

# Reduced Ischemic Lesion Growth with Heparin in Acute Ischemic Stroke

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*Objective:* The role of heparin in acute ischemic stroke is controversial. We investigated the effect of heparin on ischemic lesion growth. *Methods:* Data were analyzed on nonthrombolized ischemic stroke patients in whom diffusion-weighted imaging (DWI)/perfusion-weighted imaging (PWI) MRI was performed less than 12 hours of last known well and showed a PWI-DWI lesion mismatch, and who underwent follow-up neuroimaging at least 4 days after admission. Lesion growth was assessed by (1) absolute lesion growth and (2) percentage mismatch lost (PML). Univariate and multivariate regression analysis, and propensity score matching, were used to determine the effects of heparin on ischemic lesion growth. *Results:* Of the 113 patients meeting study criteria, 59 received heparin within 24 hours. Heparin use was associated with ~5-fold reductions in PML (3.5% versus 19.2%,  $P = .002$ ) and absolute lesion growth (4.7 versus 20.5 mL,  $P = .009$ ). In multivariate regression models, heparin independently predicted reduced PML ( $P = .04$ ) and absolute lesion growth ( $P = .04$ ) in the entire cohort, and in multiple subgroups (patients with and without proximal artery occlusion; DWI volume greater than 5 mL; cardio-embolic mechanism; DEFUSE-3 target mismatch). In propensity score matching analysis where patients were matched by admission NIHSS, DWI volume and proximal artery occlusion, heparin remained an independent predictor of PML ( $P = .048$ ) and tended to predict absolute lesion growth ( $P = .06$ ). Heparin treatment did not predict functional outcome at discharge or 90 days. *Conclusion:* Early heparin treatment in acute ischemic stroke patients with PWI-DWI mismatch attenuates ischemic lesion growth. Clinical trials with careful patient selection are warranted to investigate the potential ischemic protective effects of heparin.

**Key Words:** Heparin—anticoagulation—neuroprotection—acute stroke—diffusion-weighted MRI—perfusion-weighted MRI—ischemic lesion growth  
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## Introduction

The role of heparin in ischemic stroke is controversial. Since the 1950s, anecdotal reports showed that stroke deficits improve with early heparin administration, especially in basilar artery thrombosis.<sup>1,2</sup> While some clinical trials showed benefit,<sup>3-5</sup> several large trials using intravenous or subcutaneous anticoagulation failed to show benefit in the broader stroke population.<sup>6-10</sup> A trend toward more favorable early outcome measures and reduced stroke recurrence was observed, but at a cost of increased hemorrhagic complications. As a result, the 2018 American Heart Association treatment guidelines do not recommend anticoagulation in the acute setting.<sup>11</sup> Some authors have attributed the negative trial results to suboptimal patient selection, delayed time to treatment, and inadequate heparin dosage. Stroke experts propose that heparin may still have utility in selected patient populations.<sup>12</sup> Indeed, subgroup analysis and subsequent studies suggest benefit in subpopulations such as symptomatic large artery atherosclerosis, intraluminal carotid or vertebrobasilar artery thrombus, and others.<sup>5,13,14</sup>

Previous trials were based on heparin's anticoagulant effects and focused on recurrent infarction rates and functional status as outcome measures. While heparin may facilitate early clot lysis, halt thrombus propagation, reduce blood viscosity and reduce recurrent thromboembolism, it also attenuates microvascular thrombosis and possibly has anti-inflammatory and neuroprotective effects.<sup>15-19</sup> The effect of heparin on tissue outcome has not been carefully investigated in humans. We investigated the effect of heparin administration on acute ischemic lesion growth.

## Materials and Methods

The study was approved by the Partners Human Research Committee.

### *Study Population*

We analyzed data from 274 ischemic stroke patients admitted to Massachusetts General Hospital between 1995 and 2009 who underwent diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) MRI within 12 hours of last known well, had a perfusion greater than diffusion lesion volume "mismatch," and underwent a follow-up CT or MRI at least 4 days from presentation to assess final infarct volume. Of these, 170 were prospectively consented and enrolled into a NIH-funded study evaluating DWI-PWI in predicting tissue outcome after acute ischemic stroke. An additional 104 patients with admission DWI-PWI and follow-up imaging within the same timeframes were retrospectively included into the NIH study of serial imaging. Some patients have been included in previous publications.<sup>20-23</sup> For this analysis we

excluded patients receiving intravenous/intra-arterial thrombolysis, experimental treatments, and in whom assessment of final infarct was not possible due to low-quality follow-up images, hemicraniectomy, extensive hemorrhagic conversion, or massive brain edema. CT or MRI was used for follow-up because they both conspicuously define infarct limits.<sup>24</sup> Because MRI volumetric determinations are unreliable for small lesions, we excluded patients with small PWI-DWI mismatch defined as "mean transit time (MTT) volume/DWI volume less than 1.2" and "MTT-DWI volume less than 10 mL."<sup>25,26</sup>

### *Clinical Data*

Demographics and clinical variables were obtained from chart abstraction. Stroke onset time was considered the time the patient was last known to be well. Stroke mechanism was ascribed using the Causative Classification of Stroke system.<sup>27</sup> Clinical outcome was assessed prospectively using the modified Rankin scale at discharge and 90 days for prospectively enrolled subjects and extrapolated from chart records for retrospectively enrolled subjects. All assessments were made blinded to mismatch findings. Heparin therapy was defined as the initiation of intravenous unfractionated heparin, or therapeutic doses of subcutaneous low-molecular-weight heparin (i.e., not for prevention of deep vein thrombosis) within 24 hours of admission. At our hospital, unfractionated heparin is typically administered intravenously, with a variable bolus dose, with PTT monitoring every 4 hours until the PTT reaches goal of 50-70 seconds, and thereafter every 8-12 hours or more frequently based on clinical discretion. Time to heparin administration was the time from stroke onset to intravenous or low-molecular-weight heparin order. Time to therapeutic partial thromboplastin (PTT) was the time from stroke onset (or last seen well) to the time of first PTT greater than 50 seconds.

### *Imaging Data*

Imaging data were collected for the majority of patients using a 1.5 Tesla MRI (GE Medical Systems, Milwaukee, WI). DWI and apparent diffusion coefficient maps were computed from raw diffusion data sets using methods described previously.<sup>28</sup> PWI was acquired using dynamic susceptibility contrast echo-planar imaging using techniques previously described.<sup>20-23</sup> CT was performed using a helical scanner (High-Speed Advantage; GE Medical Systems).

Acute lesions on admission DWI and PWI (MTT) and final infarcts on fluid-attenuated inversion recovery or CT were manually outlined. Lesion volumes were manually outlined as previously described.<sup>20-23</sup> All MRI measurements were performed by investigators experienced in image analysis and processing, blinded to clinical data.

Lesion growth was assessed by (1) absolute lesion growth, that is, final infarct volume – admission DWI lesion volume, and (2) percentage mismatch lost (PML), that is, (final infarct volume – admission DWI volume)/(mismatch volume)  $\times$  100%.

Proximal artery occlusion was defined as embolic cut-off or reduced/absent filling of the basilar artery, internal carotid artery (ICA), or M1 segment of the middle cerebral artery before its bifurcation. Stroke arterial territory was classified as ICA, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, and vertebro-basilar.

### Statistical Analysis

Data are expressed as percentages, mean  $\pm$  SD or median (interquartile range [IQR]) as appropriate. The heparin-treated and heparin-untreated groups were compared using the chi-square test for categorical variables, Student's *t* test for normally distributed continuous variables, and Mann-Whitney *U* test for non-normally distributed continuous variables. Univariate analysis explored the relationship between clinical-imaging variables (including heparin treatment) and PML and absolute lesion growth using Mann-Whitney *U* and Kruskal-Wallis tests for categorical variables, and Spearman's correlation ( $\rho$ ) for continuous variables. Variables that were significantly different, and factors known to affect lesion growth, were included in linear and logistic regression models to identify independent predictors of PML and absolute lesion growth. For logistic regression, PML and absolute lesion growth were dichotomized by their mean values. The effect of heparin treatment was assessed in several subgroups (absence or presence of proximal artery occlusion, large artery atherosclerosis and cardioembolic stroke mechanisms, DWI lesions greater than 5 mL, NIHSS  $\leq$  5, prospective enrollment, DAWN criteria and DEFUSE-3 target mismatch criteria using MTT maps to define perfusion deficit<sup>29</sup>). We examined the effect of heparin on clinical outcome by constructing a logistic regression model where the dependent variable was modified Rankin scale 0-2 (favorable outcome). Finally, to control for selection bias and confounding by unmeasured factors, we conducted a propensity score-matched analysis to determine the effects of heparin on PML and absolute lesion growth. Prespecified admission NIHSS values ( $\geq$  or  $<$ 10), admission DWI volume ( $\geq$  or  $<$ 30), and presence of large vessel occlusion were used in the propensity score matching. The linear assumptions such as linearity, normal distribution of residuals, and homoscedasticity were met. A 2-tailed value of  $P < .05$  was considered significant. Analyses were performed using the RStudio statistical software (version 1.1.383, RStudio Inc., Boston, MA).

### Results

A total of 274 patients with acute ischemic stroke had admission MRI and follow-up imaging available for

analysis. Of these, 82 were excluded based on revascularization treatment, 22 for poor-quality MRI, and 57 for mismatch volume less than 10 mL or mismatch less than 20%, leaving 113 patients in the study cohort of whom 66 were prospectively enrolled.

Heparin was given to 59 patients within 24 hours of admission (median 5.0 [IQR, 3-8] hours), including 33 of 66 (50%) and 26 of 47 (55%) patients who were prospectively and retrospectively enrolled into the NIH-funded serial imaging study. Two of these patients received low-molecular-weight heparin (dalteparin) and the rest received unfractionated intravenous heparin. The median time to heparin was 9.0 (IQR, 6-11) hours, and median time to therapeutic PTT was 14 (IQR, 9-20) hours. Decisions concerning anticoagulation were made by the treating team; chart review suggested that indications for heparin were proximal artery occlusion in 32, cervical-artery dissection in 3, cardio-embolism in 18, hypercoagulable state in 2, and was unspecified in 4 patients.

Clinical-imaging features are shown in [Table 1](#). There were no significant differences in age, gender, admission blood pressure, and glucose levels between heparin-treated and nontreated groups. The groups were balanced with regards to Causative Classification of Stroke mechanism, arterial territory involved, proximal artery occlusion, and time from onset to initial MRI. Over half had proximal artery occlusions. Only 5 had infarcts in the vertebro-basilar territory. Patients receiving heparin had significantly lower admission NIHSS scores and DWI volumes; however, the absolute mismatch volumes were similar between groups. Heparin-treated patients tended to have a larger percent mismatch volumes. Yet, the heparin-treated group had significantly smaller final infarcts, and correspondingly lower absolute lesion growth and PML. In the heparin-treated group 5 patients had asymptomatic hemorrhagic transformation and 3 patients had mild hematuria. In the other group 6 patients had asymptomatic hemorrhagic transformation and 1 patient had mild hematuria. Functional outcome was significantly better in the heparin-treated group at discharge but not at 90 days.

Results of the univariate analysis are shown in [Table 2](#). Both PML and absolute lesion growth correlated positively with admission glucose levels, admission DWI volume, and heparin use. The NIHSS score and presence of proximal artery occlusion correlated significantly with absolute lesion growth, and tended to correlate with PML.

Heparin use was associated with approximately 5-fold reductions in both PML (3.5% versus 19.2%,  $P = .002$ ) and absolute lesion growth (4.7 versus 20.5 mL,  $P = .009$ ). The effects were even stronger in patients achieving therapeutic PTT within 18 hours (PML, 2.6 versus 19.2,  $P < .001$ ; absolute lesion growth, 3.6 versus 20.5 mL,  $P = .008$ ). As depicted in [Figure 1](#), heparin use was associated with significantly reduced infarct growth in patients with

**Table 1.** Baseline characteristics and clinical and imaging features

Variable	All (n = 113)	Heparin (n = 59)	Non-heparin (n = 54)	P value
Age	70 (53, 79)	70 (51.5, 78.5)	71 (54.5, 81.7)	.42
Gender male	70 (61.9%)	38 (64.4%)	32 (59.3%)	.71
Admission glucose (mg/dL)	118 (105, 137)	117 (106, 128)	122 (104, 147)	.36
Admission SBP (mmHg)	153 (25.2)	154 (24)	153 (27)	.90
Admission NIHSS	7.5 (4, 14)	6 (3, 11.5)	11 (6, 15.5)	.04
CCS subtypes				.29
Large artery	25 (22%)	16 (27%)	9 (17%)	.25
Cardioembolic	53 (47%)	23 (39%)	30 (55%)	.09
Other	16 (14%)	10 (17%)	6 (11%)	.42
Cryptogenic	19 (17%)	10 (17%)	9 (17%)	1.0
Arterial territory involved				.42
ICA	7 (6%)	3 (5%)	4 (7%)	.70
ACA	4 (3%)	2 (3%)	2 (4%)	1.0
MCA	92 (81%)	49 (83%)	43 (80%)	.8
PCA	5 (5%)	1 (2%)	4 (7%)	.19
VB	5 (5%)	4 (7%)	1 (2%)	.36
Large vessel occlusion				.31
Complete	50 (44%)	25 (42%)	25 (46%)	.45
Partial	14 (12%)	10 (17%)	4 (7%)	.15
Time to first MRI (h)	6.0 (2.7)	6.2 (2.5)	5.7 (2.8)	.36
Admission DWI vol. (mL)	17.2 (5, 50)	12.9 (4, 30)	26.8 (8, 60)	.03
Admission mismatch vol. (mL)	93.6 (46, 174)	88.3 (40, 183)	95.1 (51, 137)	.99
Percent mismatch (%)	548 (169, 2053)	770 (228, 2074)	293 (120, 1675)	.069
Time to follow-up exam (days)	9.7 (5.9, 37.6)	10.1 (6.1, 34)	9.4 (5.5, 42.7)	.79
Final infarct volume (mL)	28.7 (9.6, 90.9)	17.4 (7.6, 51.8)	56.6 (15.1, 107)	.004
Absolute lesion growth (mL)	8.48 (.1, 41.5)	4.7 (-1.1, 15.2)	20.5 (2.4, 54.2)	.009
Percentage mismatch lost (%)	7.4 (.1, 31.2)	3.5 (-.9, 17.0)	19.2 (2.6, 56.0)	.002
Discharge mRS 0-2	37 (33%)	25 (43%)	12 (22%)	.03
90-day mRS 0-2	53 (47%)	30 (73%)	23 (55%)	.13

Abbreviations: ACA, anterior cerebral artery; CCS: Causative Classification System; ICA, Internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; SBP, Systolic blood pressure; VB, vertebro-basilar arteries; Vol, volume.

proximal artery occlusion (PML, -0.9% versus 17.4%,  $P = .03$ ; absolute lesion growth, 5.4 versus 23.1 mL,  $P = .01$ ), and without proximal artery occlusion (PML, -0.7% versus 8.0%,  $P = .02$ ; absolute lesion growth, 10.5 versus 30.4 mL,  $P = .048$ ).

Table 3 shows results of the linear regression model. After adjusting for variables shown in the table, heparin use proved to be the only independent predictor of PML and absolute lesion growth (both  $P = .04$ ). In logistic regression models, heparin use was again an independent predictor of absolute lesion growth (odds ratio 0.17, 95% confidence interval 0.03-0.64;  $P = .01$ ) and tended to predict PML (odds ratio 0.35, 95% confidence interval 0.11-1.1;  $P = .07$ ).

For the propensity score analysis, patients were matched by admission NIHSS ( $\geq$  or  $<10$ ), DWI volume ( $\geq$  or  $<30$ mL), and proximal artery occlusion (absent or present). Despite the small number of matched patients ( $n = 29$ ), heparin remained a predictor of PML ( $P = .048$ ) and tended to predict absolute lesion growth ( $P = .059$ ).

We performed sensitivity analyses in several subgroups by constructing regression models using the variables

shown in Table 3. In the subgroup with DWI volume greater than 5 mL ( $n = 84$ ), heparin was an independent predictor of reduced PML ( $P = .046$ ) and showed a trend for reduced absolute lesion growth ( $P = .07$ ). In cardioembolic stroke ( $n = 53$ ), heparin use was not an independent predictor of reduced PML ( $P = .11$ ) but tended to predict reduced absolute lesion growth ( $P = .08$ ). There was no significant difference in patients with large-artery atherosclerosis subtype although the number of patients was small ( $n = 25$ ). In patients meeting the DEFUSE-3 criteria<sup>29</sup> for "target mismatch" ( $n = 109$ ), heparin tended to independently predict reduced PML ( $P = .06$ ) and was an independent predictor of absolute lesion growth ( $P = .04$ ). In patients meeting the DAWN criteria ( $n = 36$ ), heparin did not predict reduced PML ( $P = .23$ ) or absolute lesion growth ( $P = .11$ ). In proximal artery occlusion ( $n = 64$ ), there was a trend for heparin to independently predict reduced PML ( $P = .06$ ) and reduced absolute lesion growth ( $P = .05$ ). In patients without proximal artery occlusion ( $n = 49$ ), heparin did not predict reduced PML ( $P = .24$ ) but showed a trend to independently predict reduced absolute lesion growth ( $P = .06$ ). In patients with

**Table 2.** Univariable predictors of infarct growth

Variable	PML (median, IQR or correlation coefficient)	<i>P</i> value	Absolute lesion growth (mL, median, IQR or correlation coefficient)	<i>P</i> value
Age	.12	.19	.14	.15
Gender		.28		.19
Male	10.2% (1.6%, 37.0%)		10.7 (1.0, 44.9)	
Female	5.1% (-.5%, 20.7%)		6.5 (-.4, 20.4)	
Admission glucose	.29	.002	.28	.003
Admission SBP	.008	.94	.05	.59
NIHSS score	.21	.06	.27	.01
CCS subtypes		.20		.01
Large artery (n = 25)	9.7% (2.3%, 27.4%)		14.3 (4.1, 56.9)	
Cardioembolic (n = 53)	7.8% (-.9%, 30.7%)		6.5 (-.8, 22.9)	
Other (n = 16)	21.6% (4.3%, 50.4%)		27.7 (9.2, 63.6)	
Cryptogenic (n = 19)	1.6% (-9.3%, 27.7%)		.5 (-5.9, 22.9)	
Stroke territory		.20		.36
ICA	7.9% (4.4%, 57.8%)		13.6 (8.3, 49.8)	
ACA	1.2% (-2.1%, 25.3%)		.5 (-.5, 17.2)	
MCA	7.6% (.4%, 29.6%)		8.5 (.2, 43.2)	
PCA	72.1% (30.7%, 136%)		16.0 (8.0, 23.2)	
VB	.0% (-7.5%, 3.5%)		.0 (-6.6, 3.6)	
Proximal-artery occlusion		.07		<.001
Yes	9.5% (2.5%, 29.9%)		14.1 (3.9, 53.4)	
No	2.7% (-8.8%, 31.4%)		2.1 (-4.1, 18.2)	
Time to MRI	-.11	.24	-.09	.36
Admission DWI volume	.27	.003	.29	.002
Heparin		.002		.009
Yes	3.5% (-1.0%, 17.1%)		4.7 (-1.2 to 15.3)	
No	19.2% (2.6%, 56.1%)		20.5 (2.4-54.2)	

Abbreviations: ACA, anterior cerebral artery; CCS, Causative Classification System; ICA, Internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; PTT, partial thromboplastin time; SBP: Systolic blood pressure; VB, vertebro-basilar arteries.

NIHSS less than or equal to 5 (n = 31), heparin did not predict reduced PML ( $P = .56$ ), or absolute lesion growth ( $P = .76$ ). In prospectively enrolled patients (n = 66), heparin did not predict reduced PML ( $P = .13$ ) but tended to reduce absolute lesion growth ( $P = .09$ ).

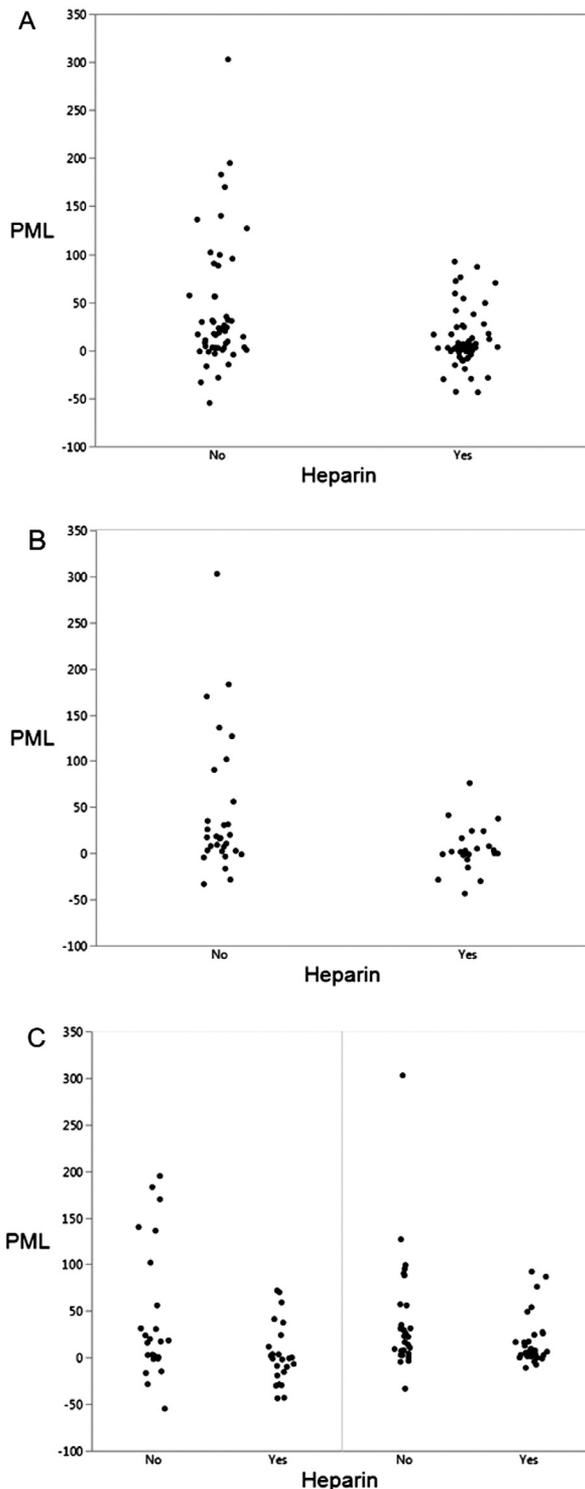
In logistic regression models (Table 4), lower age, admission NIHSS, and DWI volumes correlated or tended to correlate with discharge and 90-day favorable outcomes, however heparin did not predict functional outcome.

## Discussion

Ischemic lesion growth is a frequent outcome measure used in neuroprotective and thrombolytic stroke trials.<sup>30-32</sup> In this study, we investigated the effects of early heparin use on ischemic lesion growth based on its antithrombotic, anti-inflammatory, and other tissue-level biologic ischemic protective effects.<sup>15-18</sup> Our results suggest that heparin is a powerful ischemic protectant, with a 5-fold reduction in PML and absolute lesion growth. These effects compare well against potent neuroprotectants such as citicoline (~2.5-fold

reduction in lesion growth),<sup>32</sup> intravenous tissue plasminogen activator (~9-fold reduction in lesion growth)<sup>33</sup> and intra-atrial thrombectomy.<sup>29,34, 35</sup>

The validity of our results is supported by the consistent benefit across PML and absolute lesion growth, and observed association for known predictors of ischemic lesion growth such as admission glucose level, NIHSS score, and DWI lesion volume.<sup>22,36,37</sup> Further, subgroup analysis showed or tended to show uniform benefit across subgroups with larger DWI volumes, cardio-embolic strokes, DEFUSE-3 "target" mismatch, and with and without proximal artery occlusion, despite the relatively small sample sizes. Patients with DWI lesions greater than 5 mL were specifically investigated since volume measurements are less reliable with small lesions.<sup>25</sup> The effect in patients with cardio-embolic strokes (which typically result in embolic occlusions), and in the subgroup with proximal artery occlusion, support our earlier results showing that prior anticoagulation is associated with 3.5-fold smaller admission lesion volumes.<sup>38</sup> The benefit of heparin appears to be similar in patients with and without proximal artery occlusion, suggesting tissue-level effects via prevention of microvascular thrombosis and ischemic



**Figure 1.** PML and heparin use. The graphs depict the relationship between Percent Mismatch Lost (PML) and heparin treatment, in the entire cohort (A), and subgroups with cardioembolic stroke (B), without proximal artery occlusion (C, left) and with proximal artery occlusion (C, right).

protection in addition to its more widely recognized effects on clot lysis and thrombus propagation.

Time to imaging, rates of proximal artery occlusion, and stroke mechanism were balanced between groups.

Heparin-treated patients had lower NIHSS and DWI volumes, suggesting that less severe strokes were offered heparin treatment, presumably to decrease the risk of postischemic brain hemorrhage. Similarly, heparin may have been avoided if ischemic lesions involved the deep-grey matter, which is supplied by perforating arteries and more susceptible to postischemic hemorrhage, although both groups had similar rates of proximal artery occlusion and arterial territory involvement. Other selection biases may have contributed to the positive results. We, therefore, performed a propensity score matching analysis, which allows one to more accurately estimate the effect of a treatment in an observational retrospective dataset accounting for the variables that determine receiving the treatment. Heparin remained beneficial in the propensity score matching analysis and in nearly all subgroups, suggesting that the observed effect is likely a true benefit. Of note, heparin was initiated after the baseline MRI in two-thirds of patients, suggesting a broad therapeutic time window.<sup>18</sup> However, heparin has been shown to have a time-dependent effect in animal models and in humans,<sup>5,39</sup> and we found a stronger effect with shorter time to therapeutic PTT.

Importantly, heparin reduced ischemic lesion growth, but did not improve functional outcome. Multiple trials have also failed to show improvement in functional outcomes. The discrepancy between reduced ischemic lesion growth and lack of improvement of functional outcome may be explained by our small sample size. Demonstration of a clinically meaningful effect on functional outcome typically requires a much larger sample size.<sup>40</sup> Also, unlike lesion growth, final absolute lesion volume is more consistently associated with improved functional outcome, and a threshold volume is routinely used as a selection criterion for thrombectomy.<sup>41</sup> It is possible that far greater reductions in lesion growth are required to yield functional improvements.

The major strengths of our study include the recruitment of a large cohort of consecutive stroke patients with early DWI, PWI and follow-up imaging, and blinded analysis of lesion volumes by experienced reviewers. The propensity score-matched analysis and subgroup analyses were attempts to bolster the validity and ensure consistency of our main results but these are not conclusive. Our study has several limitations. This was a single-center study using advanced imaging, and treatment was rendered by stroke neurologists based on their own preferences and following established anticoagulation-monitoring protocols, so our results are not generalizable and should be interpreted with caution. Unfortunately it was difficult to determine the duration of heparin from our retrospective chart review. We did note several elevated PTT values during the inpatient stay, suggesting heparin was continued for at least 2-5 days or more in most patients (this is consistent with our usual practice when heparin is administered for stroke). The retrospective analysis of the

**Table 3.** Independent predictors of PML and absolute lesion growth

Variable	PML		Absolute lesion growth	
	$\beta$ value	P value	$\beta$ value	P value
Age	.01	.91	.03	.80
Male gender	.07	.55	.11	.31
Admission glucose	-.006	.96	-.05	.66
Admission NIHSS	.14	.26	.17	.16
Time to MRI	-.18	.12	-.12	.28
Admission DWI volume	-.10	.45	.002	.99
Heparin use	-.25	<b>.04</b>	-.23	<b>.04</b>

Abbreviations: DWI, diffusion-weighted MRI; NIHSS, NIH stroke scale score.

**Table 4.** Independent predictors of good outcome (mRS 0-2) at discharge and 90 days

Variable	Discharge			90 Days		
	OR	95% CI	P value	OR	95% CI	P value
Age	.97	.94, 1.00	.09	.93	.88, 9.76	.007
Male gender	1.15	.35, 3.80	.80	1.31	.34, 4.97	.68
Admission glucose level	.98	.96, 1.00	.12	.99	.97, 1.00	.23
Admission NIHSS	.88	.78, .97	<b>.02</b>	.90	.79, 1.01	.10
Admission DWI volume	.96	.92, .99	<b>.03</b>	.98	.97, 1.00	.21
Heparin use	1.84	.59, 5.93	.29	.92	.23, 3.40	.91

Abbreviations: DWI, diffusion-weighted MRI; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale.

influence of heparin on lesion expansion might have led to our study being underpowered to detect an effect on functional outcomes. Since thresholded MTT maps or the RAPID software (used in the DEFUSE-3 trial) were not available at the time of the study, PWI volumes were assessed using nonthresholded MTT maps. This remains a limitation with regards to the DAWN and DEFUSE-3 subgroup analysis, and may have resulted in overestimation of the tissue-at-risk. Patients with extensive postischemic intracranial hemorrhage were excluded, and we did not collect data on systemic bleeding, so safety could not be fully assessed. Of note however the rates of asymptomatic postischemic hemorrhage and hematuria were comparable in this selected population. The strong influence of collateral circulation on lesion growth and outcome has been recognized only recently;<sup>42</sup> we did not collect data on collaterals although we did incorporate PWI data. We do not have data concerning reperfusion and arterial recanalization. It is conceivable that nontreated patients with more severe strokes also developed more complications such as infection, which may have contributed to infarct growth in controls; however, lesion growth observed in our study is within the range reported in the control population of large trials.<sup>33</sup>

Thrombolysis and emerging acute stroke therapies are associated with a relatively high cost and require a robust 24/7 stroke team and infrastructure. In comparison, heparin is relatively inexpensive, globally

available, and routinely used to treat deep vein thrombosis and pulmonary embolism. Our positive results are most likely explained by the presence of substantial DWI and PWI mismatch. Clinical trials using contemporary selection criteria, short therapeutic time windows and advanced neuroimaging, could better investigate the potential benefit of heparin.

### Conflicts of Interest

Ona Wu is coinventor of US Patent 7,512,435, March 31, 2009, licensed to General Electric, Siemens, Imaging Biometrics, and Olea Medical and consultant to Penumbra, Inc. The other authors report no relevant conflicts.

### Author Contributions

A.B.S. and E.A.R. conceived and designed the study; R.J., E.A.R., H.A., E.M.A., O.W., A.G.S., and A.B.S. acquired the data; E.A.R., Z.L., O.W., and A.B.S. analyzed the data; A.B.S. and E.A.R. drafted the manuscript and figure. E.M.A., R.J., H.A., E.M.A., G.S.S., A.G.S., and O.W. provided critical revisions to the manuscript.

### Supplementary Material

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.jstrokecerebrovasdis.2019.03.016](https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.03.016).

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