**Supplement**

**Table S1. Comparison of Baseline Characteristics of Participants Included in the Cohort Study Sample vs. Those Excluded.**

|  |  |  |  |
| --- | --- | --- | --- |
| **No. of patients** | **Included (n=251)** | **Excluded (n=54)** | **p-value\*** |
| Age – year | 66.4 (12.7) | 64.8 (15.3) | 0.413 |
| Female sex | 91 (36.2%) | 26 (48.1%) | 0.103 |
| Race |  |  |  |
| Non-Hispanic/white | 217 (86.8%) | 48 (88.9%) | 1.0 |
| Hispanic | 6 (2.4%) | 1 (1.8%) | NA |
| Black | 1 (0.4%) | 0 (0%) | NA |
| Asian | 19 (7.6%) | 4 (7.4%) | NA |
| Other | 7 (2.8%) | 1 (1.8%) | NA |
| Hypertension | 143 (57.0%) | 31 (57.4) | 0.953 |
| Diabetes mellitus | 62 (24.7%) | 10 (18.5%) | 0.332 |
| Hyperlipidemia | 118 (47.0%) | 19 (35.2%) | 0.113 |
| Current smoker | 60 (23.9%) | 12 (22.2%) | 0.792 |
| Heart failure | 2 (0.8%) | 0 (0%) | 1.00 |
| Coronary artery disease | 19 (7.6%) | 1 (1.8%) | 0.220 |
| Myocardial infarction | 16 (6.4%) | 2 (3.7%) | 0.749 |
| Percutaneous coronary intervention/angioplasty or coronary artery bypass grafting | 12 (4.8%) | 0 (%) | 0.135 |
| Carotid endarterectomy or stenting | 1 (0.4%) | 0 (0%) | 1.0 |
| Peripheral artery disease | 4 (1.60%) | 0 (0%) | 1.0 |
| Previous stroke or TIA | 60 (23.9%) | 11 (20.4%) | 0.577 |
| History of gastrointestinal bleeding | 13 (5.2%) | 0 (0%) | 0.135 |
| Qualifying stroke subtype † |  |  |  |
| Large-artery atherosclerosis | 13 (5.2%) | 2 (3.7%) | 0.849 |
| Small vessel occlusion | 69 (27.5%) | 15 (27.8%) | NA |
| Cardioembolism | 12 (4.8%) | 4 (7.4%) | NA |
| Cryptogenic | 157 (62.5%) | 33 (61.1%) | NA |
| Other | 0 (0%) | 0 (0%) | NA |
| NIHSS scoreat randomization – Median (IQR) ‡ | 1 (0-2) | 1 (0-2) | 0.693 |
| baseline mRS score – Median (IQR) § | 0 (0, 0) | 0 (0, 1) | <0.001 |
| Blood pressure at randomization – mm Hg |  |  |  |
| Systolic | 149.43 (24.03) | 153.69 (27.27) | 0.262 |
| Diastolic | 84.23 (13.45) | 85.53 (14.11) | 0.534 |
| eGFR – mL/min/1.73m2 || | 88.34 (31.16) | 85.41 (38.19) | 0.548 |
| Time from qualifying stroke to randomization – hours – Median (IQR) | 46 (27, 54) | 40 (27, 55) | 0.721 |
| Chronic macrohemorrhages # | 16 (6.4%) | 3 (5.6%) | 1.0 |

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 National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores representing worse neurologic deficits.

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

|| eGFR calculated according to the local laboratory.

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

**Table S2. Baseline Characteristics by Presence of Cerebral Microbleeds and Treatment Arms**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **CMB (n=82)** | | **No CMB (n=169)** | |
| **No. of patients** | **Total (251)** | **Dabigatran**  **(b=35)** | **Aspirin (n=47)** | **Dabigatran**  **(n=90)** | **Aspirin (n=79)** |
| Age – year | 66.4 (12.7) | 68.0 (13.8) | 71.7 (9.9) | 62.7 (12.6) | 66.8 (12.7) |
| Female sex | 91 (36.2%) | 12 (34.3%) | 15 (31.9%) | 37 (41.1%) | 27 (34.2%) |
| Race |  |  |  |  |  |
| Non-Hispanic/White | 217 (86.8%) | 28 (80.0%) | 40 (85.1%) | 81 (90.0%) | 68 (87.2%) |
| Hispanic | 6 (2.4%) | 0 (0%) | 0 (0%) | 2 (2.2%) | 4 (5.1%) |
| Black | 1 (0.4%) | 0 (0%) | 0 (0%) | 1 (1.1%) | 0 (0%) |
| Asian | 19 (7.6%) | 6 (17.1%) | 6 (12.8%) | 4 (4.4%) | 3 (3.8) |
| Others | 7 (2.8%) | 1 (2.9%) | 1 (2.1%) | 2 (2.2%) | 3 (3.8) |
| Hypertension | 143 (57.0%) | 25 (71.4%) | 31 (66.0%) | 46 (51.1%) | 41 (51.9) |
| Diabetes mellitus | 62 (24.7%) | 11 (31.4%) | 13 (27.7%) | 22 (24.4%) | 16 (20.2) |
| Hyperlipidemia | 118 (47.0%) | 15 (42.9%) | 25 (53.2%) | 37 (41.1%) | 41 (51.9%) |
| Current smoker | 60 (23.9%) | 7 (20.0%) | 9 (19.1%) | 24 (26.7%) | 20 (25.3%) |
| Heart failure | 2 (0.8%) | 0 (0%) | 0 (0%) | 1 (1.1%) | 1 (1.3%) |
| Coronary artery disease | 19 (7.6%) | 3 (8.6%) | 6 (12.8%) | 7 (7.8%) | 3 (3.8%) |
| Myocardial infarction | 16 (6.4%) | 1 (2.9%) | 7 (14.9%) | 6 (6.7%) | 2 (2.5%) |
| Percutaneous coronary intervention/angioplasty or coronary artery bypass grafting | 12 (4.8%) | 1 (2.9%) | 3 (6.4%) | 6 (6.7%) | 2 (2.5%) |
| Carotid endarterectomy or stenting | 1 (0.4%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1.3%) |
| Peripheral artery disease | 4 (1.6%) | 0 (0%) | 2 (4.3%) | 1 (1.1%) | 1 (1.3%) |
| Previous stroke or TIA | 60 (23.9%) | 16 (45.7%) | 19 (40.4%) | 13 (14.4%) | 12 (15.2%) |
| History of gastrointestinal bleeding | 13 (5.2%) | 0 (0%) | 4 (8.5%) | 4 (4.4%) | 5 (6.3) |
| Qualifying stroke subtype\* |  |  |  |  |  |
| Large-artery atherosclerosis | 13 (5.2%) | 0 (0%) | 1 (2.1%) | 6 (6.7%) | 6 (7.6%) |
| Small vessel occlusion | 69 (27.5) | 9 (25.7%) | 14 (29.8%) | 24 (26.7%) | 22 (27.8%) |
| Cardioembolism | 12 (4.8%) | 0 (0%) | 2 (4.3%) | 6 (6.7%) | 4 (5.1%) |
| Cryptogenic | 157 (62.5%) | 26 (74.3%) | 30 (63.8%) | 54 (60.0%) | 47 (59.5%) |
| Other | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| NIHSS scoreat randomization –Median (IQR) † | 1 (0-2) | 1 (0-2) | 1 (0-2) | 1 (0-2) | 1 (0-2) |
| Baseline mRS score – median (IQR) ‡ | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| Blood pressure at randomization – mm Hg |  |  |  |  |  |
| Systolic | 149.43 (24.03) | 156.54 (26.19) | 151.93 (21.39) | 147.10 (27.56) | 147.6 (19.60) |
| Diastolic | 84.23 (13.45) | 88.24 (15.80) | 85.17 (12.88) | 83.64 (13.91) | 82.64 (11.98) |
| eGFR – mL/min/1.73m2 § | 88.34 (31.16) | 83.54 (38.93) | 78.57 (25.03) | 94.70 (29.44) | 89.04 (31.27) |
| Median time from qualifying stroke to randomization (IQR) – hours | 40 (27, 55) | 30 (24, 49) | 40 (27, 50) | 40 (28, 56) | 43 (30, 56) |
| Within 24 hours | 34 (13.5%) | 9 (25.7%) | 6 (12.8) | 14 (15.6%) | 5 (6.3) |
| Median infarct volume (IQR) \_ ml | 0.9 (0.2-3.6) | 0.8 (0.1-2.1) | 0.7 (0.1-1.9) | 1.1 (0.3-5.4) | 0.9 (0.3-3.9) |
| Subcortical/brain stem/cerebellum infarct | 110 (43.8%) | 17 (48.6%) | 22 (46.8%) | 34 (37.8%) | 37 (46.8%) |
| Median CMB number – (IQR) | 0 (0, 1) | 2 (1, 3) | 1 (1, 2) | N/A | N/A |
| Median total Fazekas score – (IQR) | 3 (2, 5) | 4 (3, 6) | 4 (3, 6) | 3 (2, 4) | 3 (2, 4) |
| Time between randomization and the MRI used to rate CMBs – days – Median (IQR) || | 0 (0, 32) | 22 (-1, 32) | 28 (0, 33) | 0 (-1, 31) | 0 (0, 31) |
| Time between randomization and the MRI used to rate Fazekas score– days – Median (IQR) # | 0 (-1, 20) | 0 (-1, 0) | 0 (0, 29) | 0 (-1, 25) | 0 (-1, 0) |
| Chronic macrohemorrhages \*\* | 16 (6.4%) | 8 (22.9%) | 3 (6.4%) | 3 (3.3%) | 2 (2.5%) |

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 ischemicattack.

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

\* 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.

**Table S3. Safety in Microbleed Subgroups - Hemorrhagic Transformation on day-30 MRI**

| **Subgroup** | **Dabigatran (N=120)** | | **Aspirin (N=123)** | |  | |
| --- | --- | --- | --- | --- | --- | --- |
| **No. Rand** | **No. Events (%)\*** | **No. Rand** | **No. Events (%)\*** | **OR†,** ‡ **(95% CI)** | **p-value (interaction)** |
| **CMB Presence** |  |  |  |  |  |  |
| None | 88 | 8 (9.1%) | 77 | 3 (3.9%) | 2.25 (0.62-8.12) | 0.433 |
| CMB | 32 | 1 (3.1%) | 46 | 2 (4.3%) | 0.85 (0.11-6.75) |  |
| **CMB Severity** |  |  |  |  |  |  |
| No CMB | 88 | 8 (9.1%) | 77 | 3 (3.9%) | 2.25 (0.62-8.12) | NA |
| 1-2 CMBs | 21 | 0 (0%) | 36 | 2 (5.6%) | NA |  |
| 3 or more CMBs | 11 | 1 (9.1%) | 10 | 0 (0%) | NA |  |
| **CMB Location** |  |  |  |  |  |  |
| No CMB | 88 | 8 (9.1%) | 77 | 3 (3.9%) | 2.25 (0.62-8.12) | 0.644 |
| Strictly deep/mixed CMBs | 16 | 1 (6.2%) | 19 | 1 (5.3%) | 1.19 (0.11-12.66) |  |
| Strictly lobar CMBs | 16 | 0 (0%) | 27 | 1 (3.7%) | NA |  |
| **Total** | 120 | 9 (7.5%) | 123 | 5 (4.1%) | 1.83 (0.62-5.41) | NA |

CMB cerebral microbleed, MRI magnetic resonance imaging, OR odds ratio.

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

† Odds ratios were calculated for each subgroup, comparing the odds of the outcome in patients randomized to dabigatran relative to those randomized to aspirin.

‡ Firth’s logistic regression is used due to low rate of hemorrhagic transformation.

**Table S4. Safety in Microbleed Subgroups - mRS Score 0-1 at 90 Days**

| **Subgroup** | **Dabigatran (N=121)** | | **Aspirin (N=119)** | |  | |
| --- | --- | --- | --- | --- | --- | --- |
| **No. Rand** | **No. Events (%)** | **No. Rand** | **No. Events (%)** | **RR\* (95% CI)** | **p-value (interaction)** |
| **CMB Presence** |  |  |  |  |  |  |
| None | 87 | 67 (77.0%) | 76 | 63 (83.9%) | 0.93 (0.80-1.08) | 0.701 |
| CMB | 34 | 25 (73.5%) | 43 | 36 (83.7%) | 0.88 (0.69-1.12) |  |
| **CMB Severity** |  |  |  |  |  |  |
| No CMB | 87 | 67 (77.0%) | 76 | 63 (82.9%) | 0.93 (0.80-1.08) | 0.974 |
| 1-2 CMBs | 22 | 17 (77.3%) | 35 | 30 (85.7%) | 0.90 (0.69-1.18) |  |
| 3 or more CMBs | 12 | 8 (66.7%) | 8 | 6 (75.0%) | 0.89 (0.50-1.59) |  |
| **CMB Location** |  |  |  |  |  |  |
| No CMB | 87 | 67 (77.0%) | 76 | 63 (82.9%) | 0.93 (0.80-1.08) | 0.855 |
| Strictly deep/mixed CMBs | 16 | 11 (68.7%) | 18 | 15 (83.3%) | 0.82 (0.55-1.22) |  |
| Strictly lobar CMBs | 18 | 14 (78.8%) | 25 | 21 (84%) | 0.92 (0.68-1.25) |  |
| **Total** | 121 | 92 (76.0%) | 119 | 99 (83.2%) | 0.91 (0.80-1.04) | NA |

CMB cerebral microbleed, mRS modified Rankin Scale, RR relative risk.

\* Relative risks were calculated for each subgroup, comparing the risk of the outcome in patients randomized to dabigatran relative to those randomized to aspirin.

**Table S5. Risk of Outcomes by Cerebral Microbleed Status, excluding those without blood-sensitive sequences on baseline MRI**

| **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 | 99 | 5 (5.0%) | Reference | Reference | 99 | 84 (84.8%) | Reference | Reference |
| CMB | 33 | 2 (6.1%) | 1.36 (0.29-6.41) | 1.06 (0.20-5.64) | 34 | 25 (73.5%) | 0.87 (0.70-1.08) | 0.99 (0.79-1.25) |

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

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

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

‡ Firth’s logistic regression is used due to low rate of hemorrhagic transformation.

**Table S6. Safety in Microbleed Subgroups – hemorrhagic transformation on day-30 MRI and mRS Score 0-1 at 90 Days, excluding those without blood-sensitive sequences on baseline MRI**

| **Subgroup** | **Dabigatran (N=65)** | | **Aspirin (N=67)** | |  | |
| --- | --- | --- | --- | --- | --- | --- |
| **No. Rand** | **No. Events (%)\*** | **No. Rand** | **No. Events (%)\*** | **Effect size** | **p-value (interaction)** |
| **Hemorrhagic transformation on day-30 MRI\*** |  |  |  |  | **OR†,** ‡ **(95% CI)** |  |
| **CMB Presence** |  |  |  |  |  |  |
| None | 51 | 3 (5.9%) | 48 | 2 (4.2%) | 1.34 (0.25-7.14) | 0.989 |
| CMB | 14 | 1 (7.1%) | 19 | 1 (5.3%) | 1.37 (0.13-14.65) |  |
| **mRS 0-1 at 90 days** |  |  |  |  | **RR† (95% CI)** |  |
| **CMB Presence** |  |  |  |  |  |  |
| None | 51 | 41 (80.4%) | 48 | 43 (89.6%) | 0.90 (0.76-1.06) | 0.947 |
| CMB | 16 | 11 (68.7%) | 18 | 14 (77.8%) | 0.88 (0.58-1.34) |  |

CMB cerebral microbleed, MRI magnetic resonance imaging, OR odds ratio, RR relative risk.

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

† Odds ratio and relative risk were calculated for each subgroup, comparing the odds or risk of the outcome in patients randomized to dabigatran relative to those randomized to aspirin.

‡ Firth’s logistic regression is used due to low rate of hemorrhagic transformation.