Dabigatran is a direct thrombin inhibitor while rivaroxaban, apixaban, and edoxaban are direct inhibitors of activated factor X (FXa) [54]. They carry several advantages over warfarin including rapidity of action, more stable pharmacokinetics, no requirement of blood monitoring, and a lower risk of hemorrhage [55]. However, they are not yet recommended for the treatment of CVT, mainly due to paucity of evidence from RCTs [19,36].

There are three RCTs published to date that have compared DOACs to warfarin in patients with a CVT. The first, published in 2019 [47], included 120 patients, half randomized to Dabigatran and the other half to Warfarin. At 24 weeks, there were no significant differences in favorable outcomes between the two groups. The second RCT published in 2021 [56], compared Rivaroxaban 20-30 mg (21 patients) to dose adjusted warfarin (target INR 2-3, 24 patients). There were no significant differences in both recanalization rates or clinical outcomes at 6 and 12 months. The third RCT showed similar findings in 50 patients equally randomized to either rivaroxaban (20mg once daily) and dose-adjusted warfarin (target INR 2-3) [57]. In all three RCTs, there were no significant differences in the risk of developing adverse outcomes (intracranial haemorrhage, major bleeding, and thrombosis recurrence) between DOAC and warfarin. However, since these studies were underpowered, so conclusive remarks on the efficacy and safety of DOACs over warfarin could not be made

Most of the published literature on DOAC use in CVT is in the form of case reports and series. Several systematic reviews have previously looked at available evidence of DOAC use in CVT from the time these drugs were approved for VTE. The first systematic review by Bose et al. [58],

included one RCT, 5 observational cohorts and 27 case studies or series. It compares 279 patients treated with DOACs with 315 patients treated with standard therapy. DOACs were found to be safe, with rates of new ICH or mortality reported as comparable to warfarin. The second systematic review by Riva et al. [59], of 615 patients with CVT that were treated with a DOAC, included two RCTs and 21 case series or cohorts. Mortality was reported in 1.76%, major bleeding in 2.41%, recurrent thrombosis in 2.05% and excellent neurological outcome defined as mRS of 0-1 in 85.9%. Where comparison was available with warfarin treated patients, no significant differences were identified.

A subsequent retrospective observational study of 845 patients (ACTION-CVT) [60] from 27 centers in four countries, found similar rates of recurrent venous thrombosis, death, and rates of partial/complete recanalization in the two arms, and a lower risk of hemorrhage with DOACs.

A recent systematic review and meta-analysis of 3 RCTs and 16 observation studies found that DOACs and warfarin therapy may have similar efficacy and safety profiles with regards to the development of recurrent VTE (RR, 0.85 [95% CI, 0.52–1.37]), major haemorrhage (RR, 0.70 [95% CI, 0.40–1.21]), intracranial haemorrhage (RR, 0.58 [95% CI, 0.30–1.12), and complete recanalization (RR, 0.98 [95% CI, 0.87–1.11]) [61]. However, the authors acknowledged several limitations of the currently published studies, including inconsistent definitions of major haemorrhage, high risk of bias in many of the included studies, and the lack of well powered randomized control trials. Therefore, findings should be interpreted with caution pending the findings of further large-scale trials such as the Study of Rivaroxaban for Cerebral Venous Thrombosis (SECRET) randomized trial [NCT03178864] and the Direct Oral Anticoagulants in the Treatment of Cerebral Venous Thrombosis [NCT04660747] observational study.

Lastly, at present no study has yet made a comparison between different DOACs, and current data do not suggest whether one is superior to another.

The role of thrombolytic therapy in the treatment of CVT

Thrombolytic therapy for acute arterial ischemic stroke is well established. [62] However, there are no randomized, double-blind, placebo-controlled trials to support systemic or local thrombolysis as a first-line therapy for CVT [63].

Only a few case studies have been published on the use of systemic thrombolysis for CVT. The first use of intra-sinus local thrombolysis was reported by Scott et al. in 1988. He catheterized the sagittal sinus via a frontal burr hole and infused urokinase over an 8-hour period, resulting in an excellent recovery [64]. Since then, safety and efficacy of local thrombolysis has been established by many case reports and series with excellent to good clinical outcomes. Two non-randomized studies have been published comparing local thrombolysis with systemic heparin therapy, and later with mechanical thrombectomy (MT). Wasay et al. [65], reviewed 40 consecutive patients with superior sagittal sinus (SSS) thrombosis, treated with local urokinase (thrombolysis group) or systemic heparin anticoagulation (heparin group). The thrombolysis group (n=20) received local urokinase (250,000 U bolus followed by 80,000 U/h continuous infusion) into the SSS followed by systemic heparin anticoagulation. The heparin group (n=20) received systemic heparin anticoagulation only. The local thrombolysis showed a better functional outcome at discharge, despite having a higher percentage of hemorrhagic complications when compared to the heparin group [66]. Siddiqui et al. [67] performed a non-randomized comparison of local thrombolysis with MT. Compared to MT, local thrombolysis alone was reserved for milder cases of CVT. Thrombolytic agents included either urokinase 80,000-100000/h, tissue plasminogen activator (tPA) 1 mg/h or tirofiban 0.5 mcg/kg/h

(in conjunction with tPA). Patients who received MT had a non-significantly higher incidence of periprocedural complications [67].

With improvements in neuro interventional technology, the use of local thrombolysis alone for the treatment of CVT has declined over the years with increasing use of MT in conjunction with local thrombolysis [68].

The role of endovascular therapy for the treatment of CVT

Endovascular treatment includes both intra-sinus thrombolysis and mechanical thrombectomy. They can be utilized individually or in combination, particularly for patients who are refractory to medical treatment. Several researchers propose that poor prognostic factors, such as coma at the time of admission or predominant involvement of deep cerebral veins, may favor the use of early endovascular interventions [69].

A major benefit of intra-sinus thrombolysis is an increased onsite drug concentration and lower hemorrhage risk [70]. A bolus dose of 10 mg recombinant tissue plasminogen activator (rtPA) could be injected and then infused through the catheter for 1-2 mg/hour. Nevertheless, large thrombi may be resistant to intra-sinus thrombolysis. Techniques for endovascular clot retrieval include rheolytic thrombectomy, [71] balloon angioplasty and/or stenting [72], microsnare [73], suction thrombectomy [74], and manual aspiration [75]. It should be noted that endovascular procedures carry a risk of catheter-associated complications, such as endothelial damage, iatrogenic thrombus, fragmented or dislodged thrombi, and pulmonary embolism [69].

Mechanical thrombectomy, with or without chemical thrombolysis, should be reserved for extreme cases such as those who do not respond to conventional therapies or those that have a poor prognosis. Furthermore, this approach should be restricted to specialist centers with

expertise. In addition, if the cause of the CVT is suspected to be traumatic, and there is evidence of concurrent ICH, intra-sinus thrombolysis is not recommended [76].

The role of decompressive cranioectomy in the treatment of CVT

Although most patients diagnosed with CVT make a good recovery with the use of anticoagulants, mortality occurs in up to 2% of patients [77], primarily due to parenchymal haemorrhagic lesions, severe cerebral oedema and brain herniation [78]. In such cases, decompressive craniectomy (DC) may be considered.

There is no consensus on indications for DC, and it is done on a case-by-case basis [79]. The guideline on CVT management from European Federation of Neurological Societies has recommended DC in patients with progressive deterioration since 2006 [80]. The main patient features used in observational studies to indicate need for DC are progressive deterioration despite medical therapy; CT signs of mass effect; lesion leading to midline shift on imaging; indication of imminent brain herniation; pupillary signs of transtentorial herniation, GCS 8 or less at admission with large infarction imaging; and post-intrasinus thrombolysis haematoma [81]. There are case studies illustrating of the use of decompressive craniectomy in pregnant patients but outcomes within these case studies vary significantly, from having significant neurological deficit to excellent recovery [82,83]. Highly variable outcomes are also found in case studies on the use of hemicraniectomy in patients with CVT and COVID-19 [84]. DC has been used in 2 case studies alongside endovascular therapy, showing patient improvement from comatose state to modified Rankin Scale (mRS) scores of 2 or 3 [85,86].

No randomised controlled trials exist, but there are multiple observational studies which describe the use of decompressive hemicraniectomy in the treatment of CVT. Most studies are case reports or series, and few prospective studies exist. A recent (2024) single-arm prospective cohort study examined the outcome of death or severe disability (mRS scores, 5–6) at 12 months post-surgery in patients with severe CVT following decompressive surgery. At the final assessment before surgery, 57.6% (n=68) patients were comatose, 22.9% (n=27) had unilateral fixed dilated pupils, and 7.6% (n=9) had bilateral fixed dilated pupils. After 12 months, two-thirds of patients were alive, and more than one-third were independent after 1 year [87]. Data allowing comparison between participants who undergo DC versus those who do not is minimal, but one small (n=12) retrospective study showed better outcomes in the participants who underwent DC (DC group: 1 (n=6), mRS 3 (n=1) and death due to pulmonary embolism (n=1). Group without surgery: death in all 4 participants) [88]. A combined retrospective registry and systematic review examined outcomes in CVT cases treated with decompressive surgery (both DC and haematoma evacuation). Of the total 69 patients, at final follow up (median 12 months), only 12 (17.4%) had an unfavourable outcome (mRS score, 5 or death) and one-third of the patients with bilaterally fixed pupils recovered completely [89]. As a result of current evidence, the European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis strongly recommends the use of decompressive surgery, including hemicraniectomy, to prevent death in patients with CVT and parenchymal lesions with impending herniation [18].

The timing of restarting anticoagulation post DC is not included in guidelines on CVT, however, a case series and systematic literature review of 243 patients suggests anticoagulation can be resumed safely 24-48 hours postoperatively. In smaller series, it may be safely resumed as early as 12 hours, especially if delivered at a prophylactic or halved dose.[90]

Treatment of seizures in CVT

Seizures in CVT are more common than seizures in strokes due to arterial occlusion, with presenting or early (< 7 days from diagnosis) seizures seen in 10.6-46.6% of CVT cases [91–96]. Late seizures (> 7 days after diagnosis) are seen in 11% of patients [97,98]. Acute symptomatic seizures in CVT patients are associated with supratentorial lesions, frontal or parietal lobe involvement, cortical vein and sagittal sinus thrombosis, CVT in the puerperal period, GCS < 8 and haemorrhagic lesions [91,93,95,99]. Risk factors for late seizures include symptomatic seizures, loss of consciousness, focal neurologic signs, hemorrhagic component, and superior sagittal sinus involvement [98,100].

Benzodiazepines are used to treat patients who are acutely seizing.[101] Evidence on the use of antiepileptic drugs in seizure management post-CVT is lacking. A Cochrane review illustrates the absence of randomised controlled trials on the use of antiepileptics in the management of primary or secondary seizures related to CVT [102]. A case control study that examined 624 patients from the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) cohort who had a presenting or early seizure found AED prophylaxis significantly reduced the risk of early seizures in patients with supratentorial lesions and presenting seizures (OR 0.006 (95% CI 0.001-0.05) but found no significant difference in patients who did not have a presenting seizure [93]. Other observational studies examine risk factors for seizures, and make comment on whether they believe AEDs are recommended, rather than explicitly examining whether AEDs reduce the risk of seizures [92,95,99,103,104]. Ferro et al [99] concludes that prophylactic treatment with AED in the first year after CVT may be justified if patients have haemorrhage on their initial imaging or early symptomatic seizures. One study examining 441 patients with any seizure between symptom onset and 7 days after diagnosis of CVT did not find a specific subgroup of patients

without pre-diagnosis seizures who had risk of postdiagnosis seizure to justify prophylactic AED treatment [92], and therefore does not recommend prophylactic AED treatment. A registry study of 1127 patients shows high recurrence risk of seizures after a single late seizure (defined as seizure >7 days after diagnosis of CVT), and recommends AED use in these patients [97]. This recommendation reflects that in stroke guidelines, which recommends AED use in those with late seizures, due the high risk of seizure recurrence.[97,105] Currently, international CVT guidelines suggest using AEDs in patients with acute CVT with supratentorial lesions and seizures to prevent early recurrent seizures, but guidelines indicate that the risk of AED use outweighs the benefit when used prophylactically to prevent late-onset seizures [18].

Treatment of COVID-19 and COVID-19 vaccine related CVT

A slight increase in incidence and mortality of CVT is well documented in patients infected with COVID-19 [10–12]. Multiple pathophysiological mechanisms have been proposed, including elevated circulating inflammatory markers, cytokine storm, decreased mobility, endothelial injury, and angiotensin pathway alterations [106]. Furthermore, the possible confounding effect of the various treatments previously trialed to manage COVID-19 infection, such as azithromycin and hydroxychloroquine, is not yet clear [107]. Nevertheless, the treatment is the same as with CVT in non-COVID-19 patients.

Post-vaccine related CVT is a different entity. It is more commonly seen with vaccines containing an adenovirus vector (such as the Oxford-AstraZeneca [ChAdOx1] and Johnson & Johnson [Ad26.COV2.S] vaccines) [13,14], compared to mRNA vaccines (such as the Moderna [mRNA-

1273] or Pfizer-BioNTech [BNT162b2] vaccines)[11] or inactivated virus containing vaccines (Sinopharm, Sinovac or CanSino) [108].

Most of the patients who developed VTE, including CVT, following administration of an adenovirus-vector containing vaccine, have tested positive for the presence of antibodies against platelet factor 4 (PF4) along with thrombocytopenia [13,14]. This phenomenon has been termed vaccine-induced immune thrombotic thrombocytopenia (VITT), a condition resembling heparin-induced thrombocytopenia (HIT), with the main difference being that the former group of the patients were not exposed to heparin [13,14,109]. This is a different disease to CVT in COVID-19 infection and it has a different pathophysiology. Interestingly, VITT is not common with non-adenoviral vaccines, i.e., mRNA-based, and inactivated virus containing vaccines [11,108].

Non-heparin anticoagulants are preferred for the treatment of VITT, with or without CVT, owing to the similar pathophysiology between VITT and HIT [109]. DOACs, as well as parenteral thrombin inhibitors, are recommended in these patients [109]. In critically ill patients with severe thrombocytopenia (platelet level $< 50 \times 109$/L), parenteral direct thrombin inhibitors may be preferred over DOACs owing to their short half-life. [110] DOACs are also preferred over warfarin in VITT due to the warfarin's potential to induce a paradoxical hypercoagulable state during the first few days of treatment initiation, which may aggravate the already hypercoagulable state induced by VITT [109]. Warfarin therapy may be considered if platelet counts have returned to normal for at least 2 days [109]. Since VITT is considered a provoked thrombosis, anticoagulation should be continued for at least 3 months [109].

Some have recommended urgent IVIG administration as soon as a diagnosis of VITT is considered [111–113]. IVIG competitively inhibits the binding of VITT antibodies with their corresponding sites on platelets, resulting in decreased platelet activation, decreased platelet aggregation, and

reduced hypercoagulability [109,114]. An alternative treatment is Bruton tyrosine kinase inhibitors, which may also decrease platelet activation by blocking the FCγRIIA receptors on platelets [115], however, its clinical benefits in VITT are yet to be seen.

The role of steroids in VITT is still not clear. Theoretically, steroids reduce antibody production and may help in the management of VITT [109] but large-scale studies are lacking, even in HIT. Some have considered the use of steroids in VITT, especially when the platelet count is <50 x 109/L [111,113]. Currently a combination of IVIG, steroids, and non-heparin anticoagulants is recommended for the treatment of VITT [111,113,116,117]. Plasma exchange may also be considered in severe and resistant VITT cases, usually for 5 days [111–113].

In VITT, routine platelet transfusion should be avoided, unless the patient has very low platelet counts (<30 x 109/L) and is actively bleeding or due surgery [112]. Platelet infusions could potentially introduce more PF4 targets for the VITT antibodies to bind to and exacerbate the thrombosis, resulting in an increased mortality. [118] Antiplatelet agents, including aspirin, have no documented beneficial role in the management of VITT. In fact, their use may increase the risk of bleeding [109,112] and should be avoided for both prophylaxis and treatment of VITT. Table 1 Summarizes the highest level of evidence for each of the mentioned therapeutic strategies used in the treatment of CVT.

Conclusion

Cerebral venous thrombosis (CVT) is an uncommon cause of stroke, accounting for around 0.5% of stroke cases. It most commonly presents in young adults, women of child-bearing age, and children; and manifests as headaches, seizures, and altered consciousness. Effective treatment is

imperative to reduce the risk of sequelae such as permanent neurological damage causing loss of function.

Heparins remain the mainstay of treatment for the management of acute CVT and warfarin is usually commenced following this. However, emerging evidence shows that DOACs may be comparable to warfarin with a lower risk of haemorrhage. Given the ease of administration, rapid onset, stable pharmacokinetics, and lack of need for monitoring, DOACs may become a more favorable management option for the management of CVT. However, current research is limited to rivaroxaban and dabigatran in non-randomized trials and further research should attempt to make a comparison between DOACs.

Recent case reports have highlighted an association between COVID-19 infection and / or vaccination and a higher incidence and mortality of CVT. The treatment is the same as with CVT in non-COVID-19 patients. Vaccine-induced CVT is a newly recognized disease with a different pathophysiology, in which treatment of CVT may be relevant and for which non-heparin anticoagulants are recommended.

Lastly, whilst local fibrinolysis and mechanical thrombectomy are used widely in ischaemic stroke, and in some centers has been shown to be effective in CVT, it should be reserved only for extreme cases and utilized by specialist centers.

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Table 1. Summary of highest level of evidence for treatment of CVT, categorized by treatment type.

Agent	Type of study	Population and setting	Intervention	Comparison	Outcome	Results
Antiplatelets						
Ferro et al., 2004	Case series	Patient's age >15 with symptomatic CVT (n=624)	IV heparin or therapeutic dose LMWH (n=401), prophylactic dose LMWH (n=218), antiplatelet drugs (type not specified, n=9), endovascular thrombolysis (n=13)	None	▪ Death/dependence (mRS>2) at end of follow-up period ▪ Death and death/dependence at 6 months (intervention and comparison group combined) ▪ Difference in death/dependence of IV heparin or treatment dose LMWH compared to prophylactic dose LMWH ▪ Rate of recurrent sinus thrombosis ▪ Rate of other thrombotic events ▪ Rate of seizures during follow up	▪ 84 (13.4%) patients categorised as death/dependence at last follow up ▪ 86 (14%) patients categorised as death/dependence at 6 month follow up ▪ No statistically significant difference in death/dependence for IV heparin or treatment dose LMWH compared to prophylactic dose LMWH or antiplatelet (66/520 (12.7%) dead/dependent versus 19/104 (18.3%); 95% CI, 0.44 to 1.21). ▪ 14 (2.2%) patients had a recurrent sinus thrombosis ▪ 27 (4.3%) had other thrombotic events ▪ 66 (10.6%) had seizures
Chu et al., 2020	Case series	Adults with CVT (n=113)	LMWH (n=91), aspirin (n=29) or LMWH and aspirin (n=7)	None	▪ Functional outcome (mRS) ▪ VTE recurrence ▪ Mortality ▪ Rate of haemorrhage ▪ CVT recurrence	▪ 94 (83.18%) patients achieved a good clinical outcome (mRS 0-1). ▪ Haemorrhage occurred in 17 (15.04%) patients ▪ 3 (2.65%) patients died, 2 of these deaths were attributed to the CVT. ▪ 10 (8.85%) patients had CVT recurrence during follow-up (6-24m).
Rim et al., 2016	Case series	Patients with CVT (n=22)	Anticoagulants +/- antiplatelet (n=14),	None	▪ mRS < 2 at discharge ▪ Mortality rate ▪ Recanalization rate	▪ 19 (86.4%) patients had mRS scores < 2 at discharge ▪ 1 (4.5%) patient died

			antiplatelet only (n=5), no treatment (n=3).			▪ 15 patients (77%) had Magnetic Resonance Venography during follow-up (mean interval, 1.13 years); 12 (80%) showed signs of thrombotic resolution.
Xu et al., 2015	Case series	Severe CVT during puerperium n=12	Mechanical thrombus maceration, local thrombolytic therapy and LMWH, followed by clopidogrel and aspirin for 1 month, followed by either antiplatelet as single agent for 6 months	None	▪ Recurrence of CVT	▪ No patient had a recurrent CVT
SUMMARY: ***For antiplatelets, case series level evidence is available for 771 patients, but heterogeneity between cases and outcomes makes summarising results difficult. All data is descriptive and there is no comparative data analysing the efficacy of antiplatelets vs other treatments.***						
Heparin and LMWH						
Coutinho et al., 2011	Systematic review and meta-analysis	Patients with CVT (n=79)	Unfractionated heparin, LMWH, or oral therapy with coumarin(s)	Placebo or open control	▪ Death from any cause at the end of the scheduled trial follow-up. ▪ Death or dependency at the end of the scheduled trial follow-up. ▪ Adverse events	▪ Non-statistically significant RR of death (0.33, 95% CI 0.08 to 1.21) in the treatment group compared to the control group ▪ Statistically significant RR of death or dependency (0.46, 95% CI 0.16 to 1.31). ▪ The ARR in the risk of death/dependency was 13% (95% CI 30% to -3%). ▪ No new symptomatic intracerebral haemorrhages were observed. One major gastro-intestinal haemorrhage occurred after anticoagulant treatment. Two control patients (placebo) had a diagnosis of probable pulmonary embolism (one fatal).
SUMMARY						

For heparin and LMWH, meta-analysis showed benefit compared to placebo or open control: risk of death or dependency following treatment with heparin or heparin derivative 0.46 that of placebo or open control.						
Warfarin vs DOAC						
Riva et al., 2022	Systematic review and meta-analysis (2 RCT, 21 observational studies)	Adults with CVT	DOAC (n=618)	Warfarin or no comparator	▪ Mortality ▪ Major bleeding ▪ Recurrent VTE ▪ Excellent neurological outcome [modified Rankin Scale (mRS) score 0–1] ▪ Recanalization rate	▪ Weighted mean mortality rate was 1.76% (95% CI 0.70%–3.24%). No significant difference between the two groups (RR 1.22; 95% CI 0.32–4.59) ▪ No significant difference between the major bleeding rate between DOAC group vs warfarin group (RR 0.79; 95% CI 0.33–1.86 ▪ 10/577 (1/73%) patients receiving DOACs had recurrent VTE. No significant difference between the rate of VTE in DOAC compared to warfarin groups (RR 0.67; 95% CI 0.26– 1.75) ▪ No significant difference in neurological outcome between DOAC group vs warfarin groups (RR 1.06; 95% CI 0.96–1.17)). ▪ No significant difference in recanalization rate between the two groups (RR 1.00; 95% CI 0.95–1.06)
Yaghi et al., 2022	Systematic review and meta-analysis (3 RCT, 16 observational studies)	Adults with CVT	DOAC (n=1950)	Warfarin	▪ Risk of recurrent venous thrombosis ▪ Risk of major haemorrhage ▪ Rates of recanalization	▪ Similar risk of recurrent venous thrombosis (RR 0.74; 95% CI 0.42-1.30) ▪ Similar risk of major haemorrhage (RR 0.85; 95% CI 0.52-1.37) ▪ Similar rates of recanalization (RR 1.00; 95% CI 0.88-1.13)
SUMMARY ***For DOACs, systematic review and meta-analysis shows no significant difference between mortality, major bleeding, VTE recurrence, neurological outcome, or recanalization rate for DOAC compared to warfarin.***						

Thrombolytic therapy						
Viegas et al., 2014	Systematic review	Patients with CVT (n=26)	Systemic thrombolysis including tPA, streptokinase and urokinase		▪ Independence, using mRS ▪ ICH ▪ Extracranial haemorrhage ▪ Recanalization rate ▪ Survival rate	▪ 22/25 (88%) of patients regained independency (mRS scores 0-2) ▪ Intracranial haemorrhages occurred in 3 cases (11.5%). Extracranial haemorrhages occurred in 5 cases (19.2%), and there were 3 cases of serious bleeding (11.5%), including 2 deaths (7.7%). ▪ Partial or complete recanalization was verified in most patients (n = 16; 61.5%). ▪ The survival rate was 92.3% (24/26 patients).
SUMMARY ***Systemic thrombolysis is effective in improving the independence of the majority (88%) of participants. However, given all evidence is from case reports/case series, it is not possible to determine the efficacy of thrombolytic therapy over other CVT treatments.***						
Endovascular treatment						
Kim and Su, 1997	Case series	Patients with intracranial Dural sinus thrombosis (n=9)	Direct alteplase infusion into the thrombosed Dural sinus	None	▪ Recanalization rate ▪ Complications of infusion ▪ Successful treatment of clinical features during 3-month follow-up	▪ Recanalization was achieved in 100% of patients. ▪ Complications of a small intrapelvic haemorrhage and oozing at a femoral puncture site occurred in two separate cases. ▪ Clinical signs and symptoms were treated successfully in all patients during the 3-month follow-up period.
Modi et al., 2009	Case series	Patients with extensive CVT, pre-existing ICH, and severe progressive neurological deficit despite heparin therapy (n=4)	AngioJet rheolytic thrombectomy	None	▪ Recanalization rate ▪ Neurological recovery rate	▪ Partial or complete sinus patency was restored in 100% of patients ▪ Complete neurological recovery was achieved in 75% (n=3) patients.
SUMMARY ***Case series level of evidence for a total of 12 patients suggests good success in recanalization (100% of patients), with complete neurological recovery in 75-100% of patients.***						

Decompressive hemicraniectomy						
Aaron et al., 2024	Cohort study	Patients with severe CVT with impending brain herniation treated by decompressive neurosurgery (n=118)	Craniectomy, only (n=82) Craniectomy and haematoma evacuation (n=37)	None	▪ Death or severe disability (mRS 5-6) ▪ Independence (mRS 0-2) ▪ Patient and caregiver opinion on the benefit of surgery ▪ Follow up at 6 and 12 months	At 12 month follow up: ▪ 46 (39%) patients were dead or severely disabled (modified Rankin Scale scores, 5–6) ▪ 42 (35.6%) patients were independent (modified Rankin Scale scores, 0–2) ▪ Of the survivors, 56 (78.9%) patients and 61 (87.1%) caregivers expressed a positive opinion on surgery.
SUMMARY ***Cohort study level of evidence for 118 patients who underwent craniectomy show two-thirds of patients with severe CVT are alive after decompressive surgery and one-third were independent.***						
Antiepileptic drugs						
Ferro et al., 2008	Case-control	Patients with CVT who experienced presenting or early seizures	Antiepileptic drug (unspecified) (n=231)	No antiepileptic drug (n=393)	▪ Risk of early seizures (within 2 weeks of diagnosis) in 4 risk strata – a) supratentorial lesion, presenting seizure b) no supratentorial lesion, no presenting seizure c) no supratentorial lesion, presenting seizure d) no supratentorial lesion, no presenting seizure	▪ Significantly lower risk of early seizures when AEDs used in patients with supratentorial lesions and presenting seizures (0.7% patients with AEDs vs 51% patients without AEDs; OR=0.006, 95% CI=0.001 to 0.05). ▪ No significant difference between AED and no AED groups for supratentorial lesion and no presenting seizure.
SUMMARY ***AEDs significantly lower the risk of early seizures when used in patients with supratentorial lesions and presenting seizures.***						

AED = antiepileptic drug, ARR = absolute risk reduction, CVT = cerebral venous thrombosis, CI = confidence interval, DOAC = direct oral anticoagulant, ICH = intracranial hemorrhage, IV = intravenous, LMWH = low molecular weight heparin, mRS = modified

Rankin score, RCT = randomized controlled trial, RR = relative risk, tPA = tissue plasminogen activator, VTE = venous thrombo embolism.

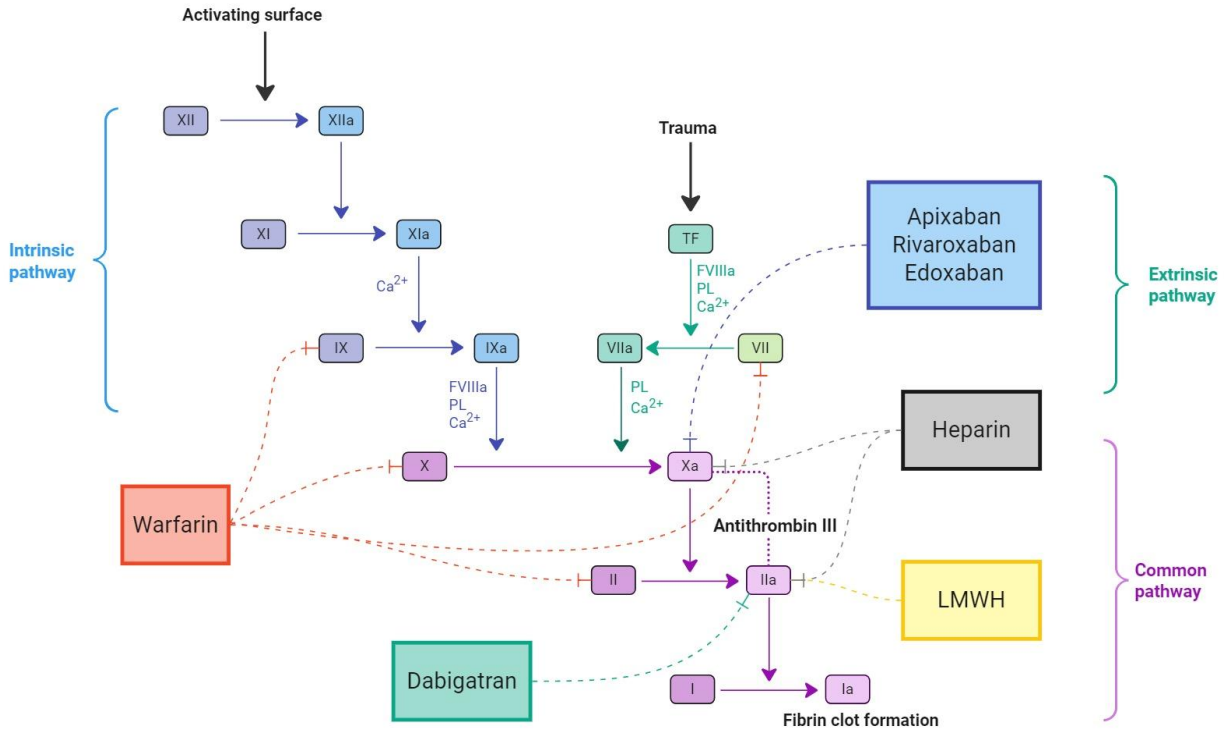

Figure 1: Anticoagulant actions on the clotting cascade. The figure above shows the actions of different anticoagulant agents on the clotting cascade. Drug site of action is highlighted in the colored boxes.