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Use of Heparin in Acute Ischemic Stroke: Is There Still a Role?

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Abstract Heparin has long been a contested therapy in acute ischemic stroke (AIS). In current practice, heparin is considered on a case-by-case basis, but there is no consensus as to the appropriate timing of anticoagulation or for which ischemic stroke subtypes heparin may be beneficial. To provide better clarity on this issue, we review current research focusing on the use of heparin in AIS in each stroke subtype and subsequently make recommendations to provide readers with a systematic approach to managing complex stroke patients for which acute anticoagulation may be valuable. We conclude that there are certain subpopulations of ischemic stroke patients that may derive benefit from heparin when given acutely, including patients with symptomatic large artery stenosis >70 %, non-occlusive intraluminal thrombus, and in patients with high-risk cardiac conditions including left ventricular thrombus, left ventricular assist devices, and mechanical heart valves.

Keywords Heparin · Acute ischemic stroke · Anticoagulation · Stroke · Thromboembolism · Hemorrhage · Anticoagulants/adverse events · Anticoagulants/therapeutic use · Brain ischemia/drug therapy · Stroke/drug therapy · Randomized controlled trials as topic · Cerebrovascular disorders/drug therapy · Heparin/administration and dosage · Heparin/therapeutic use · Intracranial hemorrhages/drug therapy · Treatment outcome · Clinical protocols · Time factors

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Introduction

The use of heparin in acute ischemic stroke (AIS) may be one of the most controversial topics in the stroke literature. Using heparin to facilitate early clot lysis, halt clot propagation, and reduce thromboembolism makes pathophysiologic sense because these processes can lead to recurrent stroke and neurologic worsening. Additionally, early recurrent stroke increases neurologic disability and leads to higher mortality [1]. However, the use of acute anticoagulation also increases the risk of hemorrhage into infarcted brain tissue. C. Miller Fisher was one of the first proponents of early heparinization [2]. This practice was supported by a small randomized trial of 45 patients with embolic stroke which showed a reduction of recurrent ischemic stroke without increased hemorrhagic conversion in patients treated with immediate heparinization [3]. Subsequent larger trials have evaluated risks and benefits of heparin in larger populations; the most influential of which were the International Stroke Trial (IST) and the Trial of ORG 10172 in Acute Stroke Treatment trial (TOAST) [4, 5] (see Table 1, which includes other randomized controlled trials for heparin in acute stroke).

In 1997, the IST enrolled 19,435 patients within 48 h of AIS. Patients were randomized to receive low-dose heparin (5000 mg twice daily) or medium-dose heparin (12,500 mg twice daily) and either aspirin (300 mg daily) or placebo in a factorial design, for a period of 14 days or until discharge. While patients on heparin had significantly fewer recurrent ischemic strokes within 14 days (2.9 vs. 3.8 %, $p<0.01$), this

Table 1 Summary of randomized controlled data for heparin in acute ischemic stroke

Study	Type of stroke patients	Treatment comparison	Maximum onset of symptoms to treatment	Result
IST (1997)	All stroke subtypes	Unfractionated heparin vs aspirin for up to 14 days	48 h	Heparin group had significantly fewer recurrent AIS but offset by increase in hemorrhagic stroke and extracranial hemorrhage
TOAST (1998)	All stroke subtypes	Danaparoid for 7 days vs placebo	24 h	Non-significant trend towards favorable outcomes of danaparoid group at 7 days but did not persist at 3 months. Increased intracranial hemorrhage in LMWH group
HAEST (2000)	Patients with stroke and atrial fibrillation	Dalteparin vs aspirin for 14 days	30 h	No significant difference in functional outcome of both groups at 14 days or 3 months with increased extracranial hemorrhage in dalteparin group
TAIST (2001)	All stroke subtypes	Tinzaparin (high and medium doses) for up to 10 days vs aspirin	48 h	No significant difference in outcomes. Higher rates of symptomatic intracranial hemorrhage with high dose tinzaparin group
Camerlingo et al. (2005)	Nonlacunar stroke	Heparin vs saline for 5 days	3 h	Functional outcomes of heparin group at 3 months significantly better than saline group
RAPID (2005)	Nonlacunar stroke	Unfractionated heparin (with bolus) vs aspirin for up to 7 days	12 h	mRS at 90 days not significantly different between groups, no difference in incidence of hemorrhage
FISS-tris (2007)	Large artery disease (mostly intracranial)	Nadroparin vs aspirin for 10 days	48 h	Significant improvement on dichotomized mRS (0–2 vs. 3–6) at 6 months for nadroparin group. No difference in Barthel Index between groups

was counterbalanced by a significant increase in hemorrhagic strokes (1.2 vs. 0.4 %, $p<0.00001$) and extracranial hemorrhage (1.3 vs. 0.4 %, $p<0.00001$) in comparison to patients not on heparin. There was no significant difference in death/dependency at 6 months between groups [4]. This trial was criticized because the levels of anticoagulation were not routinely monitored; subcutaneous rather than intravenous administration was used, and for some patients, heparin was started prior to imaging to evaluate for intracranial hemorrhage.

One year later, the TOAST trial compared the use of danaparoid, a low-molecular-weight heparin (LMWH), given over 7 days to placebo, in 1281 acute stroke patients within 24 h of stroke onset. Overall, while there was a trend towards more favorable outcomes at 7 days with LMWH (59.2 vs. 54.3 % $p=0.07$), this did not translate into a significant improvement in outcomes at 3 months (75.2 vs. 73.7 %, $p=0.49$) and led to significantly greater risk of serious intracranial bleeding within the first 10 days of treatment in the heparin group (0.02 vs. 0.008 %, $p<0.05$), confirming the results of the IST trial [5]. In TOAST, patients with National Institutes of Health Stroke Scale (NIHSS) >15 were more likely to have hemorrhagic conversion. It should be noted that this trial did not have an antiplatelet arm.

These results have been confirmed by subsequent trials [6–8] and in the 2009 Cochrane review which evaluated 11 trials with over 2000 patients showing that acute anticoagulation for ischemic stroke patients leads to 11 additional fatal intracranial hemorrhages per year for every 1000 patients given with anticoagulant therapy [9]. Hence, for all-comers with AIS, while anticoagulation may reduce recurrent ischemic stroke and improve short-term outcome, this benefit is outweighed by the risk of hemorrhagic transformation and does not translate into improved long-term functional outcome. For these reasons, heparin is not recommended in standard use for AIS patients.

Subsequent studies have examined whether timing of anticoagulation or presence of medical comorbidities may influence the benefit of heparin in AIS. One study found improved 3-month functional outcomes when patients were started on intravenous heparin in comparison to saline within 3 h of symptom onset [10]. This result was not confirmed in a subsequent trial comparing heparin to aspirin, which reported no significant difference in recurrent ischemic stroke, hemorrhage, or outcomes between the two treatment arms. [11] A recent meta-analysis tested the hypothesis that acute anticoagulation should be targeted to patients with the highest risk of venous or arterial thromboembolism. Overall, those assigned to a heparin regimen had an absolute 1.4 % reduction in thrombotic events that was outweighed by an absolute 1.6 % increase in hemorrhage in comparison to those assigned to aspirin or placebo. Interestingly, greater age and NIHSS and the presence of atrial fibrillation were all factors associated with both increased risk of recurrent stroke and increased risk of hemorrhagic events, making it difficult to predict which patients would benefit from acute anticoagulation [12••].

Acute anticoagulation has also been studied to prevent early neurologic deterioration after AIS, with the presumption that anticoagulation may reduce the risk of early recurrent stroke, halt infarct progression, and improve flow in the

collateral circulation. In two randomized trials, there was no reduction in early neurologic worsening with the use of anticoagulation in comparison to antiplatelet therapy [5, 6].

While heparin may not benefit the overall ischemic stroke population, there still may be subgroups of patients who could benefit from acute anticoagulation. In the next section, we summarize data for heparin in AIS subcategorized by stroke mechanism.

Heparin in Stroke Subtypes

Large Artery Atherosclerosis

Early recurrent stroke is particularly high in patients presenting with symptomatic large artery atherosclerosis, with 30-day recurrence rates ranging from 14 to 18 % [13, 14] and mortality in the first 30 days estimated at 13.9 % [13]. Multiple studies have shown that large artery atherosclerosis is an independent risk factor for recurrent stroke within 30 days [13–16], and one study even showed that large artery atherosclerosis subtype predicted reduced survival in unstable neurologic patients with a symptomatic carotid disease [17].

Extracranial Disease

Carotid endarterectomy (CEA) or stenting is the standard of care for patients with a symptomatic carotid stenosis (>70 % stenosis) and recent small non-disabling strokes [18, 19], but stroke recurrence risk may be as high as 20 % within the first 72 h in patients with severe carotid stenosis [20]. While it is clear that the absolute benefit of CEA appears to be in the first 2 weeks after an ischemic event, the timing of when to perform CEA is uncertain, with older studies reporting reperfusion hemorrhage with early CEA [21, 22] and one study even suggesting that the risk of stroke and death is significantly higher in patients undergoing emergency CEA [17].

While there are no randomized controlled trials specifically addressing the use of heparin in extracranial large artery atherosclerosis, post hoc analysis from the TOAST trial revealed that patients with large artery atherosclerosis stroke subtype who received danaparoid had favorable outcomes at 90 days (68 vs. 55 % (p=0.04)) [5]. This result has not been replicated. In a trial of another LMWH, patients with large artery atherosclerosis receiving tinzaparin did not have improved outcomes in comparison to aspirin [6]. Nevertheless, based on the results of the TOAST trial, many centers use heparin as a bridge to carotid endarterectomy in patients with severe extracranial carotid stenosis, high risk of early recurrent stroke, small stroke burden, and low risk of hemorrhagic transformation. There has been one prospective study of 29 patients with severe carotid stenosis (>70 %) and repetitive transient ischemic attacks using heparin as a bridge to in-hospital CEA. While 92 % of patients had recurrent TIAs, 40 % of these occurred while holding heparin prior to angiography and none progressed to infarction. There were also no hemorrhagic complications in this study, indicating that it may be safe to use heparin in this setting [23].

Heparin may also be beneficial in the setting of free-floating thrombus, which can occur secondary to large vessel atherosclerosis or thromboembolism. No randomized trials exist, but in a review of case series evaluating 145 patients with free-floating thrombus, 30 % of patients received medical treatment, 77 % of whom were anticoagulated for a median of 5 weeks. Of the 28 patients who were anticoagulated that had follow-up imaging, 86 % had complete resolution of the thrombus without neurologic events, 0.07 % (2 patients) had persistent thrombus, and 0.07 % (2 patients) progressed to carotid occlusion despite anticoagulation. In the 35 medically treated patients, 20 % of the patients improved, 77 % had stable neurologic deficit, and 3 % (one patient) worsened. There were no posttreatment deaths, and hemorrhagic complications were not reported. In comparison, outcomes for 67 surgically treated patients were reported including 37 % improvement, 54 % stable, and 9 % worsening [24]. Morbidity of emergent carotid endarterectomy is increased in patients with free-floating thrombus of the carotid artery [25, 26]; hence, there may be a role for heparin in patients with free-floating thrombus as definitive treatment or as a bridge to surgical therapy if thrombus does not resolve on subsequent imaging.

Recommendations: In patients who have >70 % extracranial carotid artery stenosis and small stroke burden (see Table 2), heparin should be used to reduce thromboembolic complications while awaiting CEA. In patients with free-floating thrombus, it is reasonable to use heparin as definitive treatment or as a bridge to surgical therapy if thrombus does not resolve on repeat imaging.

Intracranial Disease

Intracranial atherosclerotic disease (ICAD) is the most common cause of stroke worldwide, with a stroke recurrence rate of 12.2 % per year, even with optimal modern medical management [30]. In comparison to extracranial atherosclerosis which is more commonly found in Caucasian populations, ICAD is more prevalent in Asian, Black, and Hispanic populations [31, 32].

In 2005, a large randomized trial (Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis (WASID)) reported increased death and major hemorrhage for ICAD patients taking warfarin within 90 days of stroke onset in comparison to aspirin [33]. Secondary analyses showed greater benefit of warfarin the closer the patient was randomized to the index event, indicating a possible role for acute anticoagulation. Post hoc analysis of this trial also demonstrated a benefit for

Table 2 Summary of recommendations for administering heparin within 48 h of acute stroke

Likely to benefit	Uncertain to benefit	Unlikely to benefit
Inclusion criteria		
Symptomatic extracranial atherosclerosis > 70 % as a bridge to CEA/carotid stenting	Extracranial carotid or vertebral artery dissection	Cardioembolic strokes secondary to atrial fibrillation without high-risk echocardiographic characteristics
Intraluminal thrombus in the intracranial or extracranial circulation	Symptomatic intracranial atherosclerosis (>70 %) without intraluminal thrombus, especially in the posterior circulation	Small vessel disease
Cardioembolic strokes associated with high-risk echocardiographic features (left atrial appendage thrombus, spontaneous echo contrast, reduced left atrial appendage emptying velocities)		
Left ventricular thrombus after myocardial infarction		
Left ventricular assist devices and mechanical heart valves		
Exclusion criteria		
1. Large stroke burden, i.e., >1/3 of MCA territory or >1/2 of PCA territory		
2. Hemorrhagic transformation on CT		
3. NIHSS >15[a]		
4. Systolic blood pressure >180 mmHg		
Guideline for starting unfractionated heparin		
1. Start heparin without a bolus, maintain PTT at the low end of the therapeutic range.		
2. Keep patient in a monitored setting while on IV heparin.		
3. Therapeutic hypertension post stroke is appropriate for first 48 h, up to systolic blood pressure 180 mmHg while on anticoagulation.		
4. Obtain head CT 24 h after therapeutic anticoagulation is achieved to monitor for intracranial hemorrhage.		
Duration of therapy—depends on underlying etiology		
1. Critical large vessel stenosis: as a bridge to CEA/carotid stent		
2. Intraluminal thrombus: repeat vessel imaging in 3 days to evaluate for ischemic stroke, resolution of thrombus, and hemorrhagic conversion[b]. If clot is fully resolved and there is no other indication for anticoagulation, switch to antiplatelet therapy.		
3. LVAD, mechanical valve, cardioembolic: lifelong anticoagulation		
4. LV thrombus: as per cardiac guidelines [27, 28]		

[a] TOAST noted reduced risk of hemorrhage if NIHSS <15 [5]

[b] Case series of intraluminal thrombus patients by Mokin: median number of days of anticoagulation prior to reimaging was 3.5 days [29•]

anticoagulation in patients with basilar stenosis, but this did not generalize to all patients with posterior circulation disease [34].

Two years later, the Fraxiparin in Stroke Study for the treatment of ischemic stroke (FISS-tris) trial evaluated patients with primarily (85 %) intracranial disease with moderate to severe stenosis treated with LMWH (nadroparin) in comparison to aspirin (160 mg daily) within 48 h of stroke onset for 10 days. While the primary outcome at 6 months (Barthel index) showed no significant differences between the two groups, evaluation of dichotomized modified Rankin (0–1 vs. 2–6) showed a significant benefit favoring anticoagulation (ARR 10 %, OR 1.55, 95 % CI 1.02–2.35) [7]. Post hoc analysis revealed a significant reduction in early neurologic deterioration with nadroparin (ARR 7.2 %, OR 0.44, 95 % CI 0.21–0.92) and reduction in stroke progression (ARR 7.7 %, OR 0.36, 95 % CI 0.16–0.81) without a significant increase in intracranial hemorrhage [35••]. Later subgroup analysis of the FISS-tris study also showed benefit of nadroparin in patients with posterior circulation stenosis (OR 5.76, 95 % CI 2.00–16.56, p=0.001) [36••], similar to the inferences drawn from WASID [34]. A more recent unblinded randomized trial compared enoxaparin and aspirin within 48 h of stroke onset in Chinese patients with large and small vessel disease. There was a significant reduction in early neurologic deterioration for patients randomized to LMWH (3.95 vs. 11.82 %, p<0.001) with no significant difference in early recurrent ischemic stroke or intracranial hemorrhage. Similar to the above studies, patients with posterior circulation stenosis and basilar artery stenosis had significantly improved outcomes on LMWH in comparison to ASA (75.2 vs. 40.5 and 82 vs. 48 %, respectively; p<0.001 for both comparisons) [37•].

Patients with intraluminal thrombosis of the intracranial vasculature are also at high risk for stroke recurrence and deterioration [38]. A case series included 18 patients with non-occlusive intraluminal thrombus in the intracranial and extracranial circulation receiving intravenous unfractionated heparin given at a mean time of 7 h after stroke onset for a

median time of 3.5 days. All patients showed reduction or resolution of thrombus and improvement of the NIHSS score with no intracranial hemorrhage. Of the 12 patients with 90 day functional outcomes, 75 % had a favorable outcome (mRS≤2) with one patient developing gastrointestinal hemorrhage after warfarin therapy [29•]. Notably, there was no comparison group of aspirin therapy alone. At our institutions, we initiate heparin for patients with intraluminal thrombus who have a small core infarct, no evidence of hemorrhagic transformation, and well-controlled blood pressure. We repeat imaging after 48–72 h to evaluate for thrombus resolution or new ischemic or hemorrhagic infarct. If thrombus has resolved and there is no other indication for long-term anticoagulation (i.e., atrial fibrillation), patients can be started on antiplatelet therapy, reducing the risks of long-term anticoagulant therapy.

Recommendations: There may be a role for anticoagulation in the acute setting for patients with symptomatic intracranial stenosis >70 % and, in particular, patients who have posterior circulation disease and those who have intraluminal thrombus.

Extracranial Dissection

Cervical artery dissection accounts for 25 % of young patients presenting with stroke. Dissection can cause stroke via thromboembolism or hypoperfusion when mass effect from the intramural hematoma narrows the lumen causing flow impairment [39]. Studies using transcranial Doppler confirm that patients with dissection have a high rate of microembolic signals, which is a surrogate in vivo marker for embolization [40, 41]. With this in mind, many centers use anticoagulation for patients presenting with acute cervical artery dissection and small stroke burden to prevent primary or recurrent stroke. This practice does not include patients with intracranial dissection, for which anticoagulation is potentially harmful because of risk for subarachnoid hemorrhage.

In 2010, a Cochrane meta-analysis included 1285 patients with cervical artery dissection enrolled in observational studies comparing antiplatelet and anticoagulant therapy. While there was no significant difference in recurrent ischemic stroke or death between the two therapies, there was a non-significant trend towards improved outcome and reduced death using anticoagulation at the expense of increased intracranial hemorrhage [42].

More recently, the CADISS trial evaluated 3 months of antiplatelet therapy in comparison to anticoagulant therapy in 250 patients with cervical artery dissection enrolled within 7 days of symptom onset. Ninety percent of the patients presented with TIA or stroke while the remainder presented with local symptoms. There was no significant difference in ipsilateral stroke recurrence at 3 months (three strokes in antiplatelet group vs. one stroke in anticoagulation group, OR 0.346, $p=0.66$), although rates of recurrence risk were extremely low in both groups with an overall 2 % risk of stroke at 3 months [43••]. There was one major bleeding event that occurred within the anticoagulation group and no deaths. This study was limited by a low event rate, diagnostic error such that 20 % of the patients were not confirmed to have dissection on central imaging review, and the use of a combination of aspirin and clopidogrel in the majority of patients in the antiplatelet therapy group, which may have reduced recurrent stroke risk in this group. It also does not address the question of acute anticoagulation, as patients were enrolled within 7 days (mean time to enrollment 3.65 days) of symptom onset.

Recommendations: Further study is needed to determine whether in the acute setting there is a definite benefit of anticoagulation over antiplatelet therapy in patients with extracranial cervical artery dissection.

Cardioembolism

Atrial Fibrillation

While the benefit of long-term anticoagulation for stroke prevention in patients with atrial fibrillation has clearly been established, acute anticoagulation for patients with atrial fibrillation remains controversial. In comparison to other stroke subtypes, cardioembolic strokes are more disabling and carry a higher mortality rate [44], but the risk of recurrent stroke within the first 2 weeks ranges from 5 to 15 % [45–48] which is less than in patients with large artery atherosclerotic stroke.

In subgroup analysis of patients with atrial fibrillation from randomized trials, the IST trial found that heparin reduced recurrent ischemic stroke, but this was outweighed by an increased risk of hemorrhagic stroke, and there was no difference in a 6-month functional outcome [44]. The TOAST and TAIST trials found no difference in outcome for patients with atrial fibrillation that were acutely anticoagulated [5]. [6].

In 2000, a randomized controlled trial (HAEST) evaluated 449 patients with atrial fibrillation and found no difference in recurrent ischemic stroke at 14 days in patients treated with dalteparin (LMWH) in comparison to aspirin (8.5 vs. 7.5 %, $p=0.73$). In addition, patients treated with LMWH had a non-significant increase in symptom progression (10.7 vs. 7.6 %, $p=0.26$), death (17.9 vs. 16.4 %, $p=0.84$), and significantly higher extracranial hemorrhage (5.8 vs. 1.8 %, $p=0.028$) at 14 days [47]. This study was later criticized for including many patients with lacunar strokes which may have been secondary to risk factors other than atrial fibrillation, but post hoc analyses did not show any benefit for LMWH in any subgroup [49].

A recent meta-analysis evaluated seven trials including 4624 patients with acute cardioembolic stroke who received anticoagulation (UFH, LMWH, and heparinoid) within 48 h

of stroke onset. While anticoagulants led to a non-significant reduction in recurrent ischemic stroke within 7–14 days (3 vs. 4.9 % p=0.09), this was counterbalanced by a significant increase in the risk of symptomatic brain hemorrhage (2.5 vs. 0.7 %, p=0.02) and no significant difference in death or disability at 3 months (73.5 vs. 73.8 %, p=0.9). Those taking aspirin in the first 14 days after stroke had reduced odds of death and disability in comparison to those taking anticoagulation (OR 1.14 (95% CI 0.95–1.38)) [50].

Based on the above studies, the benefit of acute anticoagulation in patients with atrial fibrillation does not seem to outweigh the risk. However, a subgroup of patients with atrial fibrillation at particularly increased risk of recurrent ischemic stroke are those with a visible left atrial appendage thrombus, reduced atrial appendage emptying velocities, or spontaneous contrast on their echocardiogram, indicating high thrombotic potential [51–54]. At our institutions, we consider acute anticoagulation for atrial fibrillation patients with small stroke burden, no or minimal hemorrhagic transformation, and these high-risk echocardiographic characteristics.

Recommendations: Acute use of intravenous heparin in patients with ischemic stroke and atrial fibrillation is not recommended. There may be a role for anticoagulation in patients with atrial fibrillation with small strokes who have left atrial appendage thrombus, spontaneous echo contrast, and reduced emptying velocities of the left atrial appendage on cardiac imaging.

LV Thrombus

Left ventricular (LV) thrombus occurs in 17–32 % of patients after myocardial infarction (MI) [55–59] and causes systemic embolization in 16–27 % of patients [55, 60, 61]. Ischemic stroke is the most common thromboembolic complication from LV thrombus, with rates ranging from 63 to 89 % of patients with intramural LV thrombus [55, 56, 60, 61]. Frequently, thromboembolic complications from myocardial infarction occur within the first several weeks after MI [55, 56, 62] and predictors of embolism on echocardiogram include protruding and mobile thrombi [55, 60–62].

There are no randomized trials to evaluate the use of heparin in secondary stroke prevention in patients with LV thrombus. In one observational study that did not use anticoagulation in patients with LV thrombus, serial echocardiograms showed only 20 % regression in thrombus size without anticoagulation [63]. In contrast, studies evaluating patients on anticoagulation have shown reduction in size or complete resolution of LV thrombus in 80 % of patients on anticoagulation [57, 64] while one study did not show any change in the size of LV thrombus with heparin [56]. Several observational studies have shown that patients with LV thrombus on heparin have no systemic embolization [55–57, 64] with control arm embolization rates ranging from 38 to 86 % [56, 57]. One study did observe several embolic events for patients on anticoagulation [61]. A meta-analysis of these observational studies showed that the odds ratio of embolization with LV thrombus after MI is 5.45 (95 % CI 3.02–9.83) and that patients with LV thrombus on anticoagulation have a reduction in the risk of systemic embolization (OR 0.14, 95 % CI 0.04–0.52) [65]. While the risk of hemorrhage was not addressed in most of these observational trials, one analysis estimated that warfarin prevents 44 nonfatal strokes at the cost of 15 nonfatal extracranial bleeds in patients with MI and LV thrombus on dual antiplatelet therapy and warfarin [66].

One open-label randomized trial did compare warfarin, aspirin, and combination therapy in patients with MI and found a 48 % reduction in thromboembolic stroke in the warfarin group in comparison to aspirin alone (p=0.03), at the expense of significantly increased nonfatal hemorrhage in the warfarin group (0.62 vs. 0.17 %/year, rate ratio of 0.25, 95 % CI 0.10 to 0.60) [67].

While we do not have a randomized trial to address the question of LV thrombus in AIS, the Cochrane review estimates a 3.2 % risk of hemorrhage with anticoagulation in the first 2 weeks after stroke [9], while the above studies estimate the risk of embolic events after LV thrombus as ranging 16–27 % of patients [55, 60, 61], with high thromboembolic potential in the first several weeks and the majority of these events being ischemic stroke. With these limited data, guidelines suggest the use of anticoagulation in the setting of LV thrombus for prevention of thromboembolic complications [27, 28].

Recommendations: In patients with LV thrombus (especially those with protrusion and mobile thrombi) with small ischemic strokes, heparin should be administered acutely after ischemic stroke.

Mechanical Heart Valves, Left Ventricular Assist Devices

In patients with mechanical aortic or mitral valves, anticoagulation is recommended chronically to reduce thromboembolic complications [68, 69]. A prospective randomized controlled trial found that anticoagulation significantly reduced thromboembolic complications (70 % of which were cerebral ischemia) in patients on anticoagulation in comparison with antiplatelet therapy at the expense of increased nonfatal hemorrhage [70]. One meta-analysis reported risk of major embolism with mechanical valve as 4 per 100 patient years and valve thrombosis as 1.7 per 100 patient years in the absence of anticoagulation, which equates to 0.016 % risk of these complications per day [71]. In another meta-analysis, the estimated daily risk of hemorrhagic conversion after ischemic stroke is 0.23 % per day [9]. While it may be safe to hold anticoagulation for a short period of time in the setting of large strokes or hemorrhagic conversion, patients with mechanical

heart valves should be anticoagulated as soon as possible because of high risk for thromboembolic events.

In patients with left ventricular assist devices (LVAD), anticoagulation with warfarin and aspirin is recommended [72]. Embolic complications with LVADs range from 5 to 35 % per patient year even on aspirin and warfarin [73]. While one case has been reported showing no ischemic complications after withholding anticoagulation secondary to recurrent GI bleeding for over a year [74], showing the possible safety of holding anticoagulation briefly for large strokes, given the high embolic risk in LVAD patients, acute anticoagulation after ischemic stroke should be considered in these patients.

Recommendations: Given high risk of recurrent embolism, acute heparinization should be considered in patients with mechanical heart valves and LVADs who have AIS unless hemorrhagic risk is exceedingly high.

Small Vessel Disease

In contrast to other TOAST subtypes, there is little evidence supporting heparin in strokes secondary to small vessel disease. In 1983, a case series was published showing no significant improvement in four patients who received heparin acutely for a progressing clinical lacunar stroke [75]. Subgroup analysis from randomized trials has confirmed these results [5]. [6]. Hence, given the lack of definitive evidence, at our institutions we do not use heparin in lacunar strokes, even if patients have progressive or fluctuating symptoms.

Recommendations: There is insufficient data at this time to support use of heparin in acute ischemic stroke for suspected small vessel stroke subtype.

Based on the discussion above, we summarize the ischemic stroke subtypes that may benefit from acute anticoagulation in Table 2. We also provide exclusion criteria, guidelines for which to start heparin, and duration of anticoagulation for specific stroke subtypes.

Conclusions

In summary, heparin may be considered as short-term therapy in the management of select patients with AIS. The conclusions we draw are based on recent research and are limited by the extent of available randomized controlled trial data. Nevertheless, this data can help guide future studies to better understand which patients may be able to benefit from acute anticoagulant therapy.

For upcoming studies, we recommend focusing on the efficacy of heparin for individual stroke subtypes including symptomatic large artery atherosclerosis, intraluminal and intracardiac thrombus, and patients with LVAD and mechanical heart valves. Second, we recommend further optimization of time to heparin administration. The concept of a narrow therapeutic window for acute stroke has already been established with the use of IV tPA; a similar phenomenon may hold true with heparin. A trend to this effect was seen in several of the randomized trials we discussed in our review [5, 33]. Third, duration of therapy should be standardized for optimal treatment effect. Both duration of therapy and subpopulations that may benefit may be guided by novel imaging modalities in the future, including high-resolution susceptibility-weighted imaging to evaluate for microhemorrhages and perfusion imaging to evaluate for core and penumbra, but this requires further study.

Ultimately, the use of heparin in acute ischemic stroke should be made by practitioners on a case-by-case basis, balancing benefit of preventing further ischemia with the risks of causing hemorrhage. In this review, we have provided some guidance for specific clinical situations in which heparin may be appropriate.

Compliance with Ethics Guidelines

Conflict of Interest IM Ruff and JA Jindal both declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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