A Therapeutic International Normalized Ratio Results in Smaller Infarcts and Better Outcomes for Patients with Ischemic Stroke

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Background: Prior studies have shown that warfarin is effective for both primary and secondary stroke prevention in individuals with atrial fibrillation. It is also known that those on warfarin with atrial fibrillation often have poorer long-term poststroke outcomes, possibly because cardioembolic strokes tend to be larger and more severe. Less is known regarding the direct effect of the international normalized ratio (INR) value at the time of stroke on severity or long-term functional status. *Methods:* We prospectively followed a consecutive series of 112 patients presenting to our institution with acute ischemic stroke between 2013 and 2018 who were on warfarin. Along with INR on admission, data were collected regarding patient demographics, vascular risk factors, stroke characteristics, and functional outcomes. Patients were stratified by INR into "therapeutic" and "subtherapeutic" groups. Stroke severity (NIH Stroke Scale), infarct volume, and outcome (modified Rankin Scale) were assessed on admission, discharge, and follow-up (3 months poststroke). Differences were calculated using Student's *t*-tests and regression analyses. *Results:* The average INR on admission was 1.6 for the entire cohort. Seventy six percent were subtherapeutic on admission (INR < 2.0). Therapeutic patients had lower National Institutes of Health Stroke Scale scores on admission (5.9 versus 9.5, $P = .033$), significantly smaller stroke volumes (19.5 cc versus 49.2 cc, $P = .036$), and were more likely to show more than 1 digit improvement on follow-up mRS than subtherapeutic patients. *Conclusions:* Stroke size and severity is significantly reduced in patients with ischemic strokes who present therapeutic on warfarin. The greater volume of brain saved may ultimately lead to better functional recovery.

Key Words: Acute stroke—warfarin—treatment—atrial fibrillation—outcome

Introduction

Stroke is common and a leading cause of long-term disability in the United States.[1] Up to one third of ischemic strokes are cardioembolic, most often the result of atrial fibrillation.[1] Patients with cardioembolic strokes tend to have poorer long-term outcomes, possibly due to larger total infarct volumes.[2,3] Numerous trials have shown the utility of warfarin for both primary and secondary stroke prevention in patients with atrial fibrillation.[3,4] Unfortunately, due to interactions with various foods and medications, it can be challenging for patients to remain within the accepted therapeutic window (international normalized ratio [INR] 2.0-3.0). While it would follow that a subtherapeutic INR value would result in a higher risk of stroke, less is known about the effect of the INR value on stroke severity and longer-term outcome in patients presenting with acute ischemic stroke.

In order to determine the impact of INR on stroke size, severity, and outcome, we prospectively followed a cohort of patients presenting to our Emergency Department with acute stroke who reported being on warfarin at the time of their event.

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Methods

Our institutional review board approved this study. We evaluated a prospectively-collected, consecutive series of patients on anticoagulation admitted to our urban academic Comprehensive Stroke Center with acute ischemic stroke between January 2013 and October 2018. As part of our stroke program, patient data are collected for quality assurance purposes and stored within a HIPAA-approved clinical research registry. Therefore, informed consent was not required for this study.

Data were collected regarding: anticoagulation status (indication, admission INR); patient demographics (age, race, and sex); past medical history and vascular risk factors (atrial fibrillation, hypertension, hyperlipidemia, diabetes, smoking, prior stroke, and coronary artery disease); stroke characteristics (National Institutes of Health Stroke Scale [NIHSS], Trial of Org 10172 in Acute Stroke Treatment classification for etiology,[5] infarct volume, occluded vessel), and outcome (discharge and 3-month modified Rankin Scale [mRS] scores). Neuroimaging was evaluated by a board-certified vascular neurologist. Stroke volumes were calculated by evaluating diffusion-weighted magnetic resonance sequences using volumetric analysis. The occluded vessel was determined using initial and follow-up neuroimaging (eg, hyperdense middle cerebral artery [MCA] on noncontrast head computed tomography, magnetic resonance angiography [MRA], computed tomography angiography [CTA], 4 vessel conventional angiogram, and vascular distribution of infarct on magnetic resonance imaging [MRI]). Patients converting from proximal (M1) to distal (M2 or M3) occlusions were identified. Administration of intravenous tissue plasminogen activator (IV tPA, n = 15) and intra-arterial mechanical thrombectomy (n = 13) were adjusted for as potential confounders.

Student's *t*-tests (for continuous variables) and chi-square tests (for dichotomous variables) were used to compare characteristics of therapeutic (INR $\geq$ 2.0) versus subtherapeutic patients. Odds ratios were calculated using logistic regression for "therapeutic" versus "subtherapeutic" individuals, and multivariable regression was performed to adjust for potential confounders. The primary outcomes of interest included infarct volume, NIHSS on admission, mRS on discharge, and follow-up. Secondary analyses included a Rankin shift analysis for the therapeutic versus subtherapeutic groups at each time-point to compare magnitude of improvement from discharge to follow-up.

Results

One hundred twelve patients on anticoagulation were admitted with stroke over the study period; 27 therapeutic and 85 subtherapeutic. Patient characteristics are listed in Table 1. The average age of the total cohort was 77.4 years (SD 13.4). Forty-three percent were black; 36 percent male. There were no major differences in demographics or vascular risk factors for patients with therapeutic versus subtherapeutic INR values. Warfarin was most commonly prescribed for atrial fibrillation[1,4]) (79% of entire cohort), while other reasons included basilar artery thrombosis, cervical arterial dissection, reduced ejection fraction (<35%), myocardial infarction, apical thrombus, pulmonary embolus, deep vein thrombosis, hypercoagulable state, and high risk intracranial large vessel stenosis.[4]

The most common etiology of stroke was cardioembolism (greater than two-thirds of patients). The average NIHSS on admission was 8.7 (SD 7.6). Overall stroke severity (NIHSS) was higher for patients with lower INR values (9.5 versus 5.9, $P = .033$), and subtherapeutic patients had significantly larger stroke volumes than those who were therapeutic (49.2 cc versus 19.5 cc, $P = .036$). Only the subtherapeutic group was eligible for IV tPA, 18% of whom ultimately received treatment; however, there were no differences between groups in the rate of intra-arterial mechanical thrombectomy.

Functional Outcomes

Although the mRS scores were not significantly different between the therapeutic group and the subtherapeutic group at discharge (3.6 in the therapeutic versus 3.7 in the subtherapeutic group, $P = .746$) or at follow-up (2.9 versus 3.2, $P = .624$), when compared to the subtherapeutic group, those with an INR $\geq$ 2.0 had a greater favorable shift or improvement of their mRS (0.63 versus 0.46, $P = .057$) at 90 days poststroke. Additionally, the therapeutic group was also almost twice as likely to show a greater than 1 digit improvement on the mRS scale (29% versus 15%; (Fig 1)

Discussion

Numerous trials have shown that warfarin is effective for both primary and secondary stroke prevention for patients with atrial fibrillation.[3,4] However, no trial has suggested that being on warfarin decreases the risk of stroke recurrence to 0%.[3] This may, in part, be due to the fact that up to 50% of patients are subtherapeutic (INR < 2.0) at any given time, even in well-run clinical trials.[4] Our study was not designed to evaluate the effect of INR on overall stroke prevention, but instead, to determine its effect on stroke severity and long-term outcome for those presenting with an acute infarct. Of note, fewer patients who presented with stroke were therapeutic over the time period, consistent with prior results that warfarin is effective in helping to prevent ischemic stroke. Importantly, our results indicate that patients who are therapeutic on arrival to the hospital have significantly smaller stroke volumes and less severe strokes (lower NIHSS scores) than patients who are subtherapeutic. One possible explanation is that warfarin helps to dissolve clots and diminish clot burden, resulting in smaller emboli that lodge in the more distal cerebral vessels. This is an important

Table 1. *Patient characteristics*

Variables	Total population n = 112	Therapeutic N = 27	Subtherapeutic N = 85	*P* value
Age, mean years (SD)	77.4 (13.4)	79.2 (12.1)	76.9 (13.8)	.433
Race, n black (%)	48 (42.9)	9 (33.3)	39 (45.9)	.415
Sex, n male (%)	40 (35.7)	8 (29.6)	32 (37.7)	.449
INR, mean value (SD)	1.6 (0.6)	2.5 (0.4)	1.3 (0.3)	**<.001**
Medical characteristics, n (%)				
Administered IV tPA	15 (13.4)	0 (0.0)	15 (17.7)	.019
Mechanical thrombectomy	13 (11.6)	2 (7.4)	11 (13.0)	.434
History of:				
Atrial fibrillation	88 (78.6)	21 (77.8)	67 (78.8)	.908
Coronary artery disease	47 (42.0)	12 (44.4)	35 (41.2)	.764
Diabetes	34 (30.4)	11 (40.7)	23 (27.1)	.178
Hyperlipidemia	67 (59.8)	17 (63.0)	50 (58.8)	.702
Hypertension	88 (78.5)	21 (77.8)	67 (78.8)	.908
Prior stroke	35 (31.3)	7 (25.9)	28 (33.0)	.493
Smoking	22 (19.6)	3 (11.1)	19 (22.4)	.200
Stroke etiology, n (%)				.124
Cardioembolic	82 (73.2)	17 (63.0)	65 (76.5)	
Large vessel	5 (4.5)	1 (3.7)	4 (4.7)	
Small vessel	6 (5.4)	4 (14.8)	2 (2.4)	
Other known cause	2 (1.8)	1 (3.7)	1 (1.2)	
Cryptogenic	17 (15.2)	4 (14.8)	13 (15.3)	
Outcome measures				
Admission NIHSS, mean score (SD)	8.7 (7.6)	5.9 (5.5)	9.5 (8.0)	**.033**
Stroke volume, mean cc (SD)	42.2 (63.3)	19.5 (28.6)	49.2 (69.3)	**.036**
Length of Stay, mean days (SD)	7.2 (6.3)	5.7 (3.5)	7.7 (6.9)	.140
Discharge mRS, mean score (SD)	3.7 (1.4)	3.6 (1.1)	3.7 (1.5)	.746
Follow-up mRS, mean score (SD)	3.1 (2.1)	2.9 (2.2)	3.2 (2.0)	.624
M1 to M2 conversion, n (%)	14 (13.1)	3 (11.1)	11 (13.8)	.725

Bolded values are statistically significant $P<0.05$.

consideration, especially when counseling patients who are discouraged that the experienced an ischemic event while on warfarin. Our study indicates that therapeutic treatment results in smaller strokes with a larger volume of infarct-free tissue.

Our results are consistent with prior studies showing that infarct volume is smaller in those with a therapeutic INR.[6] However, unlike previous work, along with stroke size we evaluate the subsequent effect on long-term outcome. Within our cohort, discharge and follow-up mRS scores did not differ significantly between the 2 groups as one might expect with smaller strokes. This may be due to the relatively small sample, but more likely the coarse nature of the mRS. We did see a trend toward lower mRS scores that increased at follow-up. Long-term outcome data were not collected, but it is possible that outcomes would have diverged further. An explanation for these findings is that it may take time for the brain to recover after stroke and for differences in recovery to be fully realized. This is supported by the fact that a larger proportion of therapeutic patients demonstrated an improved mRS between discharge and follow-up of more than one point. While this may seem small, improving from a score of 5 to a score of 3 is defined by the ability to walk without assistance, a life-changing outcome. The need for time to realize the full impact of recovery is supported the National Institute of Neurological Disorders and Stroke trial, which demonstrated a statistically significant difference in outcome at 3 months but not 24 hours post-IV tPA treatment.[7,8]) Smaller strokes result in larger amounts of noninfarcted brain with the potential to reorganize and improve function.

Of interest, there was a small but higher rate of lacunar disease in therapeutic patients compared to those with subtherapeutic INRs. This may because anticoagulation is not as effective as antiplatelet therapy at preventing lacunar infarcts; however, the rate of diabetes and hyperlipidemia was also higher, though not significantly, in the therapeutic group. A larger study would be needed to determine the effect of therapeutic on risk of lacunar disease.

Our study is not without limitations. This is a relatively small cohort of patients from a single center with a relatively high rate of atrial fibrillation that may not be generalizable to all populations. However, our rates are not inconsistent with those reported in other populations,[3,4] and we feel that our data nicely illustrate that patients who do embolize on warfarin have significantly

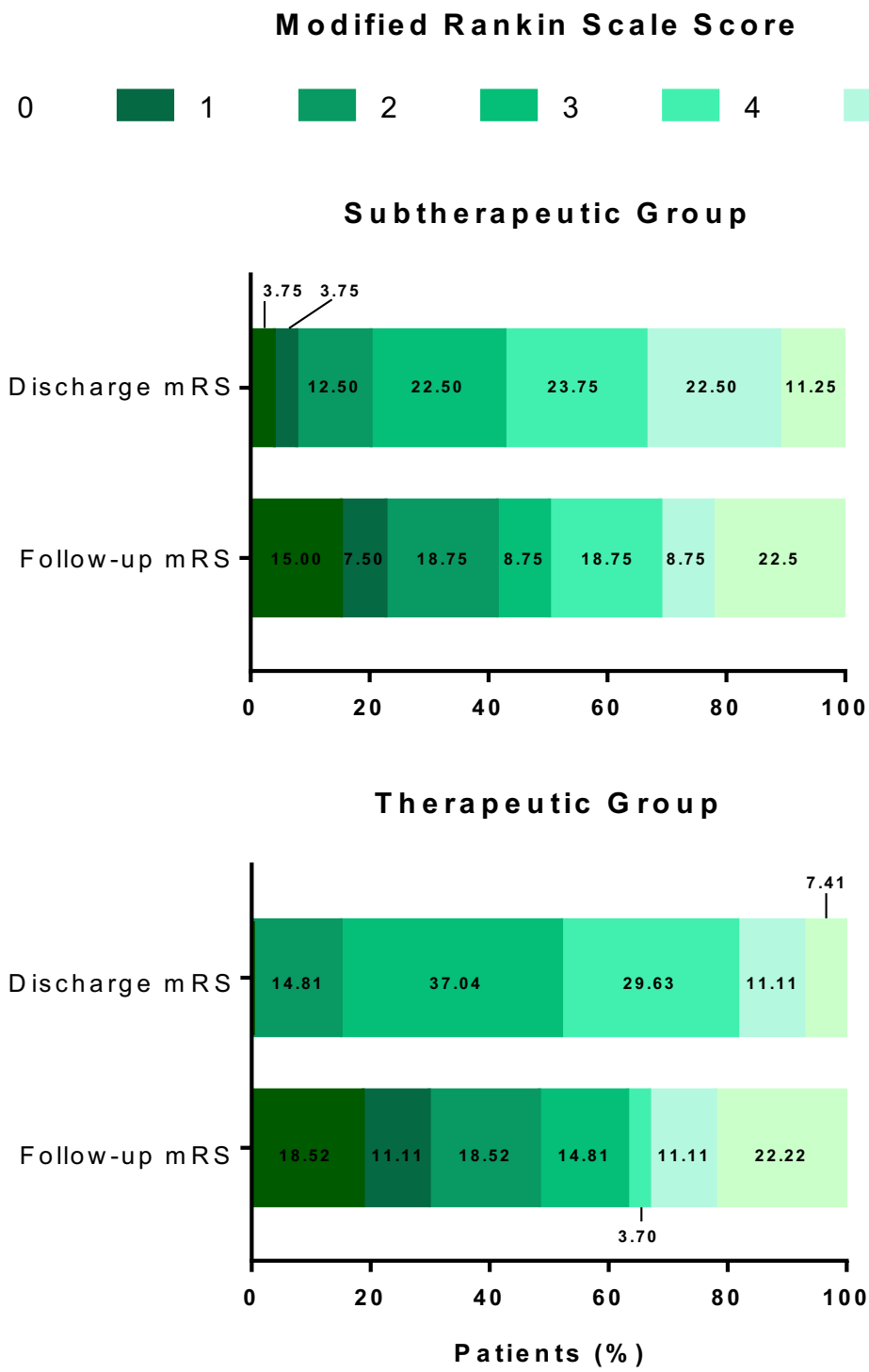

Figure 1. *Patients with a therapeutic INR were more likely to show greater improvement on the modified Rankin Scale between discharge and follow-up.*

smaller infarcts if they are therapeutic than patients who are not and are more likely to have a more favorable recovery long term. Our findings not only have important implications for patient outcomes, as reducing infarct size may significantly improve the potential for long-term recovery, but also should influence the way that we counsel patients presenting with stroke. Having a stroke while being therapeutic on warfarin should not be looked at as a medication "failure," but instead, as an opportunity to avoid a larger, more catastrophic event. Alternatively, consideration could be given to the use of the direct oral anticoagulants (DOACs) that tend not to interact with foods and medications, in order to prevent such fluctuations in INR. Further studies are needed to evaluate the impact of DOACs on stroke size, severity, and outcome.

Conclusions

Infarct volume is significantly smaller in patients with ischemic strokes on warfarin who have therapeutic INR values on presentation. In addition, they are more likely to see a greater degree of improvement over time, indicating that a greater volume of brain saved may ultimately lead to better functional recovery. It also highlights the importance of maintaining a therapeutic INR, and agents such as the DOACs that do not result in variation in coaguability, may have greater added benefit than previously thought.

Conflict of Interest

The authors report no conflicts of interest.

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