Selected Summaries

Antiplatelet therapy after intracerebral haemorrhage

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SUMMARY

In this multicentric trial conducted between May 2013 and May 2018 in 122 hospitals in the United Kingdom, the RESTART collaboration randomized 537 adults (≥18 years) who had a spontaneous intracerebral haemorrhage (ICH) while on antithrombotic drugs (antiplatelets or anticoagulants) for occlusive vascular disease. Seventy-five per cent of patients were taking either aspirin or clopidogrel and about 20% were on oral anticoagulants at the onset of ICH. ICH may be due to antithrombotic therapy or due to hypertension and/or smoking, which are risk factors common for both ischaemic stroke and ICH. These patients were taking antithrombotic therapy to prevent ischaemic events to which they remained at risk even after ICH. Restarting anticoagulants would have posed a higher risk of recurrent ICH than that of antiplatelets. Therefore, restarting antiplatelet therapy was tested in the trial. The patients were randomly allocated to either start (268 patients) or avoid (269 patients, one withdrew) antiplatelet therapy. The patients were followed up for 5 years (median 2 years) to record the primary outcome—recurrent symptomatic ICH and two of the secondary outcomes—a composite of all major haemorrhagic events and a composite of all major occlusive vascular events.

The study design was parallel-group, pragmatic, randomized, open-label trial with blinded end-point assessment. The investigators could not achieve the planned sample size of 720 patients even after the period of recruitment was extended by 1 year and, therefore, they increased the duration of follow-up by 1 year to accrue the planned number of person-years of follow-up.

The results were contrary to the expectations. Twelve (4%) of 268 participants allocated to start antiplatelet therapy had recurrence of ICH compared with 23 (9%) of 268 participants who did not start antiplatelet therapy (adjusted hazard ratio [HR] 0.51; 95% CI 0.25 to 1.03, p=0.06). For the composite secondary outcomes, 18 (7%) of 268 participants allocated to start antiplatelet therapy experienced major haemorrhagic events compared with 25 (9%) of 268 participants allocated to avoid antiplatelet therapy (adjusted HR 0.71; 95% CI 0.39 to 1.30, p=0.27). Thirty-nine (15%) of 268 participants in the antiplatelet group had major occlusive vascular events compared with 38 (14%) of 268 participants in the avoidance group (adjusted HR 1.02; 95% CI 0.65 to 1.60, p=0.92).

COMMENT

RESTART is an example of how a well-planned and well-executed trial may become 'uninformative' due to unexpectedly slow recruitment resulting in smaller than planned sample size and small number of events, pointing in a direction contrary to the expectation.

The trial has maximized internal validity through the choice of pragmatic, randomized design. The process of random allocation achieved concealment through the use of a central, web-based assignment and email communication. Baseline balance of major prognostic factors was ensured through incorporation of minimization algorithm. Although participants and clinicians were aware of the treatment assignment, the end-point assessors were masked to it. Outcome event adjudicators were also masked to treatment allocation and use of antithrombotic drug. The study achieved 99% follow-up through completion of questionnaire by primary care practitioners (79% by post, 16% by telephone and 4% by both), and 99% of participants or their caregivers also completed the follow-up questionnaire at 6 months or 1 year, 98% at 3 years and 94% at 4 years.

Poor adherence to allocated treatment may threaten internal validity. However, it was reasonably good in this trial (99% at discharge, 93% after 6 months or 1 year, 89% after 2 years, 86% after 3 years and 82% after 4 years). The participants also had good control over their blood pressure (median systolic BP 130 mmHg). Unfortunately, there were small numbers of events: only 41 recurrent symptomatic spontaneous ICH. Furthermore, most probably by chance, the distribution of ICH across the two arms was contrary to expectations (27 in the avoid antiplatelet

therapy group against only 14 in the start antiplatelet therapy group).

How does one interpret such counter-intuitive results? How can avoiding antiplatelet therapy be associated with increase in ICH? There is no valid biological explanation for this, though the authors of the article have attempted to explain this citing some tenuous reasons such as 'arterial thrombosis can trigger haemorrhage'. If this was so, the large antiplatelet trials for primary prevention of stroke would have detected it with greater precision. Most probably, this is a spurious association which in general can arise due to bias, confounding or chance.

Bias including confounding is controlled well through random allocation and blinded outcome assessment and, therefore, the most probable explanation of the counter-intuitive results is 'chance'. This is reflected in p=0.057 (log-rank test), 0.62 (unadjusted analysis) and 0.60 (adjusted analysis)—all statistically non-significant and 95% CIs which include 1. More important than the p value and CI is the fact that antithrombotic therapy appeared to reduce ICH—a finding inconsistent with biology and the results of major antiplatelet trials.[1]

Another problem with this trial is its low power. Small number of events in a trial diminishes its power and replicability.[2] Even if we accept the authors' conclusion that starting antiplatelet therapy is safer than avoiding it, the low power associated with the small number of events means that probability of this discovery being true is low. There is a phenomenon called 'winner's curse' which means that the lucky scientist who makes the discovery in a small study is cursed by finding an inflated size of effect. Such findings have low replicability. For example, in 2011, *Lancet Neurology* published the randomized, placebo-controlled FLAME trial,[3] which was conducted at nine centres in France. The trial was small with 118 adult patients; 59 patients each in fluoxetine (20 mg once per day, orally) arm and placebo arm. At the end of 3 months, motor score (Fugl Meyer motor scale) was statistically significantly greater in the fluoxetine group (mean 34.0 points) than in the placebo group (mean 24.3 points) with p=0.003. A large trial with 3127 patients could not demonstrate any benefit of fluoxetine at 6 months.[4]

Therefore, the RESTART trial is an uninformative trial. More trials are needed to establish the safety of restarting antithrombotic therapy in patients who develop ICH while on antithrombotic therapy for the prevention of occlusive vascular diseases.

Conflicts of interest. None declared

REFERENCES

1 Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, *et al*. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373:**1849–60.

2 Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, *et al*. Power failure: Why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci* 2013;**14:**365–76.

3 Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, *et al*. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): A randomised placebo-controlled trial. *Lancet Neurol* 2011;**10:**123–30.

4 FOCUS Trial Collaboration. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): A pragmatic, double-blind, randomised, controlled trial. *Lancet* 2019;**393:**265–74.

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