Effects of Antiplatelet Therapy After Stroke Caused by Intracerebral Hemorrhage

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Effects of Antiplatelet Therapy After Stroke Caused by Intracerebral Hemorrhage
Extended Follow-up of the RESTART Randomized Clinical Trial

Importance
The Restart or Stop Antithrombotics Randomized Trial (RESTART) found that antiplatelet therapy appeared to be safe up to 5 years after intracerebral hemorrhage (ICH) that had occurred during antithrombotic (antiplatelet or anticoagulant) therapy.

Objectives
To monitor adherence, increase duration of follow-up, and improve precision of estimates of the effects of antiplatelet therapy on recurrent ICH and major vascular events.

Design, Setting, and Participants
From May 22, 2013, through May 31, 2018, this prospective, open, blinded end point, parallel-group randomized clinical trial studied 537 participants at 122 hospitals in the UK. Participants were individuals 18 years or older who had taken antithrombotic therapy for the prevention of occlusive vascular disease when they developed ICH, discontinued antithrombotic therapy, and survived for 24 hours. After initial follow-up ended on November 30, 2018, annual follow-up was extended until November 30, 2020, for a median of 3.0 years (interquartile range [IQR], 2.0-5.0 years) for the trial cohort.

Interventions
Computerized randomization that incorporated minimization allocated participants (1:1) to start or avoid antiplatelet therapy.

Main Outcomes and Measures
Participants were followed up for the primary outcome (recurrent symptomatic ICH) and secondary outcomes (all major vascular events) for up to 7 years. Data from all randomized participants were analyzed using Cox proportional hazards regression, adjusted for minimization covariates.

Results
A total of 537 patients (median age, 76.0 years; IQR, 69.0-82.0 years; 360 [67.0%] male; median time after ICH onset, 76.0 days; IQR, 29.0-146.0 days) were randomly allocated to start (n = 268) or avoid (n = 269 [1 withdrew]) antiplatelet therapy. The primary outcome of recurrent ICH affected 22 of 268 participants (8.2%) allocated to antiplatelet therapy compared with 25 of 268 participants (9.3%) allocated to avoid antiplatelet therapy (adjusted hazard ratio, 0.87; 95% CI, 0.49-1.55; \( P = .64 \)). A major vascular event affected 72 participants (26.8%) allocated to antiplatelet therapy compared with 87 participants (32.5%) allocated to avoid antiplatelet therapy (hazard ratio, 0.79; 95% CI, 0.58-1.08; \( P = .14 \)).

Conclusions and Relevance
Among patients with ICH who had previously taken antithrombotic therapy, this study found no statistically significant effect of antiplatelet therapy on recurrent ICH or all major vascular events. These findings provide physicians with some reassurance about the use of antiplatelet therapy after ICH if indicated for secondary prevention of major vascular events.

Trial Registration
isrctn.org Identifier: ISRCTN71907627
A Wor...
System tool to review anonymized digital images of diagnostic brain computed tomography or MRI to confirm or refute eligibility and to support the adjudication of cerebral outcome events.

We restricted starting antiplatelet therapy to 1 or more of oral aspirin, dipyridamole, or clopidogrel, administered within 24 hours of randomization with doses determined at the discretion of the consultant responsible for the participant. The comparator was a policy of avoiding antiplatelet therapy. Participants could start or discontinue antithrombotic therapy if clinically indicated by events during follow-up. We measured adherence after randomization by recording antiplatelet therapy use before the first outcome event according to the preceding clinic or hospital discharge form or follow-up questionnaire. We collected information about blood pressure-lowering drugs and blood pressure control at discharge and during follow-up.

We followed up participants by sending a postal questionnaire to their primary care practitioners (who hold a comprehensive lifelong medical record for each patient registered with them), followed by a postal questionnaire to surviving participants (or caregivers) who had not withdrawn, to check survival, medication use, modified Rankin scale score, and the occurrence of outcomes. We sent questionnaires after randomization at 6 months or 1 year and then annually for up to 7 years. We interviewed participants who did not respond to the questionnaire by telephone. We performed extended follow-up was approved by the funder on February 25, 2019, by the research ethics committee on July 12, 2019, and by the sponsor on July 18, 2019, so that accrual of follow-up resumed on July 26, 2019, and ended on November 30, 2020.

We recorded serious adverse events (that were neither an outcome event nor an expected complication of stroke) via investigators if they occurred before hospital discharge or via primary care practitioners’ annual reports of hospital admissions. Investigators reported protocol deviations and violations to the trial coordinating center and the sponsor.

Monitoring included central statistical monitoring of trial conduct, data quality, and participant safety, supplemented by triggered onsite monitoring visits if required and detailed source data verification at the trial coordinating center. We conducted completeness, range, consistency, validation, and logic checks on all baseline and outcome data from the web-based case report forms.

Outcomes

The primary outcome was fatal or nonfatal radiologically or pathologically proven recurrent symptomatic ICH assessed in all participants (except 1 participant who withdrew before the first follow-up). The secondary outcomes of major hemorrhagic events and major occlusive vascular events were prespecified. In the protocol, we had specified a composite secondary outcome of all major vascular events defined by the Antithrombotic Trialists’ Collaboration (nonfatal myocardial infarction, nonfatal stroke [ischemic, hemorrhagic, or uncertain cause], or death from a vascular cause). The process of outcome adjudication was described in the main report.

Statistical Analysis

We aimed to recruit 720 participants and continue their follow-up for at least 2 years to cover several combinations of published estimates of the primary outcome event rate in cohort studies (1.8%-7.4% per year) and an up to 4 times proportional increase in the absolute risk of the primary outcome with the use of antiplatelet therapy in observational studies. Throughout the recruitment period and during extended follow-up, unblinded trial statisticians supplied the independent data monitoring committee with analyses of the accumulating baseline and follow-up data at the same frequency and for the same purposes as described previously. Two statisticians (A.R. and S.L.) and the chief investigator (R.A.-S.S.) prepared an updated statistical analysis plan for the analysis of extended follow-up, which was approved by the RESTART Steering Committee before database lock. All group comparisons were made using the intention-to-treat populations. All group comparisons were made using the intention-to-treat populations.

We estimated survival in each treatment group using a Kaplan-Meier survival analysis of time to first occurrence of a primary or secondary outcome event during all available follow-up after randomization, censored at death unrelated to an outcome event or last available follow-up. We quantified completeness of follow-up as the proportion of participants with a complete follow-up questionnaire at each planned interval after randomization and as the proportion of the planned duration of follow-up that was observed. After assessing the proportional hazards assumption graphically and including a treatment by log(time) interaction, we compared survival by allocated treatment using the log-rank test. The primary method of analysis was to construct an unadjusted Cox proportional hazards regression model and a second model adjusted for all 5 covariates included in the minimization algorithm to calculate the HRs. We used the Mann-Whitney test to compare group summaries of modified Rankin scale scores by randomized group. We performed sensitivity analyses by adding symptomatic stroke of uncertain subtype or deaths of undetermined cause to the primary outcome.

We performed prespecified exploratory subgroup analyses of the primary outcome with statistical tests of interaction to estimate heterogeneity of treatment effect between the prespecified subgroups: the 5 covariates used by the minimization algorithm, antithrombotic therapy before ICH, and history of atrial fibrillation. The unblinded trial statistician (A.R.) performed statistical analyses with SAS statistical software, version 9.4 (SAS Institute Inc). A 2-sided P < .05 was considered to be statistically significant.

Results

A total of 537 patients (median age, 76.0 years; IQR, 69.0-82.0 years; 360 [67.0%] male; median time after ICH onset, 76.0 days; IQR, 29.0-146.0 days) were randomly allocated to start (n = 268) or avoid (n = 269 [1 withdrew]) antiplatelet therapy. Between May 22, 2013, and May 31, 2018, a total of 562 participants consented to take part in the study from 104...
of 122 activated hospital sites. A total of 268 participants were randomly assigned to start antiplatelet therapy and 269 to avoid antiplatelet therapy, of whom all but 1 participant was included in the outcome analyses. The flow diagram (Figure 1) and baseline characteristics (eTables 2 and 3 in Supplement 1) were unchanged from the main trial results. Extended follow-up ended on November 30, 2020. We obtained 1805 of a potential 1844 person-years of follow-up (overall completeness, 97.9%) for a median follow-up of 3.0 years (IQR, 2.0-5.0 years) per participant.

Immediate adherence to allocated treatment was good, with some decrease in adherence over time, but no clear overall change between the main results of the trial and when extended follow-up ended (eTable 4 in Supplement 1). Few participants used anticoagulant therapy during follow-up (eTable 5 in Supplement 1). Most participants took at least 1 blood pressure-lowering drug during follow-up and achieved a median systolic blood pressure of approximately 130 mm Hg, with good balance by treatment allocation (eTable 6 in Supplement 1). The proportional hazards assumption was fulfilled for analyses of primary and secondary outcomes during follow-up, apart from the composite outcome of any major hemorrhagic or occlusive event.

For the primary outcome, 22 of 268 participants (8.2%) allocated to start antiplatelet therapy had recurrent ICH compared with 25 of 268 participants (9.3%) allocated to avoid antiplatelet therapy (adjusted HR, 0.87; 95% CI, 0.49-1.55; P = .64) (Table 1, Table 2, and Figure 2), without a significant risk difference in any individual year of follow-up (eTable 7 in Supplement 1). This finding was similar in unadjusted and adjusted models and in 2 sensitivity analyses that involved the addition of symptomatic stroke of uncertain subtype or death of undetermined cause (Table 2). At the time of their recurrent ICH, 3 of the 22 participants (13.6%) in the start antiplatelet therapy group were not taking an antiplatelet agent, and 6 of the 25 participants (24.0%) assigned to avoid antiplatelet therapy were taking an antiplatelet agent. There was no evidence of heterogeneity of the effects of antiplatelet therapy on the primary outcome in prespecified exploratory subgroup analyses (eFigure 1 in Supplement 1).

For the composite secondary outcomes, no significant differences were found between participants assigned to start vs avoid antiplatelet therapy during the entire period of follow-up (Table 2). For the composite secondary outcome of all major vascular events (ie, nonfatal myocardial infarction, nonfatal stroke [ischemic, hemorrhagic, or uncertain cause], or death from a vascular cause) as used by the Antithrombotic Trialists Collaboration,8,12 which seemed to be reduced by starting antiplatelet therapy in the main results of the trial (adjusted HR, 0.65; 95% CI, 0.44-0.95; P = .03),14 no statistically significant reduction was found for the entire period of extended follow-up (Table 2). However, during the first 3 years of follow-up when almost all trial participants were followed up until they were censored or an outcome occurred, signifi-
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Original Investigation Research

Figure 3

The sample size and number of outcomes in RESTART were too small to be definitive. Most participants were male. 27 Although we did not blind the assigned treatment to participants and physicians, the outcomes were objective and adjudicated blinded to treatment allocation, which minimizes bias. 28 Adherence to the allocated treatment decreased over time but was greater than 80% even after 5 years of follow-up and did not seem to be affected by the publication of the main results. Some of the secondary composite outcomes included venous thromboembolism, which may not be affected by antiplatelet therapy that principally reduces the risk of occlusive arterial events by reducing platelet aggregation 29; this effect may explain why an early effect of antiplatelet therapy after 1, 2, and 3 years.

Our findings are consistent with the expected effects of antiplatelet therapy. 8 However, extended follow-up in RESTART still lacked the power to detect these effects with precision, despite a 70% increase in the total person-years of follow-up from 1064 to 1805, a 34% increase in primary outcomes from 35 to 47, and a 45% increase in major vascular events from 110 to 159. 14 The change in the nonsignificant magnitude and precision of the effect of antiplatelet therapy on recurrent spontaneous ICH that we have observed after extended follow-up may reflect the small numbers of these outcomes in the main results 14; the 95% CI of the estimate of the effect of aspirin on hemorrhagic stroke when used for secondary prevention of occlusive vascular disease (rate ratio, 1.67; 95% CI, 0.81–3.44) 8 includes the effect of antiplatelet therapy on recurrent spontaneous ICH in the extended follow-up of RESTART (adjusted HR, 0.87; 95% CI, 0.49–1.55). Furthermore, more than half of the reduction in major vascular events observed after starting vs avoiding antiplatelet therapy in the main results of RESTART (45 vs 65; adjusted HR, 0.65; 0.44–0.95) was attributable to the difference in recurrent spontaneous ICH (12 vs 23); the numbers of participants with recurrent spontaneous ICH after extended follow-up is similar (22 vs 25), making the observed differences in major vascular events in the first 3 years (eTable 8 in Supplement 1) less driven by differences in numbers with recurrent ICH. 14

To our knowledge, RESTART remains the only completed randomized clinical trial that compares starting vs avoiding antiplatelet therapy after ICH. 10 We minimized selection bias by using central, computerized random sequence generation and concealing allocation on the web application until all baseline data were entered. Event rates in RESTART were comparable to community-based studies in the UK. 5 Blood pressure was controlled comparably in RESTART were comparable to community-based studies in the UK. 5

Limitations

The sample size and number of outcomes in RESTART were too small to be definitive. Most participants were male. 27 Although we did not blind the assigned treatment to participants and physicians, the outcomes were objective and adjudicated blinded to treatment allocation, which minimizes bias. 28 Adherence to the allocated treatment decreased over time but was greater than 80% even after 5 years of follow-up and did not seem to be affected by the publication of the main results. Some of the secondary composite outcomes included venous thromboembolism, which may not be affected by antiplatelet therapy that principally reduces the risk of occlusive arterial events by reducing platelet activation and aggregation 29; this effect may explain why an early effect of antiplatelet therapy after 1, 2, and 3 years.

Discussion

During extended follow-up of participants in RESTART for a median of 3.0 years, survivors of an ICH that occurred while they were receiving antithrombotic therapy who were assigned to start antiplatelet therapy experienced similar numbers of ICH recurrences compared with participants assigned to avoid antiplatelet therapy. Effects on various secondary outcomes were not significant, but significantly fewer major vascular events occurred after allocation to start antiplatelet therapy after 1, 2, and 3 years.

No differences were found in the distribution of the modified Rankin scale score during extended follow-up (eTable 8 in Supplement 1). Few serious adverse events occurred, which were neither outcomes nor expected complications of stroke (eTable 9 in Supplement 1).

Table 1. Frequencies of the First Occurrence of Primary and Secondary Outcome Events During Follow-up

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%) of participants</th>
<th>Start antiplatelet therapy (n = 268)</th>
<th>Avoid antiplatelet therapy (n = 268)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent symptomatic spontaneous intracerebral hemorrhage</td>
<td>22 (8.2)</td>
<td>25 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Arterial events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major hemorrhagic events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous or traumatic intracranial extracerebral hemorrhage</td>
<td>6 (2.2)</td>
<td>4 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Major extracranial hemorrhage</td>
<td>6 (2.2)</td>
<td>2 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Major occlusive vascular events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>28 (10.4)</td>
<td>39 (14.6)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11 (4.1)</td>
<td>10 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Peripheral arterial occlusion</td>
<td>8 (3.0)</td>
<td>3 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>13 (4.9)</td>
<td>26 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Retinal arterial occlusion</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mesenteric ischemia</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stroke of uncertain subtype</td>
<td>1 (0.4)</td>
<td>5 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Venous events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>8 (3.0)</td>
<td>2 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>5 (1.9)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal outcome event</td>
<td>22 (8.2)</td>
<td>24 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Other cardiovascular death</td>
<td>8 (3.0)</td>
<td>13 (4.9)</td>
<td></td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>3 (1.1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular deaths</td>
<td>52 (19.4)</td>
<td>53 (19.8)</td>
<td></td>
</tr>
<tr>
<td>Deaths of undetermined cause</td>
<td>2 (0.7)</td>
<td>5 (1.9)</td>
<td></td>
</tr>
</tbody>
</table>

Significant differences were found in the cumulative risk of all major vascular events between participants assigned to start vs avoid antiplatelet therapy after 1 year (cumulative risk difference, −7.0%; 95% CI, −12.6 to −1.4), 2 years (cumulative risk difference, −8.9%; 95% CI, −15.7 to −2.1), and 3 years (cumulative risk difference, −7.8%; 95% CI, −12.6 to −2.1) (Figure 3; eTable 7 in Supplement 1).
antiplatelet therapy was detected on major vascular events but not on other composite outcomes (Table 2). Participants were recruited from similar state-funded healthcare services in 4 countries of the UK, but the generalizability of our findings to other populations is unknown.

These findings alongside published observational studies provide reassurance about the use of long-term antiplatelet therapy after ICH associated with antithrombotic therapy. Since RESTART’s main results were published, 1 stroke guideline has recommended, “In patients with an indication for continued antiplatelet treatment, resuming antiplatelet therapy is reasonable (Evidence Level B).” However, we did not observe a change in participants’ adherence during extended follow-up after the main results were published, so patients and guidelines will require greater strength and certainty of evidence to change clinical practice.

A much larger randomized clinical trial could investigate several remaining uncertainties about antiplatelet therapy after ICH, including whether there is an overall reduction in major vascular events after ICH of similar magnitude to that seen in patients without ICH; whether time since ICH and duration of antiplatelet therapy modify these effects; whether effects vary in other subgroups (such as lobar ICH location, which is a risk factor for ICH recurrence [Evidence Level B]); and whether antiplatelet therapy is beneficial for ICH survivors without prior antithrombotic drug use or major vascular events.

Table 2. Risks of First Occurrence of Primary and Secondary Outcome Events During Extended Follow-up

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%) of participants</th>
<th>Unadjusted hazard ratio</th>
<th>Adjusted hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent symptomatic spontaneous intracerebral hemorrhage</td>
<td>Start (n = 268)</td>
<td>Avoid (n = 268)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 (8.2)</td>
<td>25 (9.3)</td>
<td>0.87 (0.49-1.54) .63</td>
</tr>
<tr>
<td>Recurrent symptomatic spontaneous intracerebral hemorrhage or symptomatic stroke of uncertain subtype</td>
<td>23 (8.6)</td>
<td>28 (10.4)</td>
<td>0.81 (0.47-1.41) .46</td>
</tr>
<tr>
<td>Recurrent symptomatic spontaneous intracerebral hemorrhage or death of undetermined cause</td>
<td>25 (9.3)</td>
<td>33 (12.3)</td>
<td>0.76 (0.45-1.27) .29</td>
</tr>
<tr>
<td>All major hemorrhagic events (all types of symptomatic spontaneous or traumatic intracerebral hemorrhage or symptomatic major extracranial hemorrhage)</td>
<td>32 (11.9)</td>
<td>30 (11.2)</td>
<td>1.07 (0.65-1.75) .80</td>
</tr>
<tr>
<td>All major occlusive vascular events (ischemic stroke, myocardial infarction, mesenteric ischemia, peripheral arterial occlusion, deep vein thrombosis, pulmonary embolism, or carotid/coronary/peripheral arterial revascularization procedures)</td>
<td>57 (21.3)</td>
<td>53 (19.8)</td>
<td>1.08 (0.74-1.56) .70</td>
</tr>
<tr>
<td>Major occlusive vascular events (as proposed in the trial protocol)</td>
<td>65 (24.3)</td>
<td>71 (26.5)</td>
<td>0.90 (0.64-1.26) .53</td>
</tr>
<tr>
<td>Major vascular events (as proposed in the trial protocol: nonfatal myocardial infarction, nonfatal stroke, or death from a vascular cause [including sudden death, pulmonary embolism, hemorrhage, and death from an unknown cause])</td>
<td>72 (26.8)</td>
<td>87 (32.5)</td>
<td>0.79 (0.58-1.08) .16</td>
</tr>
</tbody>
</table>

Figure 2. Risk of the First Occurrence of Recurrent Symptomatic Intracerebral Hemorrhage

Figure 3. Risk of the First Occurrence of a Major Vascular Event
Conclusions

After final, extended follow-up of the only completed randomized clinical trial of antiplatelet therapy after ICH, no statistically significant increase in the risk of recurrent ICH after restarting antiplatelet therapy was found. This finding provides physicians with some reassurance about the use of antiplatelet therapy after ICH if secondary prevention of major vascular events.

ARTICLE INFORMATION

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Author Contributions: Dr Al-Shahi Salman and Ms Rodriguez had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Group Information: The members of the RESTART Collaboration are listed in Supplement 3.

Meeting Presentation: This paper was presented at ESOC 2021, the 7th European Stroke Conference; September 3, 2021; virtual conference.


Additional Contributions: Imaging acquisition, processing, and data collection were performed at the Edinburgh Imaging Facility, University of Edinburgh, which is part of the SINAPSE (Scottish Imaging Network: A Platform for Scientific Excellence) collaboration (funded by the Scottish Funding Council and the Chief Scientist Office). We thank the British Heart Foundation for funding the trial, continuing to support it while recruitment was ongoing, and all serious vascular events.

REFERENCES

1. Béjot Y, Cordonnier C, Durier J, Aboa-Eboulé C, Rouaud O, Giroud M. Intracerebral haemorrhage profiles are changing: results from the Dijon Clinical Trials Unit staff for their involvement.


32. Girotra T, Feng W. Effects of antiplatelet therapy after stroke due to intracerebral hemorrhage (RESTART): are neurologists feeling more comfortable to RESTART antiplatelet? Ann Transl Med. 2019;7(suppl 6):5214. doi:10.21037/atm.2019.08.84

