# Risks of Overinterpreting Interim Data

## Lessons From the TOTAL Trial (Thrombectomy With PCI Versus PCI Alone in Patients With STEMI)

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Thrombus aspiration in ST-segment–elevation myocardial infarction has been an area of intense debate among interventional cardiologists. A prior single-center trial (n=1071) observed an unexpected nearly 50% reduction in mortality with routine thrombus aspiration.[1] These findings led to the development of the randomized trial of routine aspiration TOTAL (Thrombectomy With PCI Versus PCI Alone in Patients With STEMI; n=10 732).[2] During the conduct of the TOTAL trial, thrombus aspiration was recommended by guidelines and was commonly used in clinical practice and believed to improve patient outcomes.

In the TOTAL trial, thrombus aspiration did not reduce the primary outcome of cardiovascular death, myocardial infarction, cardiogenic shock, or heart failure at 180 days but was associated with a significant increase in stroke at 30 days.

The objective of this research letter is to show the importance of a data monitoring committee (DMC) continuing a trial despite emerging treatment findings.

A Cox proportional hazards model was used to compare patients randomized to thrombus aspiration with percutaneous coronary intervention (PCI) and PCI alone. A modified intent-to-treat analysis was prespecified to include only patients who underwent PCI because patients were randomized before angiography. Outcomes presented are at 30 days given that during early analyses data at longer-term follow-up had few patients and were not reliable. The data were compiled from actual DMC reports. The outcomes analyzed for this article include the primary outcome (cardiovascular death, myocardial infarction, cardiogenic shock, or heart failure), death, and stroke. The stopping guidelines for efficacy were exceeding a difference of 4 SDs at the first interim analysis or 3 SDs at the second interim analysis for the primary outcome and 3 SDs at the first interim analysis and 2 SDs at the second interim analysis for mortality.

An institutional review committee approved the trial at sites, and subjects gave informed consent.

At the first interim analysis in December 2012, with 2791 patients who were randomized and underwent PCI (2520 patients completed 30 days), there was a significant reduction in death at 30 days, with 22 (1.6%) in the thrombus aspiration group versus 39 (2.8%) in the PCI alone group (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.33–0.93; *P*=0.025; Figure) with no statistically significant increase in stroke: 11 (0.8%) in the thrombus aspiration versus 5 (0.4%) the PCI alone group (HR, 2.15; 95% CI, 0.75–6.19; *P*=0.16; Figure). There was no significant reduction in the primary outcome, and the DMC elected to continue the trial.

As the trial progressed, the effect on death was no longer significant, and the increase in stroke became apparent. At the end of the trial, with 10 064 patients who underwent PCI and were included in the primary analysis, stroke occurred in 33 (0.7%) in the thrombus aspiration group versus 16 (0.3%) in PCI

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**Key Words:** myocardial infarction ■ percutaneous coronary intervention

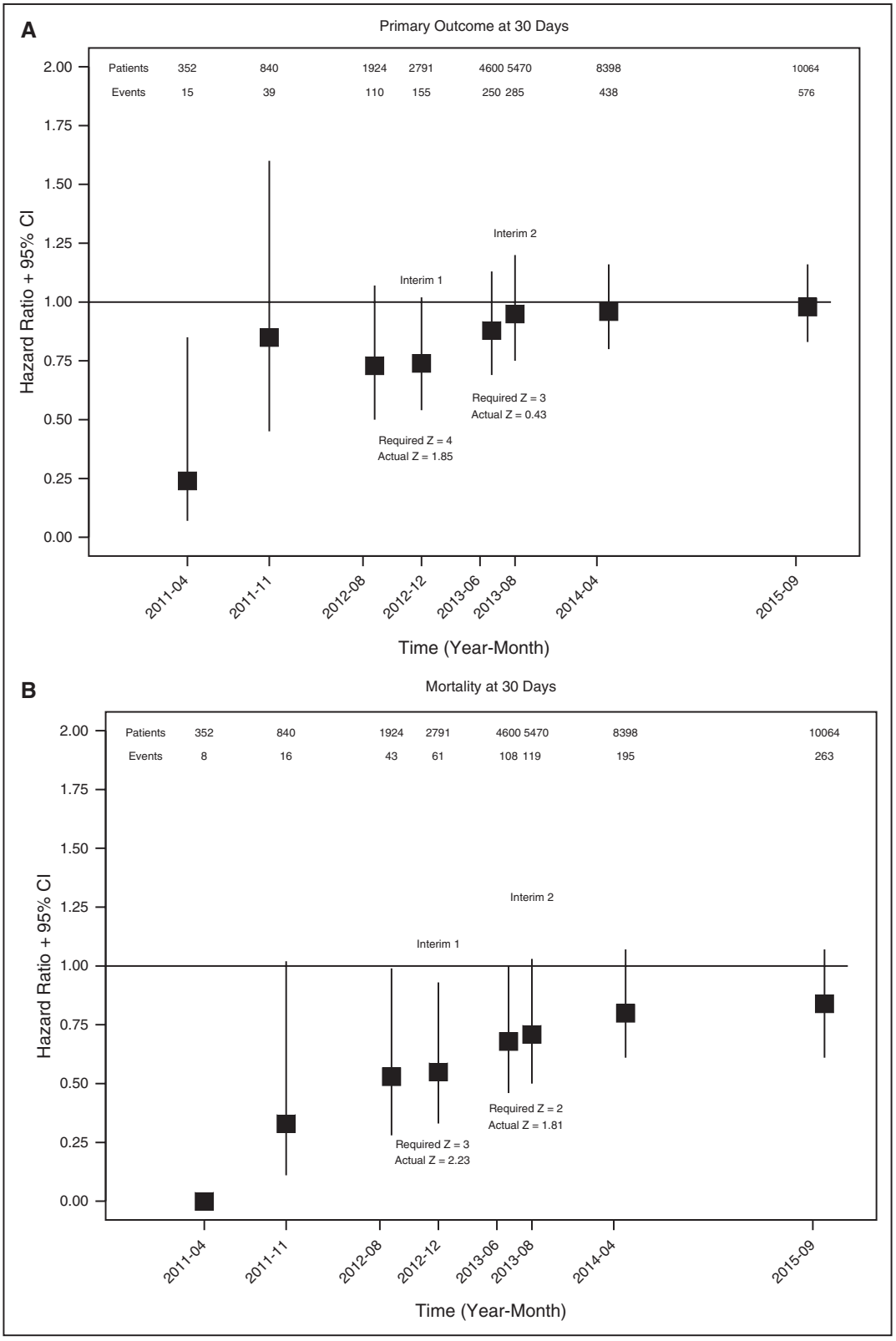


**Figure. Interim analyses for the TOTAL trial.**
**A**, Interim analyses for the primary outcome. **B**, Interim analyses for death. **C**, interim analyses for stroke. CI indicates confidence interval. (*continued*)

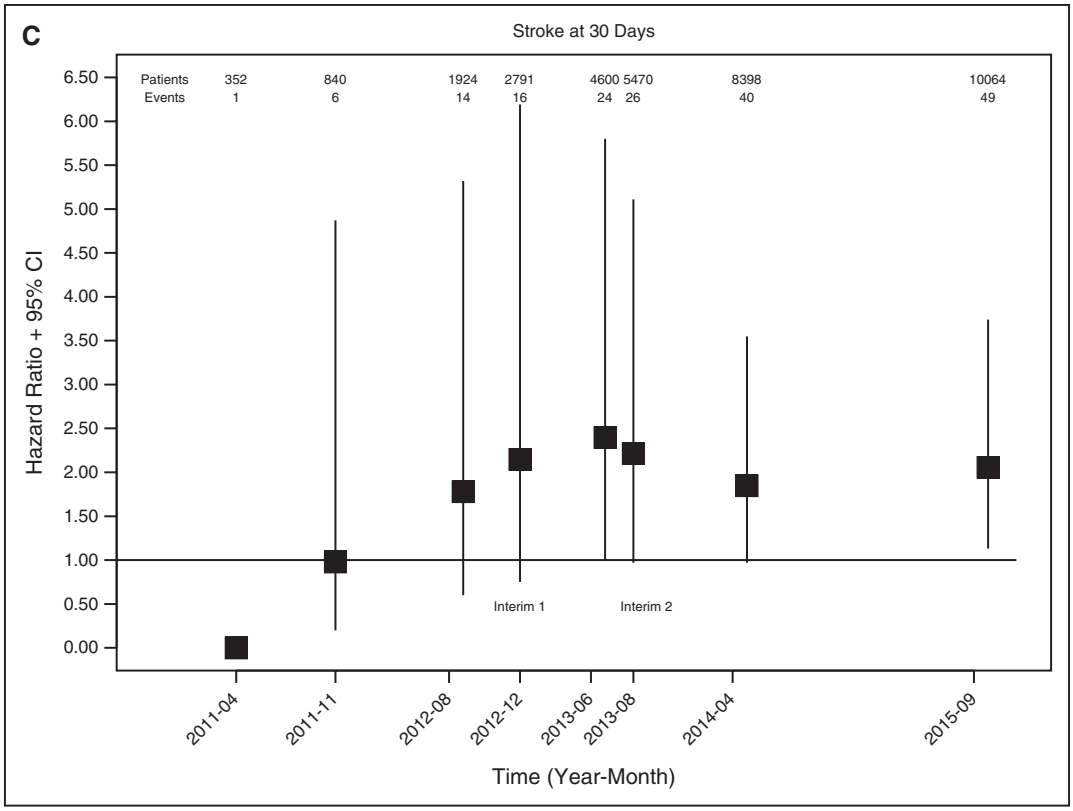


**Figure Continued.**

alone group (HR, 2.06; 95% CI, 1.13–3.75; *P*=0.02) at 30 days. There was no significant reduction in the primary outcome (353 [7.0%] in the thrombus aspiration group versus 355 [7.1%] in the PCI alone group; HR, 0.99; 95% CI, 0.85–1.15) or death at 180 days (176 [3.5%] in the thrombus aspiration group versus 188 [3.7%] in the PCI alone group; HR, 0.93; 95% CI, 0.76–1.14; *P*=0.50).

Before the TOTAL trial, routine thrombus aspiration during primary PCI was thought to reduce mortality on the basis of the TAPAS trial (Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study), and guidelines recommended it. On the basis of this preexisting evidence and the emerging treatment findings in TOTAL, if the DMC had stopped the trial early, the stroke finding would not have been uncovered, and the mortality benefit would have been overestimated. Because the results of the TOTAL trial showed no benefit and an increased stroke rate, routine thrombus aspiration is now no longer recommended in the guidelines (Class III indication).[3]

A systematic review of randomized trials that were stopped early for benefit versus those that continued for the same question showed that trials that were stopped early provided biased estimates of treatment effect.[4] Trials stopped early showed a nearly 30% greater treatment effect than trials continued for the same question. These results and the case example of the TOTAL trial suggest that it is important for the DMC to avoid stopping a trial early for benefit on the basis of small numbers of events. It should be noted that the stopping guideline was not crossed for the first interim analysis, which required a difference exceeding 3 SD for mortality at the first interim analysis. In addition, external data from other trials should affect the decision to stop or continue a trial. During TOTAL, the TASTE trial (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) was published and demonstrated no reduction in mortality with thrombus aspiration, but it was published after the first interim analysis.[5]

DMCs play an important role for safety events such as stroke in TOTAL and base their decisions on the totality of the data.

In summary, small trials or trials stopped early are more susceptible to bias and should be interpreted cautiously, and in general, premature termination of trials for presumed efficacy should be avoided. The interim analyses of TOTAL, in the context of the previous trials, highlight the important role that DMCs play.

## SOURCES OF FUNDING

The TOTAL trial was funded by the Canadian Institutes of Health Research and Medtronic.

## DISCLOSURES

Drs Wyse, Bhatt, and Wells were members of the DMC, and the remaining authors were part of the steering committee. Drs Jolly, Gao, Yusuf, Džavík, and Cairns received institutional grant support from Medtronic. Dr Bhatt discloses the following relationships: advisory board, Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; board of directors, Boston VA Research Institute, Society of Cardiovascular Patient Care; chair, American Heart Association Quality Oversight Committee; DMCs, Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, and Population Health Research Institute (including for the TOTAL trial); honoraria, American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor in chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor, associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (CME steering committees); other, *Clinical Cardiology* (deputy editor), National Cardiovascular Data Registry-ACTION Registry Steering Committee (chair), and Veteran Affairs Clinical Assessment Reporting and Tracking Research and Publications Committee (chair); research funding, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, and The Medicines Company; royalties, Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); site coinvestigator, Biotronik, Boston Scientific, and St. Jude Medical (now Abbott); trustee, American College of Cardiology; and unfunded research, FlowCo, Merck, PLx Pharma, and Takeda.

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## FOOTNOTES

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because of agreements with sponsor.

*Circulation* is available at http://circ.ahajournals.org.

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*Circulation.* 2018;137:206-209
doi: 10.1161/CIRCULATIONAHA.117.030656
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539