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Short title: Safety of Dabigatran in Patients with Microbleeds

Safety of Dabigatran in Acute Ischemic Stroke Patients with Microbleeds: Post hoc Analysis of DATAS-II Randomized Trial

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Abstract

Background: Cerebral microbleeds are associated with an increased risk of hemorrhagic transformation (HT) following acute ischemic stroke. We investigated whether the effect of dabigatran (vs. aspirin) in patients with acute minor non-cardioembolic ischemic stroke/TIA is modified by baseline microbleeds on MRI.

Methods: The DATAS-II trial randomized 305 patients with acute minor non-cardioembolic ischemic stroke/TIA to dabigatran (150/110mg twice daily) or aspirin (81mg daily) for 30 days. Microbleeds were centrally adjudicated in patients with an interpretable blood-sensitive sequence on baseline MRI. In this post hoc analysis, we used multivariable regression models to determine the association between microbleeds and any incident HT on day-30 MRI and excellent functional outcome (modified Rankin Scale=0-1) at 90 days.

Results: A total of 251 (82.3%) participants (mean age=66±13 years, 36% women, median[IQR] onset-to-randomization time=40[27-55] hours; median[IQR] NIHSS=1[0-2]) were included, of whom 82 (33%) had microbleeds. On day-30 MRI, 6% (n=14) developed HT, and 80% (n=191) achieved 90-day mRS of 0-1. We found no association between microbleeds presence and HT (adjusted OR=0.84; 95%CI:0.21-3.25) or excellent functional outcome (adjusted RR=1.09; 95%CI:0.94-1.26). The rate of HT in patients with microbleeds was 3% with dabigatran and 4% with aspirin (OR=0.85; 95%CI:0.11-6.75). Excellent functional outcome occurred in 74% and 84% of dabigatran and aspirin-treated patients, respectively (RR=0.88; 95%CI:0.69-1.12). The presence, severity, or location of microbleeds did not modify the effect of dabigatran on these outcomes (p-interaction>0.05).

Conclusions: Early dabigatran treatment appears safe in patients with acute minor non-cardioembolic ischemic stroke/TIA and hemorrhage-prone cerebral small vessel disease marked by microbleeds on MRI.

Trial Registration: ClinicalTrials.gov; identifier: NCT02295826.

Keywords: Microbleeds; ischemic stroke; dabigatran; anticoagulation; cerebral small vessel disease; stroke prevention

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Highlights

- We did not identify a treatment interaction between cerebral microbleeds and random assignment to dabigatran (vs. aspirin) for the outcomes of hemorrhagic transformation or excellent functional outcome at 90 days in patients with minor non-cardioembolic ischemic stroke.
- Dabigatran treatment appears safe in patients with minor non-cardioembolic stroke and microbleeds.
- These exploratory subgroup analyses were underpowered to exclude the potential for treatment effect, particularly in patients with higher microbleed burden.

Introduction

Cerebral microbleeds are 2-10 mm hypointense foci detectable on blood-sensitive magnetic resonance imaging (MRI) sequences that indicate prior brain microhemorrhages in patients with underlying hemorrhage-prone cerebral small vessel disease, such as arteriolosclerosis or cerebral amyloid angiopathy.[1] Microbleeds are present in approximately 30% of patients with ischemic stroke and are associated with an increased risk of hemorrhagic transformation (HT) and poor outcome following thrombolysis or endovascular thrombectomy.[2–5] The association of microbleeds with HT of recent ischemic strokes in patients receiving anticoagulation is less well studied.

Dabigatran, a direct thrombin inhibitor, has been approved for secondary stroke prevention in patients with atrial fibrillation. Dabigatran 150 mg daily, compared to warfarin, was reported to be associated with a lower risk of ischemic stroke with a reduced risk of intracranial hemorrhage in patients with atrial fibrillation.[6] The safety of dabigatran in patients with acute minor non-cardioembolic ischemic stroke was assessed in the DATAS-II (Dabigatran Treatment of Acute Stroke II) randomized trial. DATAS-II trial suggested that early treatment with dabigatran vs. aspirin within 72 hours of symptom onset was not associated with a significantly higher risk of asymptomatic HT in patients with acute minor non-cardioembolic ischemic stroke or transient ischemic attack (TIA). However, a higher incidence of asymptomatic petechial HT was reported in patients assigned to dabigatran vs. aspirin (7.8% vs. 3.5%).[7] Of note, the original analysis did not find an association between baseline microbleeds on MRI and

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the risk of hemorrhagic transformation at 30 days. However, it remains unknown whether these associations vary among different subgroups of distribution and severity of microbleeds. Additionally, the comparative safety of dabigatran versus aspirin in patients with versus without microbleeds was not specifically addressed. In this post hoc analysis, we aimed to determine the contribution of microbleeds to the risk of HT of the qualifying infarct on day-30 MRI and excellent clinical outcome (modified Rankin Scale [mRS] of 0-1) at 90 days. Additionally, we sought to investigate whether the effect of dabigatran compared with aspirin is modified by microbleeds on MRI. We hypothesized that microbleeds would be associated with an excess risk of HT and a lower probability of achieving a mRS score of 0-1 at 90 days, but that there would be no treatment interactions between microbleeds and dabigatran treatment for these outcomes.

Methods

Study Design

The detailed trial protocol and main findings are reported elsewhere.[7,8] The study protocol was approved by the institutional review boards of each participating center. To ensure diverse representation, where possible and appropriate the DATAS-II trial sought woman site principal investigators and steering committee members from different levels in their career. Patients or their legally authorized representatives were provided with written informed consent. In brief, DATAS-II (Dabigatran Treatment of Acute Stroke II; clinicaltrials.gov NCT02295826) was a multicenter, open-label, blinded endpoint randomized trial conducted in six stroke centers across Canada. Patients with acute minor non-cardioembolic ischemic stroke or TIA were randomly assigned to dabigatran or aspirin for 30 days, underwent a baseline and a follow-up 30-day MRI, and were followed for three months. The primary outcome was symptomatic HT within 37 days of randomization.[7,8] This is a post hoc analysis of patients with an interpretable susceptibility-weighted MRI sequence, allowing for microbleed detection as part of their baseline MRI.

Study Participants

Patients were eligible for the trial if they were 18 years old or older, diagnosed with TIA (irrespective of ABCD2 score)/minor ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] score ≤9), and presented within 72 hours of symptom onset.[9] Exclusion criteria were estimated acute diffusion-weighted imaging (DWI) lesion volume ≥25 mL, treatment with a thrombolytic/endovascular thrombectomy, additional pathology identified on brain imaging,

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planned carotid endarterectomy/stent within 30 days, creatinine clearance rate (CrCl) <30 mL/minute, ongoing bleeding risks defined by the site investigator, history of spontaneous intracranial bleeding, contraindication to dabigatran or aspirin, an indication for anticoagulation, contraindications to MRI, or life expectancy <90 days.[10] Study participants qualified for this subgroup analysis if they had an interpretable susceptibility-weighted MRI sequence at baseline MRI available for microbleed detection. This study adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[11]

Intervention

Patients were randomly assigned in a 1:1 ratio to receive aspirin 81 mg daily or dabigatran 150 mg twice daily for 30 days. The dose of dabigatran was adjusted to 110 mg twice daily for patients older than 80 years old and/or having a CrCl of 30-50 mL/minute.[12] Patients were followed up for three months. After 30 days, dabigatran was discontinued, and aspirin 81 mg daily was initiated for patients who were assigned to dabigatran treatment.

Data collection

Demographic information, medical history, clinical and neuroimaging data were collected at randomization. All data were collected, stored, and analyzed at Population Health Research Institute (PHRI). Race/ethnicity was self-reported. NIHSS, mRS, and neuroimaging outcomes were assessed by investigators masked to the treatment assignment.

Imaging Acquisition and Analyses

All individuals underwent a baseline MRI prior to randomization and a follow-up MRI at 30 days following randomization, including diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), fluid-attenuated inversion recovery (FLAIR), and susceptibility-weighted imaging (SWI)/GRE-T2* (gradient recalled echo T2*-weighted) sequences based on the imaging protocol at each center.

Microbleeds and white matter hyperintensities were centrally adjudicated using SWI/GRE-T2* and FLAIR MRI sequences, respectively by two trained raters at McMaster University who were blinded to treatment allocation and individual clinical data. Microbleeds and white matter hyperintensities were identified using Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) and Fazekas scale.[13,14] Disagreements were resolved by consensus. Baseline MRI was used for rating microbleeds where an interpretable blood-sensitive

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sequence was available, and if not available at baseline, then the day-30 MRI was used instead. HT on the day-30 MRI SWI/GRE-T2* sequence was reported centrally at the DATAS-II Imaging Core Laboratory at the University of Alberta based on modified ECASS (European Cooperative Acute Stroke Study) criteria.[15,16] Petechial hemorrhages were classified as hemorrhagic infarction type 1 (HI1) if they could only be detected on SWI/GRE-T2* sequences or hemorrhagic infarction type 2 (HI2) if they were visible on other MRI sequences as well.[7,17] Parenchymal hemorrhages (PH) were defined as PH1 if they occupied less than one-third of the primary infarct volume and PH2 if they occupied ≥1/3 infarct volume. Remote ICH was defined as any ICH not topographically related to the infarct lesion. In this study, subdural, epidural, and subarachnoid hemorrhage also were categorized as remote ICH.

Microbleeds were categorized based on i. presence or absence, ii. their distribution; strictly lobar (lobar microbleeds with or without cerebellar involvement), strictly deep (deep hemispheric/brainstem, cerebellar, or both), or mixed (both lobar and deep/brainstem), and iii. severity; absent (0 microbleeds), mild (1-2 microbleeds), moderate (3-10 microbleeds), and severe (>10 microbleeds).[18,19]

Outcomes

The primary outcome was any incident HT of the qualifying infarct on day-30 MRI, and the secondary outcome was excellent functional outcome defined as a mRS score of 0-1 at 90 days.

Statistical Analysis

Patient characteristics were compared using independent t-test for continuous variables and Fisher exact test or Chi-square for categorical variables as appropriate. To determine the baseline clinical and neuroimaging features independently associated with microbleed presence, we entered variables associated with microbleeds in the univariable logistic regression analysis (p-value<0.2) into a stepwise multivariable logistic regression model. The contribution of microbleeds to the risk of HT on day-30 MRI was measured using Firth's penalized multivariable logistic regression model and the risk of achieving a mRS score of 0-1 at 90 days was calculated using multivariable robust Poisson regression model adjusted for treatment assignment and variables independently associated with microbleed presence. These analyses were repeated for microbleed location and severity subgroups. Due to the small number of

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patients with severe microbleed number (>10), they were collapsed into one group inclusive of patients with moderate microbleed number (3-10 microbleeds) to form a moderate-severe microbleed category (3 or more microbleeds) for these analyses. Additionally, we assessed whether there is an interaction between treatment assignment and microbleeds using Firth's penalized logistic regression model for risk of HT and robust Poisson regression model for achieving mRS score of 0-1 and calculating the p-value for interaction. All analyses followed the intention-to-treat paradigm. p-values were two-sided, and a p-value of <0.05 was considered statistically significant. For interaction analysis, we considered a p-value of <0.1 as statistically significant. The analyses were conducted between February 8, 2023, and March 28, 2023, using STATA software, v.17.0.

Results

A total of 251 of 305 (82.3%) DATAS-II participants who were enrolled between February 2015 and March 2018 had an interpretable SWI (n=245, 97.6%) or GRE-T2* (n=6, 2.4%) sequence as part of their study MRI and were included in these post hoc analyses. The mean (SD) age was 66.4 (12.7), and 36.2% were female. The median (interquartile range [IQR]) time from symptom onset to randomization was 40 (27-55) hours, and the median (IQR) NIHSS score was 1 (0-2). Patients included in this analysis had similar baseline characteristics compared to excluded patients, except for better baseline functional status (Figure 1 and Table S1).

The inter-rater reliability was excellent for both microbleed presence (Cohen κ=0.82, p-value<0.001) and white matter hyperintensities severity – measured by Fazekas scale – (interclass correlation=0.91, 95% confidence interval [CI] 0.87-0.93). Microbleeds were present in 82 of 251 patients (33%). The severity of microbleeds was mild in 59 (72%), moderate in 19 (23%), and severe in 4 (5%) of the participants with microbleeds. The median number of CMBs in patients categorized as moderate-severe (3 or more microbleeds) was 4 (IQR 3-8). Additionally, microbleeds were distributed as strictly deep in 19 (23%), strictly lobar in 46 (56%), and mixed in 17 (21%). Patients with microbleeds were older, less likely to have non-Hispanic/White ethnicity, more likely to have Asian ethnicity, history of hypertension, previous stroke/TIA, higher systolic blood pressure, and lower estimated glomerular filtration rate at randomization plus more severe white matter hyperintensities and chronic macrohemorrhages on their baseline MRI (Table 1). The baseline characteristics of patients stratified by the presence of

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microbleeds, and treatment arms are presented in Table S2. The associations with Asian ethnicity (adjusted odds ratio [aOR], 4.11; 95% CI, 1.45-11.64), previous stroke/TIA (aOR, 3.48; 95% CI, 1.80-6.73), and severity of white matter hyperintensities on MRI (aOR per one unit increase in total Fazekas score, 1.42; 95% CI, 1.16-1.73) withstood adjustment (Table 2).

Outcomes

Symptomatic HT did not develop in any of the trial participants throughout the study follow-up. Asymptomatic HT was present in three (1.2%) patients at baseline MRI (all categorized as HI2), of whom one was assigned to dabigatran and two to aspirin, and no evidence of incident or worsening of HT was observed on their day-30 MRI. Asymptomatic HT was observed in 14 (6%) patients on 30-day MRI, all graded as HI1. No PH1 or PH2 occurred in any of the study participants. The risk of incident HT was not different between patients with vs. without microbleeds (3.8% vs. 6.7%, aOR, 0.84; 95% CI, 0.21-3.25).

Over a median (IQR) follow-up of 91 (55-148) days, 191 (80%) patients achieved an excellent functional outcome (mRS 0-1). The proportion of patients achieving an excellent functional outcome at 90 days did not differ between patients with and without microbleeds (79.2% vs. 79.7%, adjusted relative risk [RR], 1.09; 95% CI, 0.94-1.26). These results remained largely consistent for different subgroups of microbleed severity and location (Table 3). Excellent functional outcome was numerically less frequent among patients with 3 or more microbleeds (Figure 2). Thirty-five (14.3%) participants underwent follow-up MRI outside of the ±5-day window and removing these patients from the analysis did not modify the relationship between microbleeds and HT. Additionally, we assessed the effect of asymptomatic HT on day-30 MRI on functional outcomes at 90 days. Eleven (84.6%) patients with asymptomatic HT on day-30 MRI vs. 177 (79.7%) patients without HT achieved an mRS score of 0-1 at 90 days (p-value for chi-square test=0.669).

Effect of Treatment Assignment

Among patients with microbleeds, asymptomatic HT was present in 3% of patients randomized to dabigatran vs. 4% randomized to aspirin (OR, 0.85; 95% CI, 0.11-6.75). The proportion of patients with excellent functional outcome among patients with microbleeds who were randomized to dabigatran was 74% vs. 84% with aspirin (RR, 0.88; 95% CI, 0.69-1.12).

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The effect of dabigatran on the risk of asymptomatic HT on day-30 MRI or the probability of achieving an excellent functional outcome at 90 days was not modified by microbleed presence, severity, or location (p-value for interaction>0.05) [Table S3-4, and Figure 3].

Sensitivity Analysis

In a sensitivity analysis excluding patients without blood-sensitive sequences on baseline MRI, the risks of incident HT on 30-day MRI and achieving mRS 0-1 at 90 days were similar among those with and without microbleeds (Table S5). The effect of dabigatran versus aspirin on the study outcomes was not modified by presence of microbleeds (Table S6).

Discussion

In this post hoc analysis of a randomized clinical trial including patients with acute minor non-cardioembolic ischemic stroke/TIA, microbleeds were common and associated with Asian ethnicity, history of ischemic stroke/TIA, and white matter hyperintensity severity. Patients with microbleeds were not at a higher risk of HT on 30-day MRI compared to those without microbleeds. Patients with and without microbleeds had similar functional outcomes at 90 days. Dabigatran did not increase the risk of HT in patients with microbleeds relative to aspirin. The effect of early treatment with dabigatran on the risk of HT or attaining excellent functional outcome was not modified by the presence, location, or severity of microbleeds.

One-third of the included participants in this study had at least one microbleed on their baseline or 30-day MRI, which is consistent with previous reports of patients with ischemic stroke.[2,20] In the present study, the risk of asymptomatic HT was not higher in patients with microbleeds; in fact, HT events were numerically less frequent in the microbleed subgroup. Although microbleeds have been suggested to increase HT risk after ischemic stroke, a previous study on patients with ischemic stroke who did not receive thrombolytic therapy demonstrated no association between the presence of microbleeds and the risk of HT.[21–23] Our study may be underpowered to detect such associations, and considering the small number of HT events in our study and particularly the absence of PH1/PH2, we cannot rule out the contribution of microbleeds to the risk of more severe HT. The small number of HT events in our study might be due to less severe strokes in our participants (median NIHSS of 1) and the exclusion of patients with larger infarct volume (DWI lesion volume >25ml; median 0.9 [IQR 0.2–3.6]), and those

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receiving thrombolytic therapy. Furthermore, it has been reported that the association between microbleeds and the risk of incident HT is more robust among those with greater severity of microbleeds, and only four patients in our study had >10 microbleeds, preventing any conclusions for this higher severity subgroup.[24]

Previously, it was shown that the presence of 5 or more microbleeds on baseline MRI in patients with ischemic stroke who received thrombolytic therapy was associated with poor functional outcomes defined as mRS>2 at 3-6 months.[25] Similarly, an observational study in Japan suggested that the presence of microbleeds was independently associated with poor functional outcome at 90 days, defined as mRS of 3-6.[26] However, the present study did not identify any statistically significant differences in the odds of achieving a mRS score of 0-1 at 90 days between patients with vs. without microbleeds, irrespective of microbleed severity or distribution. Albeit patients with 3 or more microbleeds were numerically less likely to achieve excellent functional outcome. This could be due to less severe stroke in our participants, which is generally associated with a better functional outcome and the fewer number of patients with severe microbleeds in our dataset.

Consistent with prior studies investigating treatment interactions between microbleeds and direct oral anticoagulants, we found no heterogeneity in the treatment effect of dabigatran vs. aspirin with microbleed presence, severity, or location for the risk of any HT at 30-day MRI or excellent functional outcome at 90 days.[19,27] However, this should be interpreted cautiously as the number of patients with microbleeds in each treatment arm was small. Overall, our results suggest that early treatment with dabigatran may be safe in patients with minor acute ischemic stroke/TIA and microbleeds on MRI within the confines of our patient population (low severity of CMB number and small infarcts).

Strengths/Limitation

This study had several strengths, including central adjudication of microbleeds with excellent interrater agreement by raters blinded to patient data and treatment assignment, the ability to assess the effect of randomly assigned direct thrombin inhibition on clinical outcomes in patients with hemorrhage-prone cerebral small vessel disease marked by microbleeds on MRI, and the multicenter prospective sample of well-characterized non-cardioembolic ischemic stroke patients with a standardized MRI protocol.

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Our study is limited by the low number of patients with severe microbleed burden (>10) and the absence of PH1/PH2, preventing us from deriving estimates on the risk of HT for these groups. The low number of HT events resulted in wide confidence intervals around our estimates for this outcome, and thus, our results regarding the treatment effect of dabigatran in patients with microbleeds for the risk of HT should be interpreted cautiously. The exclusion of patients with moderate-to-severe ischemic stroke, in addition to almost 20% of the trial participants being excluded from this post hoc analysis due to lack of the prerequisite MRI sequence, and the predominant white ethnicity of our Canadian population may limit the generalizability of our results. Our generalizability may have been further limited by selection bias towards patients with better clinical status who were able to undergo MRI. Thirteen percent of patients with acute ischemic stroke have been reported to develop new microbleeds in the first weeks following their infarct. As such, we are unable to determine for certain whether microbleeds identified only on the 30-day MRI were present at baseline pre-randomization. We attempted to mitigate this potential for bias in sensitivity analysis of microbleed presence vs. absence excluding those without blood-sensitive sequences as part of their baseline MRI which did not alter our findings. However, due to small numbers, we were unable also confirm this for microbleed number or topography. It is important to distinguish our results focused on the risk of HT and functional outcomes with early anticoagulation in patients with microbleeds from other studies examining the risks and benefits of long-term antithrombotic use in this high-risk subgroup of ischemic stroke patients[18,19,27]. Lastly, this was a post hoc analysis with limited number of included participants and future studies with larger sample size are required to validate the safety of direct oral anticoagulants, including novel factor XIa inhibitors in patients with microbleeds.

Conclusion

We did not identify an increased risk of HT at 30-day MRI or attaining excellent functional outcome at 90 days in patients with acute minor non-cardioembolic ischemic stroke/TIA and microbleeds on MRI participating in the DATAS-II trial. Early treatment with dabigatran may be safe in patients with minor acute ischemic stroke or TIA who have evidence of hemorrhage-prone cerebral small vessel disease on MRI. However, the low number of event rates led to broad uncertainty surrounding the point estimates for the outcome of hemorrhagic transformation and there were few patients with high microbleed burden in our trial.

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Disclosure

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Statement of authorship

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Acquisition, analysis, or interpretation of data: All authors.

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433 **Table1. Baseline Characteristics by Presence of Cerebral Microbleeds**

No. of patients	**Total (251)**	**CMB (n=82)**	**No CMB (n=169)**	**p-value***
Age – year	66.4 (12.7)	70.1 (11.8)	64.6 (12.8)	0.001
Female sex	91 (36.2%)	27 (32.9%)	64 (37.9%)	0.445
Race				
Non-Hispanic/White	217 (86.8%)	68 (82.9%)	149 (88.7%)	0.014
Hispanic	6 (2.4%)	0 (0%)	6 (3.6%)	
Black	1 (0.4%)	0 (0%)	1 (0.6%)	
Asian	19 (7.6%)	12 (14.6%)	7 (4.2%)	
Others	7 (2.8%)	2 (2.4%)	5 (3.0%)	
Hypertension	143 (57.0%)	56 (68.3%)	87 (51.5%)	0.012
Diabetes mellitus	62 (24.7%)	24 (29.3%)	38 (22.5%)	0.243
Hyperlipidemia	118 (47.0%)	40 (48.8%)	78 (46.1%)	0.696
Current smoker	60 (23.9%)	16 (19.5%)	44 (26.0%)	0.256
Heart failure	2 (0.8%)	0 (0%)	2 (1.2%)	1.0
Coronary artery disease	19 (7.6%)	9 (11.0%)	10 (5.9%)	0.155
Myocardial infarction	16 (6.4%)	8 (9.8%)	8 (4.7%)	0.127
Percutaneous coronary intervention/angioplasty or coronary artery bypass grafting	12 (4.8%)	4 (4.9%)	8 (4.7%)	1.0
Carotid endarterectomy or stenting	1 (0.4%)	0 (0%)	1 (0.6%)	1.0
Peripheral artery disease	4 (1.6%)	2 (2.4%)	2 (1.2%)	0.599
Previous stroke or TIA	60 (23.9%)	35 (42.7%)	25 (14.8%)	<0.001
History of gastrointestinal bleeding	13 (5.2%)	4 (4.9%)	9 (5.3%)	1.0
Qualifying stroke subtype†				
Large-artery atherosclerosis	13 (5.2%)	1 (1.2%)	12 (7.1%)	0.126
Small vessel occlusion	69 (27.5)	23 (28.0%)	46 (27.2%)	
Cardioembolism	12 (4.8%)	2 (2.4%)	10 (5.9%)	
Cryptogenic	157 (62.5%)	56 (68.3%)	101 (59.8%)	
Other	0 (0%)	0 (0%)	0 (0%)	
NIHSS score at randomization – Median (IQR) ‡	1 (0-2)	1 (0-2)	1 (0-2)	0.507
Baseline mRS score – median (IQR) §	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.410
Blood pressure at randomization – mm Hg				
Systolic	149.43	153.86 (23.46)	147.32 (24.08)	0.046

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	(24.03)			
Diastolic	84.23 (13.45)	86.46 (14.16)	83.17 (13.01)	0.074
eGFR – mL/min/1.73m^2 ||	88.34 (31.16)	80.69 (31.59)	92.05 (30.35)	0.006
Median time from qualifying stroke to randomization (IQR) – hours	40 (27, 55)	37.5 (26, 50)	46 (27, 54)	0.110
Within 24 hours	34 (13.5%)	15 (18.3%)	19 (11.2%)	0.126
Median infarct volume (IQR) _ ml	0.9 (0.2-3.6)	0.75 (0.1-2.0)	1.1 (0.3-4.4)	0.119
Subcortical/brain stem/cerebellum infarct	110 (43.8%)	39 (47.6%)	71 (42.0%)	0.406
Median CMB number – (IQR)	0 (0, 1)	1 (1, 3)	N/A	N/A
Median total Fazekas score – (IQR)	3 (2, 5)	4 (3, 6)	3 (2, 4)	<0.001
Time between randomization and the MRI used to rate CMBs – days – Median (IQR) #	0 (0, 32)	27 (0, 32)	0 (-1, 31)	0.140
Time between randomization and the MRI used to rate Fazekas score – days – Median (IQR) **	0 (-1, 20)	0 (-1, 27)	0 (-1, 0)	0.458
Chronic macrohemorrhages ††	16 (6.4%)	11 (13.4%)	5 (3.0%)	0.004

CMB, cerebral microbleed, eGFR estimated glomerular filtration rate, IQR interquartile range, MRI magnetic resonance imaging, mRS modified Rankin Scale, NIHSS National Institutes of Health Stroke Scale, and TIA transient ischemic-attack.

Data is presented as mean (SD) or median (IQR) for continuous and number (%) for categorical variables.

* p-value for continuous variables is calculated using t-test or Wilcoxon Rank Sum test. The p-value for categorical variables is calculated using Fisher's exact or chi-square test as appropriate.

† TOAST criteria applied by the local investigators

‡ Scores on the NIHSS range from 0 to 42, with higher scores representing worse neurologic deficits.

§ Scores on the mRS range from 0 to 6, with higher scores representing worse functional deficits.

|| eGFR calculated according to the local laboratory.

Baseline MRI unavailable or inadequate in 114 (45.2%) participants

** Baseline MRI unavailable or inadequate in 64 (25.5%) participants

†† Any chronic intracranial hemorrhage other than microbleeds was counted as chronic macrohemorrhage.

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Table 2. Univariable and Multivariable Models of Patient Characteristics Associated with Microbleed Presence.

Variable	Crude OR (95% CI)	P-value	Adjusted OR (95%CI)	P-value
Age	1.04 (1.01-1.06)	0.002	NA	NA
Race				
Non-Hispanic/White	Reference	-	Reference	NA
Hispanic	1	-	NA	NA
Black	1	-	NA	NA
Asian	3.76 (1.42-9.96)	0.008	4.11 (1.45-11.64)	0.008
Others	0.88 (0.17-4.63)	0.877	NA	NA
Hypertension	2.03 (1.17-3.53)	0.012	NA	NA
Coronary artery disease	1.96 (0.76-5.03)	0.161	NA	NA
Myocardial infarction	2.18 (0.79-6.02)	0.134	NA	NA
Previous stroke or TIA	4.29 (2.33-7.89)	<0.001	3.48 (1.80-6.73)	<0.001
Qualifying stroke subtype				
Large-artery atherosclerosis	Reference	NA	Reference	NA
Small vessel occlusion	6.0 (0.73-49.02)	0.095	NA	NA
Cardioembolism	2.40 (0.19-30.52)	0.500	NA	NA
Cryptogenic	6.65 (0.84-52.51)	0.072	NA	NA
Other	N/A	N/A	NA	NA
SBP at baseline	1.01 (1.0-1.02)	0.048	NA	NA
Median total Fazekas score	1.57 (1.30-1.89)	<0.001	1.42 (1.16-1.73)	0.001
eGFR	0.99 (0.98-1.0)	0.008	NA	NA
Infarct volume	0.98 (0.93-1.02)	0.314	NA	NA
Chronic macrohemorrhages	5.08 (1.70-15.16)	0.004	NA	NA

eGFR estimated glomerular filtration rate, OR odds ratio, SBP systolic blood pressure, and TIA transient ischemic attack.

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453 **Table 3. Risk of Outcomes by Cerebral Microbleed Status**

Characteristic	Hemorrhagic Transformation on day-30 MRI*				mRS 0-1 at 90 days			
	# of patients n	# of events n (%)	OR (95% CI)	aOR (95% CI)†,‡	# of patients n	# of events n (%)	RR (95% CI)	aRR (95% CI)†
CMB Presence								
None	165	11 (6.7%)	Reference	Reference	163	130 (79.7%)	Reference	Reference
CMB	78	3 (3.8%)	0.62 (0.18-2.13)	0.84 (0.21-3.25)	77	61 (79.2%)	0.99 (0.86-1.14)	1.09 (0.94-1.26)
CMB Severity								
No CMB	165	11 (6.7%)	Reference	Reference	163	130 (79.7%)	Reference	Reference
1-2 CMBs	57	2 (3.5%)	0.60 (0.15-2.46)	0.84 (0.19-3.77)	57	47 (82.4%)	1.03 (0.90-1.19)	1.11 (0.96-1.29)
3 or more CMBs	21	1 (4.8%)	0.98 (0.17-5.73)	1.14 (0.15-8.68)	20	14 (70.0%)	0.88 (0.65-1.18)	1.01 (0.75-1.35)
CMB Location								
No CMB	165	11 (6.7%)	Reference	Reference	163	130 (79.7%)	Reference	Reference
Strictly deep/mixed CMBs	35	2 (5.7%)	1.00 (0.24-4.14)	1.29 (0.27-6.09)	34	26 (76.5%)	0.96 (0.78-1.17)	1.04 (0.85-1.28)
Strictly lobar CMBs	43	1 (2.3%)	0.47 (0.08-2.69)	0.64 (0.10-4.07)	43	35 (81.4%)	1.02 (0.87-1.20)	1.13 (0.97-1.31)

454 CMB cerebral microbleed, MRI, magnetic resonance imaging; mRS modified Rankin Scale, OR odds ratio, RR
455 relative risk.

456 *Any incident hemorrhagic transformation visible on the day-30 MRI.

457 †Adjusted for Asian Ethnicity, previous stroke/TIA, total Fazekas score, and treatment assignment.

458 ‡ Firth's logistic regression is used due to the low rate of hemorrhagic transformation.

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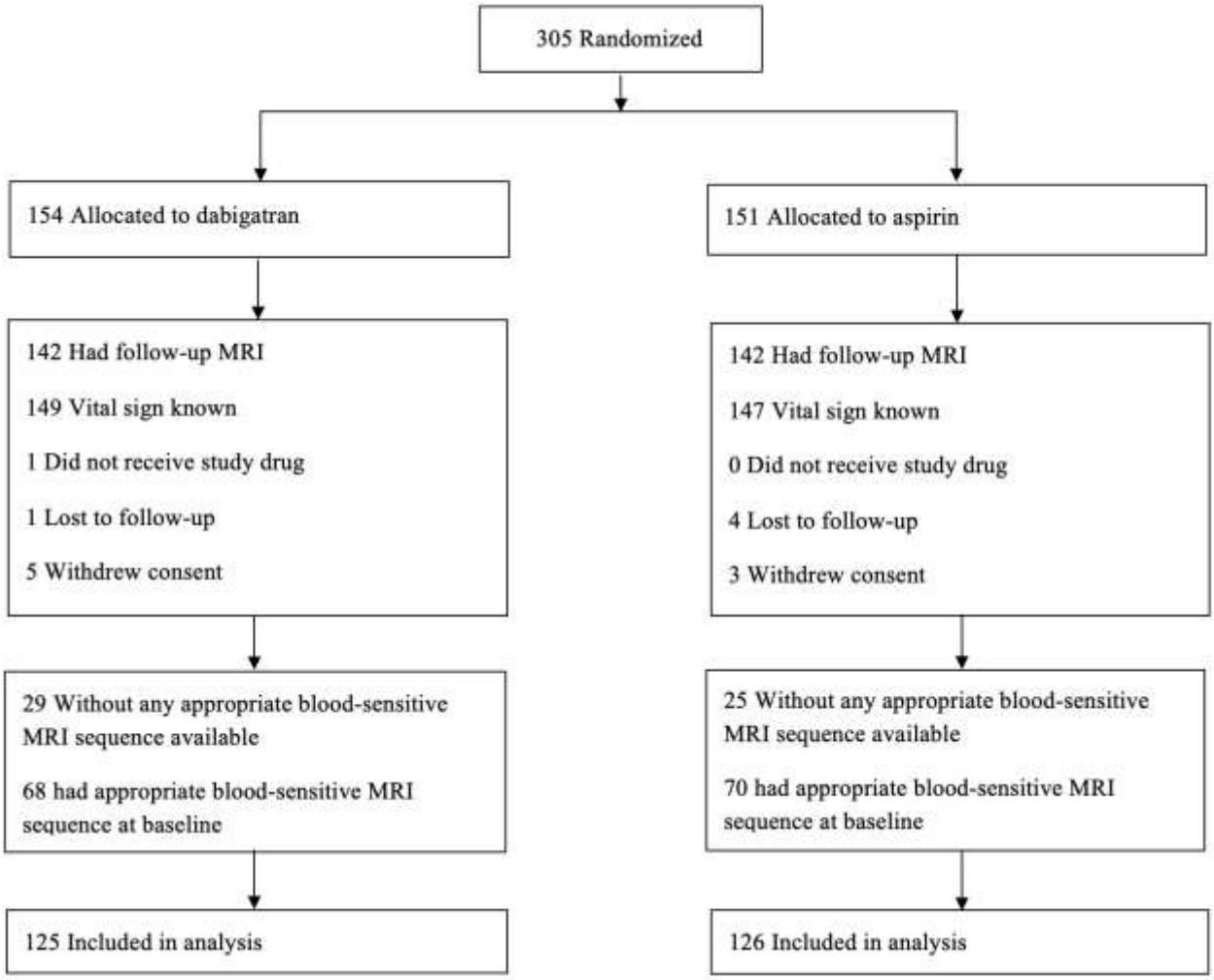

Figure 1. CONSORT Flow Diagram

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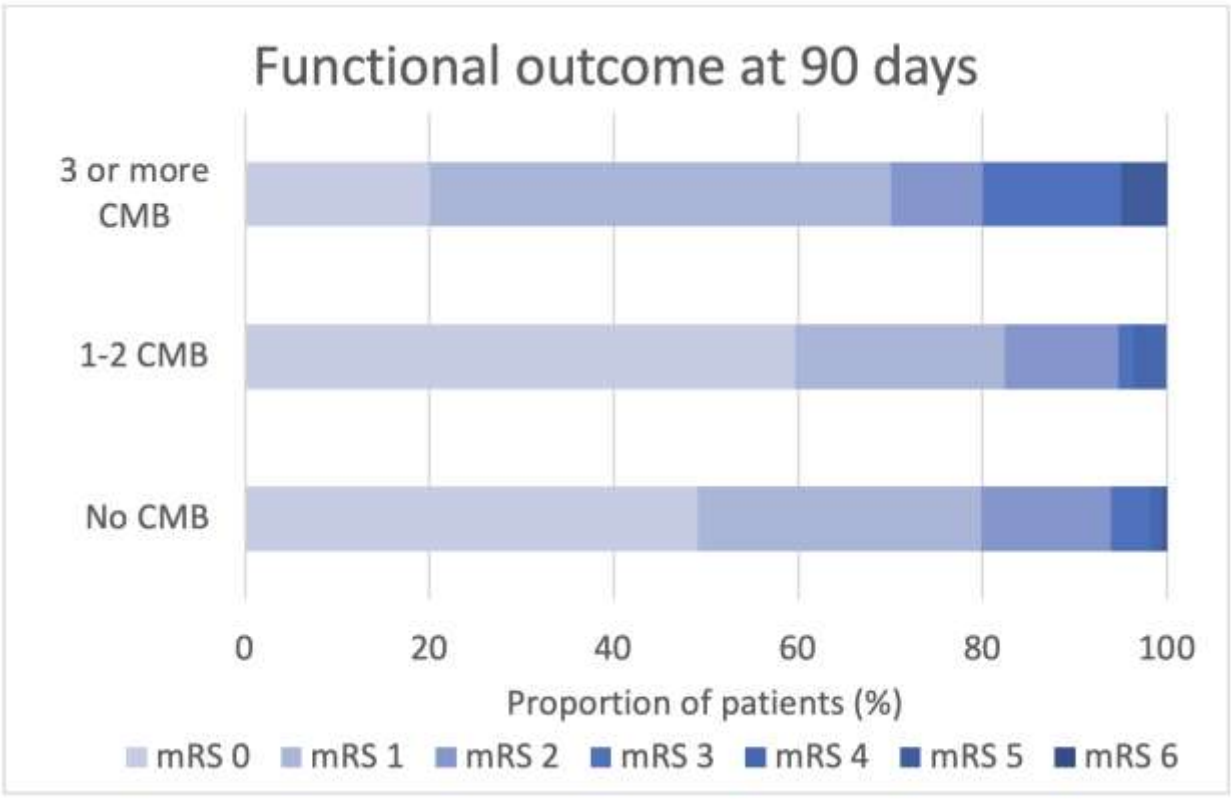

Figure 2. Functional Outcome at 90 Days Stratified by Microbleed Severity.

CMB, cerebral microbleed

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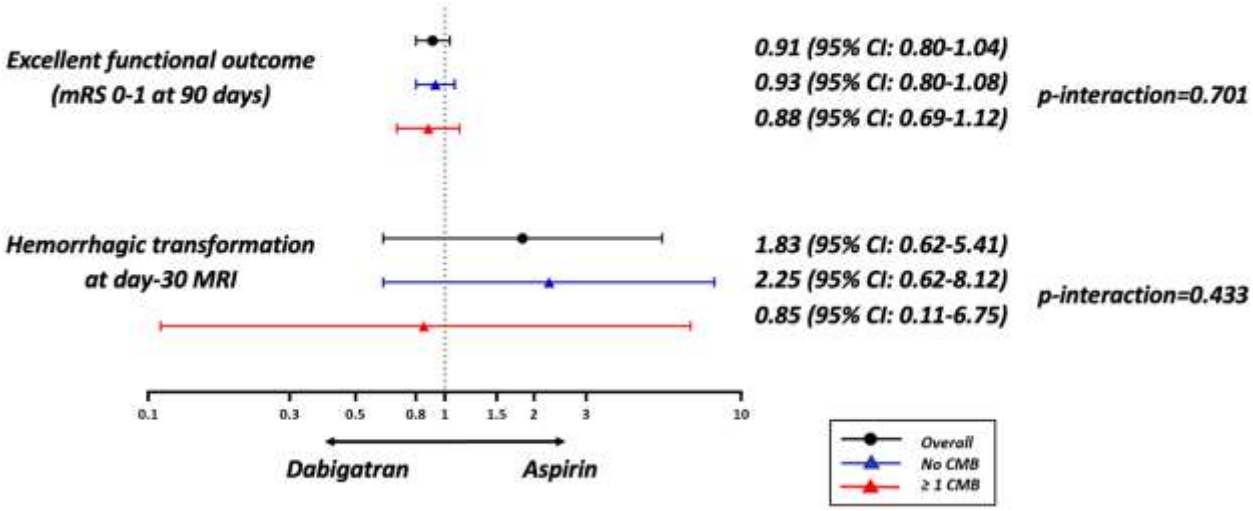

464

465 **Figure 3. The Effect of Dabigatran in Patients with vs. without Microbleeds for Clinical**
466 **Outcomes**

467 CMB, cerebral microbleed; MRI, magnetic resonance imaging; mRS, modified Rankin Scale

468 The effect of treatment assignment on the outcomes is reported as odds ratio (95% confidence
469 interval [CI]) for Hemorrhagic transformation and as relative risk (95% CI) for excellent
470 functional outcome.

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