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Ischemic Stroke in the Young

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Abstract

The purpose of this article is to address several challenging questions in the management of young patients (those age 60 and under) who present with ischemic stroke. Do genetic thrombophilic states, strongly associated with venous thrombosis, independently cause arterial events in adults? Should cases of patent foramen ovale be closed with mechanical devices in patients with cryptogenic stroke? What are the optimal treatments for cerebral vein thrombosis, carotid artery dissection, and antiphospholipid syndrome and are DOACs acceptable treatment for these indications? What is the mechanism underlying large vessel stroke in patients with COVID-19? This is a narrative review. We searched PubMed and Embase and American College of physicians Journal club database for English language articles since 2000 looking mainly at randomized clinical trials, Meta analyses, Cochran reviews as well as some research articles viewed to be cutting edge regarding anticoagulation and cerebrovascular disease. Searches were done entering cerebral vein thrombosis, carotid dissection, anticoagulation therapy and stroke, antiphospholipid antibody and stroke, stroke in young adults, cryptogenic stroke and anticoagulation, patent foramen ovale and cryptogenic stroke, COVID-19 and stroke.

Keywords

stroke, young, thrombosis, cerebral, anticoagulation, closure

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Cerebral Vein Thrombosis

Cerebral vein thrombosis (CVT) is associated with an identifiable hypercoagulable state in 85% of cases. These are most frequently hormone related conditions such as pregnancy, birth control pills and estrogens.[1] Other causes include paroxysmal nocturnal hemoglobinuria, myeloproliferative disorders, antiphospholipid antibody, and hereditary thrombophilia such as factor V Leiden or prothrombin 20210A mutations.[1] The patient frequently presents with headaches, which can be mistaken for a migraine with aura. It generally is slow in onset, building over several days, however, it also can present as a severe, ice-pick headache mimicking an acute migraine.[2,3]

Papilledema is a frequent finding in thrombosis involving the superior sagittal sinus and should be sought after. Because a thrombosis can involve the inferior, sagittal, sigmoid, or straight sinus, funduscopic examination can be negative. Head CT is abnormal in only 30% of cases.[4]The diagnosis is frequently made by MRI, but the best screening tests, depending on the institution, would be either a CT angiogram. CT Venogram, MRI, MRA and MR Venogram.

Predictive factors of poor prognosis includes CNS infection, thrombosis of the deep veins, intracranial hemorrhage, any malignancy, abnormal mental status, age greater than 37 and male gender.[1] There is a good outcome in 80% patients on heparin or low molecular weight heparin (LMWH).[1] CVT may present with intracranial bleeding due to back pressure from the thrombosis and presentation may be with a brain hemorrhage, counterintuitively requiring heparin.[5]

Two studies comparing heparin or low molecular weight heparin versus placebo have shown a trend favoring heparin, but did not reach statistical significance.[6,7] Both studies lacked precision due to small sample size. A Cochrane review with meta-analysis of the same 2 trials involved only 79 patients and revealed a relative risk of .33 and relative risk of death or dependency of 0.46 in heparin treated patients versus untreated.[8] There was no increase in symptomatic cerebral hemorrhages with the anticoagulants.[8]

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Based upon these studies, international organizations such as the American College of Chest physicians and the American Heart Association/ American Stroke Association have recommended either unfractionated or low molecular weight heparin as initial treatment for cerebral vein thrombosis.[9,10] LMWH seems to be more effective and equally safe as heparin based on 2 comparative studies.[11,12]

There is insufficient evidence that endovascular thrombolysis may be performed as a therapeutic option, however in patients with a poor prognosis and/or poor response to anticoagulation, it is not unreasonable to try.[3] With respect to duration of therapy, European guidelines recommend 3 months of oral anticoagulation for patients with CVT provoked by a transient risk factor and 6 to 12 months for patients with idiopathic CVT and those with "mild" thrombophilia. They recommend indefinite oral anticoagulation for patients with either recurrent CVT or 1 episode of CVT and "severe" thrombophilia.[5]

With respect to direct oral anticoagulants (DOACs), the European stroke organization 2017 guidelines recommended against their use, because patients with this diagnosis weren't included in the pivotal trials of deep venous thrombosis comparing DOACs and vitamin K antagonists.[13] However it would not be unreasonable to use them since they were non-inferior to vitamin K antagonist in treatment of venous thromboembolism in all of the pivotal trials and were associated with a 50% reduction in cerebral hemorrhage.[14,15]

The randomized RESPECT trial was performed with 60 patients with cerebral vein thrombosis randomized to each group in a parallel group, open label, multicenter clinical trial with blinded endpoint adjudication.[16] One group received Dabigatran 150 mg twice a daily and the other adjusted dose warfarin with the INR maintained between 2 and 3. They were followed for 22-23 weeks. These were patients who had acute cerebral vein thrombosis and were stable after 5-15 days of treatment with parenteral heparin.

Patients with CVT associated with central nervous system infection or major trauma were excluded, however, those with intracranial hemorrhage were allowed. No recurrent venous thromboembolism was noted in either group. There was 1 major bleed in the Dabigatran group and 2 with warfarin. Whether other DOACs would perform equally was not addressed in this trial. This would be a concern in someone with CVT and renal disease, who would not be a candidate for Dabigatran.

A second prospective observational trial involved consecutive patients with clinical features of cerebral vein thrombosis confirmed with either CT or magnetic resonance imaging.[17] People with infection or trauma were excluded.

A total of 111 patients were included, 45 on DOACs and 66 on warfarin. The groups were comparable except the DOAC patients had a higher incidence of headaches, 93% versus 63% and were significantly more likely than those in the warfarin group to have intracerebral hemorrhage on initial imaging. Follow-up ranged from 6-13 months and all patients underwent neurological examination at 6 months. Clinical neurologic worsening was reported in only 1 patient, and that was in the warfarin group. 6 patients reported major bleeding, 2 in the DOAC arm and 4 in the warfarin arm. This trial seems to confirm the RESPECT finding that DOACs are safe in this situation, including Rivaroxaban, which was the main DOAC in this trial.

A Meta-analysis of 5 studies published in 2020 consisting of 1 randomized and 4 observational trials showed an excellent functional outcome in 81.8% of DOAC patients versus 76.1% with warfarin.[18] There was a 56% decrease in major bleeding with the DOACs at 1.32% versus 3.45%; however this was not statistically significant (CI 0.12 to 1.59).

Another trial of 20 patients receiving Rivaroxaban with no previous heparin reported an excellent outcome in 19 of 20 patients at 6 months.[19] Two other relatively small trials also showed favorable results with DOACs[20,21] (see Table 1).

A new phase 3 trial called Secret will compare Rivaroxaban 20 mg daily versus standard of care which would be either unfractionated heparin, low molecular weight heparin with transition to vitamin K antagonists or continuation with low molecular weight heparin.[22] The primary outcome measure will be a composite rate of all-cause mortality, symptomatic intracranial bleeding, and major extracranial bleeding over 180 days. Secondary outcome measures will be all cause mortality, symptomatic intracranial bleeding, major extracranial bleeding, recurrent venous thromboembolism, and major bleeding or clinically relevant non major bleeding.

At this time it would seem that DOACs, particularly Dabigatran, and to a lesser degree Rivaroxaban would be reasonably safe alternatives to warfarin for preventing recurrent DVTs in patients with CVT after initial unfractionated heparin or preferably LMWH. While the American Heart Association and American Stroke Association recommended against DOACs, those statements were generated in 2013.[23] The American Society of Hematology in their 2019 DVT treatment guidelines was silent in this area.

Cervical Artery Dissection

Cervical artery dissection (CD) is a rare cause of stroke, but among people under 45, it comprises 25% of cases.[24] CD are more commonly seen in the upper cervical spine internal carotid or vertebral artery.[25] It may seem risky and counterintuitive to administer anticoagulation for a torn blood vessel, but cerebrovascular dissections are rarely actual ruptures of the vessel; more often, they are separations of the intima from the rest of the vascular wall and the prothrombotic intimal flap is a source of distal emboli.[26]

Dissections can occur from trauma associated with mechanical forces of rapid acceleration, deceleration, and torsional forces (e.g. motor vehicle accident, chiropractic neck manipulation, roller coasters), but most occur spontaneously and are labeled as "idiopathic."[27,28] The etiology of spontaneous dissections is unknown but structural anomalies (e.g. Eagle Syndrome) or underlying collagen vascular diseases have been associated with CD.[29,30] In a large series of patients with cervical artery dissections, those with internal carotid artery

Table 1. DOACS in Cerebral Vein Thrombosis.

Study	Trial design	DOACS	Comparator	Results
Ferro JM, et al. JAMA/ NEUROLOGY 2019 Reference 16	Phase III, Prospective, Randomized, Parallel-Group, Open-Label, Multicenter, Blinded Endpoint Adjudication	LMWH/heparin then Dabigatran 60 patients	LMWH/heparin then VKA 60 patients	a.) No recurrent VTEs observed in either group b.) One (1.7%) major bleeding event dabigatran (95% CI, 0.0-8.9) and 2 (3.3%; warfarin (95% CI,0.4-11.5)
Wasay M, et al. Journal of Stroke 2019 Reference 17	Multicenter, Prospective, Observational	LMWH/heparin then Dabigatran or Rivaroxaban 45 patients	LMWH/heparin then VKA 66 patients	Pts underwent neurological exam at 6 months Clinical neurologic worsening reported only in 1 patient in warfarin group. 6 patients with systemic bleeding (ISTH classification—1 Major, 1 Non-Major, and 4 Minor), 2 were on DOACs, 4 on warfarin
Shankar R, et al. Clinical Neurology and Neurosurgery 2018 Reference 19	Prospective, Single arm, Observational	Rivaroxaban 20 mg a day 20 patients	No comparator group-single arm study	Rivaroxaban with no previous heparin reported an excellent outcome in 19 of 20 patients at 6 months. Critically ill and surgical intervention patients were excluded
Herweh C, et al. European Journal of Neurology 2016 Reference 20	Retrospective Chart and Imaging Review	LMWH/heparin and then DOAC 13 patients	LMWH/heparin-3 remained on LMWH, other 83 patients on VKA	89 of 99 with excellent outcome (mRS 0-1); death 2 of 99. No severe hemorrhagic complications or recurrence of CVT on follow-up at median of 8 months. Complete recanalization in 57.6% at 6 months. Partial recanalization in 29.3% at 4 months
Mendonca M et al. International Journal of Stroke 2015 Reference 21	Retrospective Chart and Imaging Review	LMWH/heparin then Dabigatran in 11 patients and 7 on Warfarin. 4 patients switched from Warfarin to Dabigatran. Total of 15 on Dabigatran	None	Median follow-up was 19 months. Excellent outcome in 87% and recanalization in 80%

dissection (ICAD) were more common than vertebral artery dissections (VAD) and ICAD had less neck trauma to report than VAD patients.[31] Patients with dissection related stroke have not been excluded from thrombolysis trials despite the theoretic risk of hematoma. Carotid dissection with flow limiting stenosis is occasionally considered for stenting, but this is a controversial point, as treatment is basically medical management with antithrombotic, either antiplatelet therapy or anticoagulation.

In a systematic review of 762 patients with cervical dissections, Menon et al did not find a significant difference in the risk of stroke with antiplatelet therapy (1.9%) versus anticoagulant therapy (2.0%).[32] The risk of death was 1.8% with antiplatelet therapy and 1.8% with anticoagulants. A 2012 meta-analysis of nonrandomized studies with over 1600 patients with cervical artery dissection also reported no significant difference in recurrent stroke risk or mortality comparing anticoagulation with antiplatelet therapy.[33]

A review of 38 studies, none of which were randomized, involving 1398 patients showed no differences in death, death and disability, ischemic stroke or symptomatic intracranial hemorrhage between recipients of antiplatelet and anticoagulant therapy. The authors felt that absent a randomized trial there was no good means of distinguishing between the options.[34]

The CADISS trial was a randomized trial comparing antiplatelet versus anticoagulation therapy in patients with cervical artery dissection. It involved 250 patients; 118 with carotid dissection and 132 with vertebral dissection. 126 patients were assigned to antiplatelet treatment versus 124 to anticoagulation. In the entire trial 4/250 (2%) patients experienced a stroke recurrence. Stroke or death occurred in 3 of the 126 patients in the antiplatelet group (2%) versus 1 of 124 in the anticoagulant room (1%). The confidence interval was 0.006-4.233. There was no difference in the efficacy of antiplatelet and anticoagulant drugs in preventing stroke and death.[35]

A second large trial, which was not randomized, looked at anticoagulation versus antiplatelet treatment in patients with carotid and vertebral artery dissection, but in contrast to CADISS, included patients with intracranial involvement. The mean follow-up in the study was 24 months. 55% of patients received antiplatelet therapy, with the choice of drug or combination at the discretion of the treating doctor. 29.4% of those in the trial received anticoagulation and 12.6% received combined treatment.

Ischemic or hemorrhagic events occurred in 9.6% of the patients on antiplatelet and 10.4% of those on anticoagulation, and 13.3% occurred on combined treatment. This study included both traumatic and spontaneous dissections. In intracranial versus cervical dissection, it was more likely the patient with intracranial dissection would be placed on antiplatelet therapy, however, the results were no different.[36] Another trial prospectively collected data from 298 patients with spontaneous dissection of the cervical carotid artery and showed very low incidence of ischemic events during follow-up. There was no difference in ischemic or hemorrhagic events between those treated with anticoagulants and those with aspirin[37] (see all trials in Table 2).

While the American College of chest physician's 2012 guidelines recommended 3-6 months of anticoagulant therapy, many studies since then indicate no evidence for superiority of anticoagulation over antiplatelet agents.[38] Given both antiplatelet and anticoagulation are acceptable treatment options for carotid dissection, stroke prevention, experts may weigh a patient's comorbidity profile or history of compliance in choosing the patient's antithrombotic treatment.

For those with recurrent ischemic events despite optimized medical management, endovascular treatment options like stenting may be considered.[39] Imaging studies indicating flow discrepancy in the culprit CD artery territory may be helpful in consideration for endovascular treatment options. Flow limitation due to CD may cause perfusion dependent dysfunction that may be salvageable, e.g. penumbral tissue. In such cases, stenting may restore vessel caliber and intracranial perfusion given antithrombotic treatment alone may not restore normal cerebrovascular flow.[40] Imaging studies such as Transcranial Doppler (TCD), CT perfusion (CTP), and MR perfusion (MRP) can demonstrate hypoperfusion associated with CD.

Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (APS) involves an arterial or venous thrombotic event, or pregnancy losses in connection with positivity of an antiphospholipid antibody. There needs to be a confirmation of the tests 12 weeks later.[41] The 3 relevant antibodies are lupus anticoagulant, anticardiolipin antibody, and anti-beta-2 glycoprotein. Anti-phosphatidyl serine has been correlated with thromboembolism in patients with APS but has not yet been accepted as an official criterion.[42]

It has been suggested that more than 20% of strokes in patients under 45 are associated with APS.[43] Although the mechanisms of cerebral involvement are not completely understood, multiple mechanisms are postulated. These include disruption of the Annexin shield, allowing antiphospholipid antibody to disrupt the endothelium, inhibition of the protein C pathway, activation of platelets as well as diffuse expression of adhesion molecules, and tissue factor in the endothelium.[44,45] More recently, and the activation of complement has been discovered and found to be particularly relevant in catastrophic antiphospholipid antibody syndrome.[46] A complement factor, platelet bound C4d, which sits at the intersection of the anticoagulation and complement pathways, also has value in predicting thrombosis risk among lupus patients.[47]

Ischemic stroke is the most common and severe complication of arterial disease of antiphospholipid syndrome.[48] The stroke mechanism in APS may be thrombotic or embolic.[49] The clinical manifestations will depend on the location and size. It can involve not only small arteries but also larger arteries as well.[50,51] Embolic stroke occurs mainly because of valvular lesions due to deposition of immune complex Libman-Sacks vegetations in association with systemic lupus erythematosus (SLE).[32,52]

Table 2. Anticoagulant Versus Antiplatelet Therapy in Cervical and Vertebral Artery Dissection.

Study	Ref	Strategy I	Strategy II	Results
Menon Systematic review of 762 patients with cervical dissection. 34 Studies, none randomized 2008	32	Anticoagulant therapy n = 484	Antiplatelet therapy n = 268	No significant difference between groups a.) stroke 5/268 −1.9% in antiplatelet group. 10/494 (2.0%) anticoagulant group CI −6% to 4% b.) death—antiplatelet 5/268 (1.8%, anticoagulation; 9/494 1.8%)
Geogiadis Prospective data collected on 298 consecutive patients 2009	31	Anticoagulant therapy n = 202	Antiplatelet therapy n = 96	a.) 5.9% incidence of new ischemic events on anticoagulation, 2.1% on aspirin. b.) Hemorrhagic events 2% on anticoagulants, 1% on aspirin
Kennedy Meta-analysis of 1636 patients with carotid and vertebral cervical artery dissection 2012	33	Anticoagulant therapy n = 1137	Antiplatelet therapy n = 499	No significant difference between groups Recurrent stroke risk was 2.6% with antiplatelets and 1.8% with anticoagulants. Risk of death was 1% with antiplatelets and 0.80% with anticoagulant
Chowdhury Cochran review pf 38 studies 1398 patients 2015 no randomized trials	34	Anticoagulant therapy n = 1047	Antiplatelet therapy n = 428	No significant differences Primary outcomes All cause death CI from −.095 to .081, *P* = .871 2. Death and disability CI −.157 TO.146 *P*.940 Secondary outcome 1. Ischemic stroke Anticoagulants 1.74% vs 1.43 in antiplatelet 2. symptomatic intracranial hemorrhage only in AC group 5/697,.72%, *P* .364
CADISS trial Randomized trial 250 patients: 126 with antiplatelet treatment versus 124 with anticoagulant 2015	29	Anticoagulant therapy n = 124 patients	Antiplatelet therapy n = 126	No significant difference between groups. Stroke or death occurred in 3 (2%) of 126 patients on antiplatelets versus 1 (1%) of 124 patients on anticoagulants (OR 0.346, CI 0.006-4..390; *P* = 0.66)
Daou et al 370 patients 2017	30	Anticoagulant therapy 29.4% n = 100	Antiplatelet therapy 55% n = 100 *Combined antiplatlet +anticoagulation treatment in 12.6% n = 100	No significant difference between groups. Recurrent ischemic or hemorrhagic events in 9.6% on antiplatelets 10.4% on anticoagulants. Pts with intracranial dissection 8.5% on antiplatelets, 15.4% on anticoagulant, and 18.2% on combined treatment

There are numerous other neurological signs of cerebrovascular disease in APS as it has been associated with cognitive dysfunction,[53] migraine,[54] seizures,[55] multiple sclerosis type syndrome,[56] neuro-ophthalmology involvement,[57] psychiatric manifestations,[58] as well as transverse myelitis,[59] and movement disorders.[60] Patients who are positive for lupus anticoagulant are more susceptible to thrombosis than those with anticardiolipin or anti-beta-2 glycoprotein.[61] Also patients who are triple positive are more susceptible than double or single positive patients to an initial event as well as recurrent thrombosis.[62]

Heparin use in antiphospholipid syndrome has been restricted to the treatment of catastrophic antiphospholipid syndrome as well as 2 studies involved with the rescue of people who were felt to be resistant to warfarin.[63] With respect to arterial disease, the recommended treatment is heparin transitioning to warfarin. More controversial is the dose of warfarin. 2 studies showed that maintaining the INR between 2 and 3 was superior to higher dosages with respect to both thrombosis and bleeding complications in both arterial and venous disease.[46,64] However, the European league against rheumatism (EULAR) recommendations are for a target INR between 3 and 4 in APS patients with ischemic stroke in antiphospholipid syndrome.[65] The American College of chest physician's recommends the INR prolongation to be between 2 and 3.

There has only been one trial which has compared antiplatelet therapy with Warfarin. Based on the APASS trial involving 1770 individuals with stroke, it appears that both warfarin and aspirin appear to be reasonable antithrombotic treatment options for patient with a first-time arterial ischemic stroke with antiphospholipid syndrome.[66]

With respect to the use of direct oral anticoagulants in APS, a trial from England involving 120 patients with thrombotic antiphospholipid syndrome compared 6 months of Rivaroxaban; 20 mg a day versus dose adjusted warfarin with an INR

Table 3. DOACs in Antiphospholipid Antibody Syndrome.

Study	Treatment group	Comparator group	Results	Comments
RAPS 2016 Ref 67	Rivaroxaban 20 mg a day for 6 months	Warfarin INR maintained between 2-3	No thrombotic or bleeding events in either group	No arterial thrombosis patients in study. About 30% triple positive. The primary endpoint was thrombin generation in favor of warfarin
TRAPS 2018 Ref 68	Rivaroxaban 20 mg a day triple positive pts	Warfarin INR between 2-3 triple positive pts	11 events (19%) in Rivaroxaban arm and 2 (3%) with warfarin. Major bleeding 6 pts, 4 Rivaroxaban (7%) and 2 (3%) warfarin no deaths	Trial terminated prematurely after enrollment of 120 pts—excessive events in Rivaroxaban arm
ORDI-ROS 2019 Ref 69	Rivaroxaban 20 mg a day 60% triple positive pts	Warfarin INR between 2-3, 3-4 in pts with previous history of multiple thrombosis 60% triple positive pts	Recurrent thrombosis 11.6% Rivaroxaban 6.3% vitamin K antagonist	Results were driven by arterial thrombosis
Dufrost 2018 Ref 70	DOACs meta-analysis 447 pts	None	73/447 (16%) recurrent thrombosis on DOACs	Increased risk for triple positive 56% vs 23%, arterial thrombosis 32% vs 14% CI 1.4-5.7
RISAPS phase2/3 2020 Ref 71	Rivaroxaban 15 mg twice a day	Warfarin target INR 3.5	Collecting data	History of APS and stroke or other ischemic brain manifestations

between 2 and 3. While the trial was not considered successful because the primary endpoint was endogenous thrombin potential (ETP) which was higher in Rivaroxaban patients than those on warfarin, the study nonetheless showed no cases of thrombosis or bleeding in either group at 6 months. However, there were very few patients with triple positive antibodies, and people with arterial disease were excluded.[67]

The TRAPS study. focusing on triple positive patients. studied a population highly enriched for thrombotic risk. The dose of Rivaroxaban was 20 mg compared with Coumadin with an INR maintained between 2-3 after initial treatment with heparin. The trial was terminated prematurely after the enrollment of 120 patients because of an excessive number of events in the Rivaroxaban arm. There were 11 events (19%) in the Rivaroxaban arm and 2 (3%) in the warfarin group. Major bleeding occurred in 6 patients, 4 in the Rivaroxaban group (7%) and 2 (3% in the warfarin group. There were no deaths.[68]

A randomized clinical trial from Spain also compared Rivaroxaban 20 mg per day versus vitamin K antagonist therapy, maintaining the INR between 2 and 3, or between 3 and 4, for people with a previous history of multiple thromboses. Approximately 60% of those had triple positivity. Recurrent thrombosis occurred in 11.6% in the Rivaroxaban arm and 6.3% on the vitamin K antagonist arm. Specifically ischemic stroke occurred in 4/ 50 in the Rivaroxaban group and 0/61 in the warfarin group. The results of overall thrombotic events were driven by arterial thrombosis and not statistically significant in venous thrombosis.[69]

Lastly, a meta-analysis involving 447 APS patients treated with DOACs including Dabigatran, Apixiban, and mostly Rivaroxaban reported a recurrent thrombosis rate of 16.9% while on factor Xa inhibitors and 15% on Dabigatran. Triple positivity was associated with an increased risk up to 56%.[70] Summary of recent trials of DOACs versus vitamin K antagonist in APS are listed in Table 3.

No precedent exists for the standard dose of DOACs in patients who have APS with arterial thrombosis and evidence from randomized clinical trials suggests that such patients are at increased risk for recurrent thrombosis while on DOACs.[71] The phase 2/3 RISAPS trial will assess the efficacy of high-intensity Rivaroxaban at 15 mg twice daily versus high intensity warfarin INR 3.5 in patients with APS with a history of stroke or other ischemic brain manifestations.[72] Also, an international Registry of DOACs use in patients with APS is being set up with the intent to capture information on all DOAC use and outcomes in these patients.[73]

Based upon these trials, the European Medicines Agency[74] and the European Society of cardiology[75] came out with recommendations against DOACs for antiphospholipid syndrome. In patients who have events on warfarin, other treatments such as rituximab, hydroxychloroquine, and statins have been discussed.

Since Coumadin requires several days of transition with low molecular heparin and has many other inconveniences, there are ongoing trials to try to isolate a population of antiphospholipid antibody patients who might be candidates for DOACs.

One of the new developments in APS is the increasingly recognizable phenomenon of complement activation in antiphospholipid antibody syndrome. Patients with catastrophic antiphospholipid antibody syndrome have a high incidence of this activity.[76] Patients, who have not responded to the usual measures for catastrophic APS such as corticosteroids, plasma

exchange, intravenous immunoglobulin, and Rituxan, could be candidates for Eculuzimab,[77] an inhibitor of C5. This drug has been very successful in the treatment of 2 other diseases characterized by excess complement activity, including paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.

It would seem at this time that triple positive patients and people with a history of arterial disease should unequivocally not receive DOACs. Whether a suitable population can be found where it would be acceptable to give DOACs will depend on future studies (summary of these trials in Table 3).

Closure of Patent Foramen Ovale to Prevent Paradoxical Embolus

Patent foramen ovale occurs in about 25% of adults. Some studies have shown young adults with strokes secondary to patent foramen ovale had a high incidence of accompanying prothrombotic states[78,79] 3 randomized trials performed a decade ago compared trans catheter surgical closure of these defects to medical therapy with antiplatelet agents or anticoagulants.[80-82] People in the surgical intervention arm also received antiplatelet therapy. None of these trials showed a statistically significant advantage in intention to treat toward closure. However, they all demonstrated trends in favor of the intervention and the trials using the Amplatzer occluder device showed greater safety versus those using the Starflex.

Of the 3, the RESPECT trial came the closest to showing superiority in intention to treat with a hazard ratio of 0.5 and a *P* value of 0.08 for superiority with respect to closure versus medication. It actually did achieve superiority in on treatment analysis. However, the study's precision was undermined by a wide confidence interval due to the small number of patients.

People with a large shunt and with a septal aneurysm did have a statistically significant advantage in that trial. The other 2 trials, the PC trial and the Closure I trials also showed a decreased hazard ratio with respect to measures such as recurrent stroke, TIA non-fatal stroke, but neither demonstrated statistical significance in intention to treat.

An editorial which accompanied the Respect and PC publications, while stating the pros and cons, opined that one should be circumspect about interpreting the low hazard ratios and decreased complication with the Amplatzer device as license to freely employ closure strategy.[83]

More recently the needle has shifted in favor of these devices, based upon new randomized trials.[84-87] Meta-analyses which include all of these trials have shown that the intervention is associated with a decreased risk for recurrent ischemic stroke compared with those on antiplatelet treatment. However, all of these trials have had limitations, including the exclusion of people over 60. They also do not show an improvement in TIA recurrence rate or mortality benefit and some of them have shown temporary increases in atrial fibrillation. Features such as large shunt size and presence of an aneurysm in the atrial septum have been factors more likely to be associated with success.[71]

Also unsettled is the role of anticoagulant therapy. If a person has an ischemic stroke and patent foramen ovale with an accompanying deep venous thrombosis, are they better off with closure versus long-term anticoagulation therapy, whether stand alone or combined with closure procedures? Long-term anticoagulation therapy for this condition would be associated with a risk of major bleeding of 3% per year and 0.3% per year of cerebral hemorrhage.

It would appear at this time that these procedures are safe and indicated in numerous patients age 60 or under, with a cryptogenic stroke and patent foramen ovale, especially people with a large shunt with or without septal aneurysm. Reasons brought up to explain the difference between the 3 most recent trials and the initial 3 could be longer follow-up, better occlusive devices, and/or better selection of patients (summary of these trials is shown in Table 4).

Hereditary Thrombophilia

Are mutations for factor V Leiden, Prothrombin 20210A, or deficiencies in antithrombin, protein C, or protein S causative or incidental in the pathogenesis of cryptogenic stroke in patients without a patent foramen ovale?

The controversy is fueled by findings from small case reports and meta-analyses which have shown mild trends of these thrombophilic conditions causing stroke mainly in children.[88-90] however it is questionable whether a single mutation would be sufficient to predispose a child to a stroke. It is also unclear why there would be a difference in this predisposition between children and adults.

Regarding adults, large prospective cohort studies like the Physician's Health Study and the Cardiovascular Health Study have not shown such a relationship in patients with factor V Leiden or prothrombin 20200A mutations, and the standard of practice has been to treat patients having these abnormalities on a case by case basis, mainly using antiplatelet therapy.[91-93] Case reports have suggested that protein S and C deficiencies may play a causative role in young patients and middle aged women with cryptogenic stroke.[94,95] However, these findings have not been substantiated in case controlled or prospective studies, therefore protein S and C levels have not been routinely sought in stroke patients.[96,97]

A large German meta-analysis showed a statistically significant increase in factor V Leiden mutation associated with patients with ischemic stroke versus those without the mutation but not with prothrombin 20210A mutations.[98]

Another trial from Italy looked at 97 patients whose main age was 40.9 years with first ever cerebrovascular events. They were compared to age-matched control patients. Factor V Leiden and prothrombin 20210A mutations were detected with a 4.7 fold greater incidence in stroke patients than in the controls. These were all patients with patent foramen ovale who had been referred for percutaneous trans catheter closure.[99] An additional retrospective review showed a 13% incidence of protein C, protein S, or antithrombin deficiency in adults less than 45 years with ischemic stroke. Only 3% had factor 5 Leiden and prothrombin 20210A mutations.[100]

Table 4. Closure of Patient Foramen Ovale Versus Medical Therapy in Cryptogenic Stroke.

Study	Ref	Strategy I	Strategy II	Results
CLOSURE I 909 adults under age 60 with cryptogenic stroke with TIA + PFO 2012	80	Starflex device closure then ASA + Plavix x6 months then ASA	ASA, Warfarin or both	Primary end point: Composite of stroke, TIA, at 2 yrs. +30 day all-cause mortality—and neurologic mortality beyond 30 day-2 years: Lower rates of events with closure device but not statistically significant. HR 0.78 (CI 0.45-1.35) *P* .37 No deaths in either group 30 days, no deaths neurologic causes 2 year follow up Cardiovascular complications greater with closure device particularly atrial fibrillation
PC 414 adults with PFO and embolic stroke or peripheral embolic event 2013	81	Amplatzer PFO Occluder Also received Asa 325mg po qd for 5-6 months	Medical treatment left to discretion of treating physician whether anticoagulation or antiplatelet therapy	Primary endpoint Death, non-fatal stroke, TIA or peripheral embolism less frequent in occluder treated patients but not statistically significant.7/204(3.4% closure vs 11/210 5.2% medical therapy HR 0.63(CI .24-1.62) *P* Slightly more adverse events with occluder
RESPECT 980 patients with PFO + cryptogenic stroke 2013	82	Amplatzer PFO occluder	Medical therapy—1 or more antiplatelet medications (74.8%) or warfarin (25.2%)	Decreased events (fatal ischemic stroke, early death, recurrent ischemic stroke) with occluder—but not statistically significant. HR.49(intention to treat (CI 0.22 to 1.11) *P* value .08 Per protocol HR 0.37(CI-0.14-0.96) $P = .03$ Serious procedure related adverse events 4.2%
CLOSE 663 patients with PFO + cryptogenic stroke 2017	86	Multiple devices	32.8% aspirin 28% anticoagulation	Randomized trial, 3 groups a.) 238 patients received closure plus APT, b.) APT or c.) oral AC 6% strokes (14/235) with medical therapy 0 with closure.—closure increased incidence of Afib
REDUCE 664 pts with PFO and cryptogenic stroke 2017	85	Gore septal occluder	Antiplatelet therapy	1.4% strokes with closure, 5.4% in medical group (CI .09-.62) *P*.002 New brain infarcts 4.7% vs 10.7 % RR = .44 (CI 0.24-.81) Device related events 1.4%. Afib 6.6% in device pts
Defense PFO 120 pts with PFO and cryptogenic stroke 2018	87	Amplatzer aspirin 100 mg/day in combination with clopidogrel 75 mg/day) for at least 6 months after the Procedure.	Antiplatelet therapy included aspirin, aspirin in combination with clopidogrel at a dose of 75 mg/day, or aspirin in combination with Cilostazol at a dose of 200 mg/day	120 patients with cryptogenic stroke and high risk PFO underwent randomization. The primary endpoint was stroke, death or major bleeding 10.5% primary endpoint with medications 0 with closure
RESPECT 2 980 patients 5.9 years follow up Ischemic stroke 2017	84	Amplatzer 81 to 325 mg aspirin and clopidogrel for 1 month then ASA for 5 months	a.Warfarin, or b ASA c. Clopidogrel or d. ASA plus dipyridamole	Recurrent ischemic stroke PFO vs medical therapy 18/499 = 0.58 events per 100 pt. years with Closure vs 28/481 = 1.07 events/ 100 pt. years with medical therapy HR 0.55 CI (.31-.999) $P = 0.046$

A retrospective review studied all patients with stroke and TIA $\leq$60 years presenting to University College London Hospital stroke unit and daily TIA clinic from 1 January 2015 to 1 August 2016 with the average age of the patients being 49.1 years. Thrombophilia testing was reported in 360 patients including 171 with stroke and 189 with TIA. 14% of patients had positive tests with antiphospholipid antibody being most common. Thrombophilia mutations and deficiencies of protein C and S, and AT, were very uncommon. Follow-up testing was done in less than 10% of patients.[101]

Another retrospective, observational, single center study involving 143 patients with stroke or TIA, reported that the most common positive tests were elevated factor VIII activity in 18% and protein S in 11%. Testing altered clinical management in

Table 5. Thrombophilia and Cryptogenic Stoke.

Study	Ref	Results	Conclusions
Gavva et al 143 patients with a stroke or TIA 2018	102	44 patients (31%) had at least 1 positive result. Most commonly elevated hereditary factor was protein S (11%) Test altered management in one pt. 33 pts (75%) had potential for missed diagnosis due to lack of confirmation. cost of testing $62,000	Thrombophilia testing rarely impacted management and was costly
Alakbarzade et al 628 pts with stroke and TIA retrospective review 2018	101	360 patients tested 13/360—4% Factor V Leiden or prothrombin 20210A. 10/360 (2.8%) AT, PC or PS deficiency C, S or antithrombin was found rarely and was very uncommon in patients with TIA. There was weak follow-up	Very low incidence of antithrombin protein C and protein S. If one decides to test it should be repeated to distinguish bona fide thrombophilia from false positives
Ji et al 215 patients with ischemic stroke or TIA between the age of 18 and 45 Mean age 37.5 years 2012	100	Factor V Leiden mutation 4/189 Prothrombin 20210A mutation 1///189 Protein C < 70% 2/189 Protein S < 70 23/189 AT <80 3/189	Possibly numerous false positives—cutoffs for PC< 70%, PS <70% and AT < 80. Most common abnormal test—PS which is subject to acute phase effects
Botto et al 97 subjects with ischemic stroke or TIA compared with 160 age-matched controls, 55 yrs or younger	99	Combination of either Factor V Leiden or prothrombin 20210A mutation and patent foramen ovale was associated with a 4.7 fold increase in ischemic stroke or TIA in young patients (95% CI = 1.4 to 16.1; $P = 0008$). No statistically significant association was found with PC or PS or AT deficiencies	In cryptogenic stroke patients with PFO, 55 years or younger, prothrombotic factors such as FV Leiden and PT G20210A can help identify those with increased risk for ischemic stroke and adjust prevention treatment as needed

only 1% of the total patients tested. 33 patients (75%) had the potential for carrying a misdiagnosis due to positive tests that were only never verified. The collective annual cost of testing was approximately $62,000. The conclusion was that thrombophilia testing in the inpatient setting rarely impacted clinical management of patients admitted with stroke or TIA.[102]

It appears that case reports are most likely to report this association between thrombophilia and cryptogenic stroke versus registry, and other larger observational trials which show that thrombophilia testing in the acute, inpatient setting of stroke or TIA, in patients without a PFO rarely changes management. This remains a controversial area (see Table 5).

COVID-19 Strokes in Young Patients

It remains to be seen exactly what the mechanisms are behind large vessel strokes in young people with COVID-19. Mechanisms for the increased risk of acute stroke include an inflammatory cascade and hypercoagulable state with serum elevated C-reactive protein, D-dimer, and ferritin.[103] According to Varga et al there was evidence of direct viral infection of endothelial cells and inflammation with the virus utilizing the ACE2 receptor.[104] The ACE2 receptor is prominent in lung epithelium but is also expressed on endothelial cells across multiple organs. Specifically in the brain, the SARS-CoV2 virus binds to angiotensin converting enzyme 2(ACE2) receptors present on brain endothelial cells. ACE2 is a key part of the renin–angiotensin system and is a counterbalance to angiotensin converting enzyme I (ACEI) which gives rise to angiotensin II, which is a pro-inflammatory vasoconstrictor, which can promote organ damage. With the depletion of ACE2 by SARS-COV2, the balance may be tipped in favor of the harmful ACEI / angiotensin II axis, with the promotion of brain injury, including both hemorrhagic and ischemic stroke.[105]

Post-mortem evaluation from patients who deteriorated from COVID-19 multiorgan dysfunction, showed evidence of endothelial disruption and large artery mononuclear and neutrophil infiltration. The cascade of endothelial dysfunction may be vascular, endothelial injury and excessive platelet activation with resultant related thrombosis in cerebrovascular vessels.[105]

A recent retrospective cohort study of 1916 patients from New York City hospitals showed that approximately 1.6% of adults with COVID-19 who visited the emergency room or were hospitalized, experienced an ischemic stroke.[106] This was a higher rate compared with a cohort of patients with influenza.

Another review of 165 patients hospitalized for Covid 9 showed that the main risk factor for stroke was severity of disease. This was confirmed in a systemic systematic review and meta-analysis involving 576 patients which showed that aside from a tendency toward a higher proportion of past history of cerebrovascular disease and increased serum interleukin-6 levels in stroke patients, no difference in

demographics, vascular comorbidities, or -19 laboratory values were present in Covid stroke patients compared to known stroke patients.[107] This finding however does not lead to a good explanation regarding the patient's to be described below with isolated large vessel stroke.

COVID-19 stroke patients who require reperfusion or mechanical thrombectomy may pose complicated management problems because of concerns regarding neuroimaging and safety to healthcare workers performing this procedure.[108] In fact, the number of these recanalization procedures has dropped considerably since the beginning of the pandemic.[109]

With respect to young patients and the possible role of antiphospholipid antibodies in COVID-19 related strokes, a recent anecdotal report looked at 3 COVID-19 patients in China with strokes and found them to have antiphospholipid antibodies (APLAs). These patients had anticardiolipin IgA antibodies as well as anti-β_2-glycoprotein I IgA and IgG antibodies. None were positive for lupus anticoagulant testing. The small number of patients, and the fact that they were predominantly IgA, generated skepticism as to their relevance, particularly since transient positivity for APLAs is common in acute infection.[110] There are, however, data to suggest that IgA positivity but not IgM is correlated with thrombosis in lupus patients with APLA syndrome.[111,112]

A recent collection of 5 COVID cases showed that large vessel stroke was a presenting sign in New York during the initial surge of COVID-19 hospitalizations in March and early April 2020.[113] These were all individuals under age 50, who were previously healthy. None required mechanical ventilation. The report did not offer enough information to determine what the precise cause was for the possible Covid-19 related strokes. None of them had echocardiograms reported except the first of the 5 cases. Furthermore, none of them had tests reported for APLA; it is unknown whether patients could have had paradoxical emboli, an arrhythmia, valvular lesions or APLAs, the most common causes of stroke in people under 50. D-dimer levels were significantly elevated in 3 of the 5 cases but there was no evidence of DIC. Furthermore among Stroke centers across the country, this spike of large-vessel occlusions in young people did not occur in the vast majority of centers.

In those people who have evidence of cytokine and thrombotic storm, strokes are probably part and parcel of the entire ongoing thrombotic process. However, there is a certain population of patients who sustain isolated large vessel thrombosis who may have other underlying pathologies that may be exacerbated by the acute viral infection, COVID-19.

Conclusions

Cerebral vein thrombosis can be treated with direct oral anticoagulants after initial heparin therapy and may possibly be used as a standalone drug in the future; however, that point needs to be clarified with further trials. Antiplatelet therapy or anticoagulation can be used to prevent stroke in cervical and vertebral dissection. There is no significant efficacy or safety difference between the 2. Anticoagulation with warfarin is preferred over DOACs for antiphospholipid syndrome; however concerns regarding negative data with DOAC use were mainly reported in arterial and triple positive patients. Eculuzumab is a promising agent for catastrophic antiphospholipid antibody syndrome.

Most cryptogenic ischemic stroke patients, age 60 or younger, with a patent foramen ovale, will benefit from closure, particularly those with large shunt size with and without septal aneurysm.

It is still unclear whether hereditary thrombophilia in patients without a patent foramen ovale predisposes to arterial stroke, however if it does, it is rare in adults. The data on COVID-19 associated strokes is still evolving. There is accumulating information regarding increased megakaryocytes deposition in multiple organs[114] NETS formation[115] as well as abnormal platelet function and cytokines driving these atypical strokes in young people.

Authors' Note

Both Dr Song and Dr Berkman wrote the manuscript equally.

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