The BMJ
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Cite this as: *BMJ* 2024;387:q2550
http://doi.org/10.1136/bmj.q2550
Published: 11 December 2024

INVESTIGATION

Doubts over landmark heart drug trial: ticagrelor PLATO study

A top selling antiplatelet drug has never quite shaken off doubts about its advantage over cheaper rivals. With generic versions of ticagrelor about to launch, Peter Doshi takes a fresh look at the evidence

Peter Doshi *senior editor*

Over the past decade the antiplatelet drug ticagrelor (Brilinta in the US and Brilique in Europe) has become firmly established in the treatment of acute coronary syndrome, recommended in guidelines from cardiology societies across the world.[1-3] As the only P2Y12 inhibitor still under patent in the US, the public expenditure is substantial, accounting for around two thirds of the total cost of P2Y12 inhibitors despite less than 10% of total prescriptions.[4] In 2022, the US federal government spent more than $750m (£593m; €712m) on ticagrelor.

But since its 2011 approval by the US Food and Drug Administration (FDA) doubts have grown about its apparent advantage over cheaper, off patent P2Y12 inhibitors like clopidogrel and prasugrel. While AstraZeneca, ticagrelor's manufacturer, reported superior efficacy to clopidogrel in the phase 3 trial that brought the drug to market, studies in the post-licensure period have repeatedly reported disappointing results,[5-14] showing similar efficacy to clopidogrel but with increased bleeding and dyspnoea, prompting calls for a reappraisal of guidelines.[15 16]

With generic versions of ticagrelor expected soon in the US, *The BMJ* took a fresh look at the evidence. Our investigation found AstraZeneca's drug was approved over the emphatic objections of FDA scientific review staff, and that ticagrelor's major clinical trial, named PLATO, was the focus of a long and rancorous dispute over its basic reliability. *The BMJ* can also disclose new details on the controversy after obtaining primary PLATO trial records and unpublished data through a freedom of information request that shows further problems in data reporting.

The US paradox

When AstraZeneca developed ticagrelor in the mid-to-late 2000s, it needed to demonstrate a clear advantage over clopidogrel (Plavix), then one of the world's best selling prescription drugs that was nearing patent expiration. The results of PLATO, a 18 624 patient randomised trial conducted across 43 countries, appeared set to actualise those hopes. PLATO investigators, writing in 2009 in the *New England Journal of Medicine* (*NEJM*), reported that at 12 months, patients assigned to ticagrelor compared with clopidogrel saw a reduction in risk of the primary endpoint—death from vascular causes, myocardial infarction, or stroke—from 11.7% to 9.8%, a 16% decrease in relative risk.[17]

Despite the results, however, the company's first bid for FDA approval failed. A subgroup analysis found that, in the US, ticagrelor patients had poorer outcomes than those randomised to clopidogrel—a 27% higher risk of the primary endpoint (fig 1).[18]

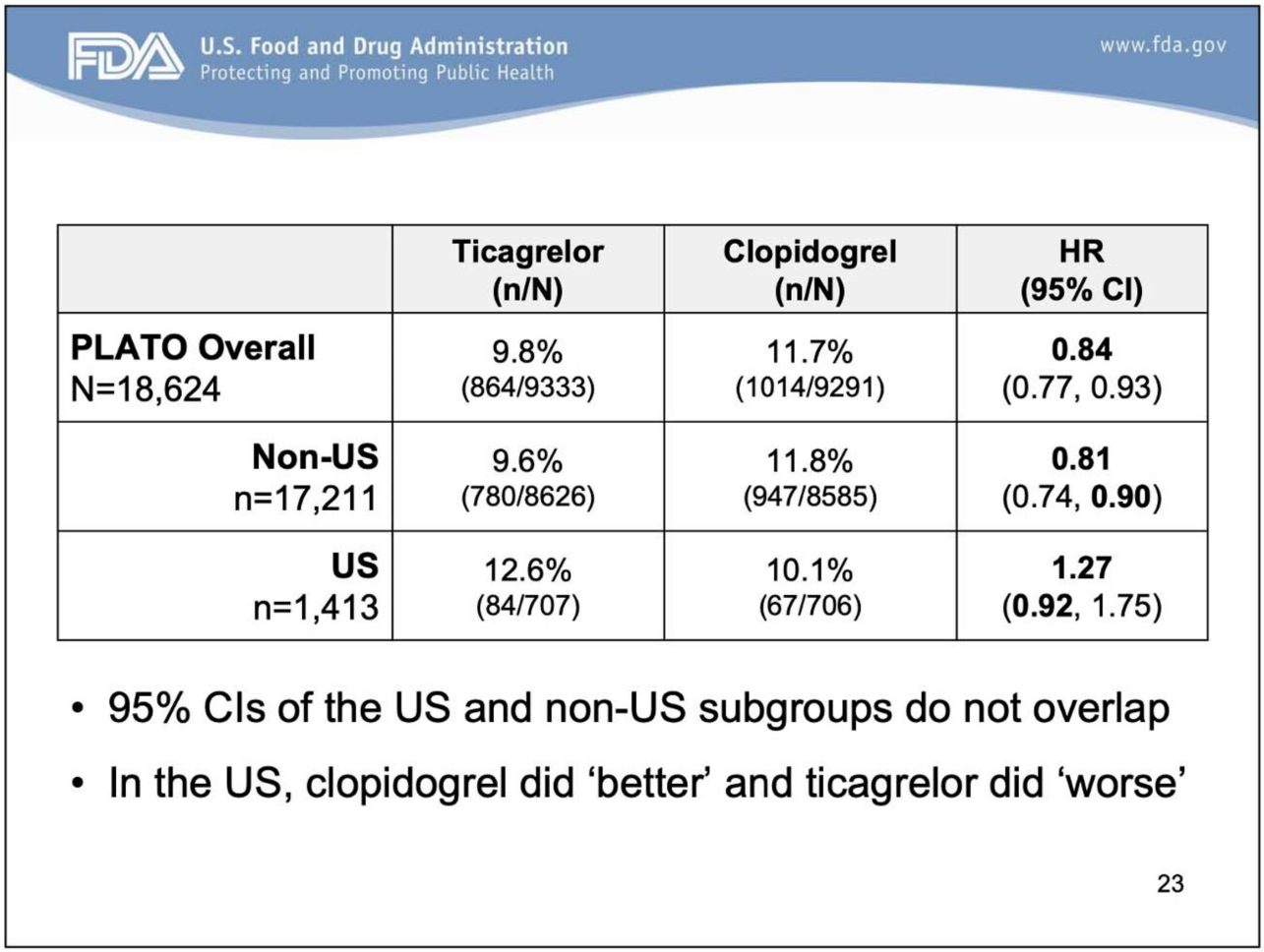

Fig 1 | FDA presentation slide from July 2010 showing PLATO's primary endpoint results: overall and comparing US *v* non-US trial sites[18]

AstraZeneca made efforts to explain that the unfavourable results were because of an unusually high aspirin dose seen almost exclusively in the US. But FDA scientists were unconvinced.

External advisers to FDA were equally concerned. At a day long meeting in 2010, organised by FDA to discuss AstraZeneca's application, advisory committee members voted 7-1 recommending ticagrelor's approval but urged FDA to require a post-approval trial in the US population.[19] Instead of approving and requiring such a study—an option under a 2007 US law—FDA invited AstraZeneca to resubmit its application with a more detailed analysis of the aspirin hypothesis.

FDA approves ticagrelor despite deepening doubts

Thomas Marciniak, an FDA medical officer with an atypical reputation for thorough reviews of drug company applications,[20 21] was assigned to evaluate AstraZeneca's resubmission. Months later, Marciniak found himself not only unconvinced of AstraZeneca's aspirin hypothesis, but deeply concerned over the basic reliability of PLATO trial data.

"I now conclude that there are sufficient problems with PLATO data quality such that, at best, the US results are representative of ticagrelor's efficacy, i.e., ticagrelor is inferior to clopidogrel in efficacy and safety," he wrote in 2011 in an unsparing 47 page review memorandum, recommending against approval.[22]

Marciniak called AstraZeneca's application "the worst in my experience regarding completeness of the submissions and the sponsor responding completely and accurately to requests."[22] But FDA leadership declined to endorse Marciniak's extensive reservations. Whether the US results were simply the play of chance or the consequence of differences in aspirin dose, a senior agency administrator reasoned that "ticagrelor should be approved."[23]

Lloyd Klein, a clinical professor of medicine at the University of California in San Francisco and an expert on the clinical value of P2Y12 inhibitors, told *The BMJ*, "At the time it was widely understood that the aspirin dosage issue was the method the company grasped as a way to move forward with FDA approval, recognising that the outcomes data in the US was different than in European centres. But there were no existing prospective trials to test if that hypothesis was accurate."[24]

A saga intensifies

Ticagrelor's approval provoked a steady stream of criticism from those who maintained that the published PLATO trial results could not be trusted.[25 26] Critics said it was noteworthy that ticagrelor failed in the US, the only high enrolling country where sites were not monitored by the sponsor itself.

Trial executive committee co-chairs Robert Harrington, then at Duke Clinical Research Institute, and Lars Wallentin, from Uppsala

Clinical Research Center in Sweden, have co-authored dozens of responses defending PLATO. They have accused their critics of "bad science"—cherry picking, self-citation, and "disregard [for] conventional statistical probability concepts"—and questioned their motives.[27-29]

The saga has played out across several cardiology journals and continues to this day. But the controversy reached a pinnacle in 2013 when the US Department of Justice opened a formal probe into PLATO that October,[30 31] followed the next month by questions from the European Medicines Agency, drawing the attention of news media and investors.[32]

The US justice department's civil investigation was guided by Victor Serebruany, an adjunct faculty member at Johns Hopkins University and arguably PLATO's earliest—and most persistent—critic, to whom FDA turned for help during its pre-approval deliberations. Serebruany was initially impressed by the trial results but became sceptical after noticing inconsistencies and anomalies in the data.[25 33] In September 2012 he sued AstraZeneca in a whistleblowing lawsuit brought in the government's name, for submitting "false and fraudulent data to the US."

But the justice department terminated its investigation in August 2014, and the PLATO investigators expressed vindication. "This decision should remove any remaining doubts about the reliability of the trial results," Wallentin, Harrington, and colleagues wrote in a rapid response on bmj.com.[34] "Now we can focus even more on providing new knowledge on how to best deliver this life saving treatment to our patients with heart attacks." In declining to pursue the whistleblowing lawsuit with Serebruany, however, the justice department wrote in a court filing, that the US government "reserves its right" to revisit its decision.

Asked why the department closed its investigation, a spokesperson for the US Attorney's Office for the District of Columbia told *The BMJ*, "After an extensive investigation . . . we determined that the allegations lacked sufficient merit such that it was not in the best interests of the US to intervene in the suit."

The PLATO paradox

In the years following the justice department's investigation, a host of observational and randomised studies have failed to replicate PLATO's results,[5-14] leading some cardiologists to question ticagrelor's place in clinical practice.[15 16]

Eric Bates, professor of internal medicine at University of Michigan, is a coauthor of the US cardiology guidelines that recommend ticagrelor.[3] He is openly calling for a reappraisal.

Following PLATO, "I was increasingly disturbed by how trial after trial came out as being not dramatically positive in any way," Bates said in an interview with *The BMJ*. In an AstraZeneca funded trial in mostly Japanese patients, for example, ticagrelor patients fared worse than those on clopidogrel, with 9.0% experiencing the primary endpoint versus 6.3% on clopidogrel.[11]

"Every time one of those negative trials came out, the news magazines would quote one of the investigators—who had an intellectual [and] financial bias—discounting it. And I said, 'Wait a second, let's just add up the skeletons here.'"

Bates did just that in a recent review article,[15] cataloguing all the trials that did not confirm benefit. He says the outlier PLATO trial "has no reason to be challenged," but argues that subsequent trials failed to replicate PLATO because patients face a smaller risk of ischaemic events because of improvements in secondary prevention, and increased use of balloon treatments and stents.

Klein also reasons[16] that in the intervening years, improved patient care and devices have played a role. "There were plenty of people, like me, who were sceptical," he said in an interview, "but the data from the randomised trial was the formal study result; and while judging only by clinical experience I would have to say nobody could really discern much of a difference, but then none of us are doing 10 000 patient trials in our practice."

The US results: red herring or coalmine canary?

Others point to a more concerning possibility: that PLATO's results were not credible from the start. These critics contend that the US data were not an aberration but were actually more reliable than other countries like Hungary and Poland.

They highlight that AstraZeneca itself carried out the data monitoring for PLATO except for sites that were monitored by third party contract research organisations (CROs).[25 35] In the four countries exclusively monitored by non-sponsor personnel—Georgia, Israel, Russia, and the US—ticagrelor fared worse.

One PLATO site principal investigator from Eastern Europe who spoke with *The BMJ* said he became sceptical of the overall results after seeing widely divergent results between Georgia and Russia on one hand, and Hungary and Poland on the other (see fig 2). In Georgia and Russia the results numerically favoured clopidogrel. In Hungary and Poland, both AstraZeneca monitored, ticagrelor's benefit over clopidogrel was dramatic. "I remember this regional analysis . . . there is no reason for this difference," he said.

PLATO leadership has attempted to dispel the argument, saying the matter was tackled in an analysis by "two senior academic statisticians." Study co-chairs Wallentin and Harrington wrote that "while it is not possible to draw firm conclusions" from the statistical analysis, "there is no reason to suspect an influence of monitoring organisation on the study outcomes."[36]

The authors of the statistical article, however, did not conduct the most straightforward analysis: overall primary endpoint results for patients at sites monitored by CROs compared with sites monitored by the sponsor.[37]

The BMJ has also found that one of the two "senior academic statisticians" authoring the analysis—Kevin Carroll, the paper's lead author—was AstraZeneca's former chief statistician, having worked at the company for over 20 years. It was Carroll who presented the PLATO results on behalf of AstraZeneca at FDA's 2010 advisory committee meeting. The paper lists Carroll as an "independent statistical consultant" and was submitted for publication the same year he left AstraZeneca but does not disclose his former employment.

Carroll told *The BMJ* that "[with respect to] to CRO, this was carefully investigated," but went on to say that "an analysis of CRO *vs* AstraZeneca makes absolutely no sense" and "we did not report an analysis of CRO *vs* AstraZeneca outcomes." He defended his declaration to *Statistics in Biopharmaceutical Research* that he had no affiliations or financial involvements that could constitute a conflict of interest or apparent conflict of interest, telling *The BMJ* that "all financial interests in AstraZeneca were disposed of" by June 2012, before submitting the article. The article was submitted for publication in August that year.

Unexpected patterns in endpoint adjudication

Assessing a drug's efficacy relies on an accurate tallying of events meeting the primary endpoint definition—in PLATO's case deaths from vascular causes (including fatal bleeding), myocardial infarction (MI), or stroke. A 51 member independent central

adjudication committee, blinded to treatment group, reviewed more than 10 000 events.

But there have been allegations of bias. In his now unsealed legal complaint from 2012, Victor Serebruany alleged that PLATO's adjudicators added 45 MIs to the clopidogrel group, "and precisely zero additional MIs for . . . ticagrelor."

The BMJ was able to confirm Serebruany's numbers. FDA records show that according to site reports there were 504 subjects with MIs on ticagrelor compared with 548 on clopidogrel. Following adjudication, the count increased only for clopidogrel—to 593.

Using trial datasets first obtained from the FDA by Serebruany and subsequently verified through a freedom of information request by *The BMJ*—which contains both pre-adjudication and post-adjudication judgments—we also found an imbalance among 20 death category decisions that the adjudication committee was in "major" disagreement over and ultimately could not resolve: 17 were in the clopidogrel arm while only 3 were in ticagrelor. The disparity raises questions over the possibility of unblinding.

Despite unresolved disagreements over the 20 deaths, a final post-adjudication cause of death classification was recorded. But in six cases, it flipped whether or not the event met the primary endpoint definition compared with the cause of death attribution provided by site investigators. In every case, *The BMJ* found the change in attribution favoured ticagrelor.

Neither adjudication committee co-chairs Kenneth Mahaffey and Claes Held, nor trial co-chairs Harrington and Wallentin, responded to *The BMJ*'s email requests for comment.

AstraZeneca was also presented with a summary of findings in this article but did not request further details and declined to be interviewed. A spokesperson said by email that the company has "nothing to add," and directed *The BMJ* to its 2014 public statement[31] following the US Department of Justice's investigation into PLATO.

Questions over the accuracy of death records

When PLATO's results were first announced, clinicians were struck by ticagrelor's apparent mortality benefit. The FDA's advisory committee meeting transcript shows just how persuasive the data were: at least two advisers stated they voted to approve because of the overall mortality benefit.

Serebruany, too, was initially fascinated with the absolute mortality reduction. A platelet expert, Serebruany struggled to explain the observed benefit. "Claiming that such a remarkable outcome was anticipated is not in agreement with the facts," he wrote in 2010, noting that phase 2 mortality data "actually looked better for clopidogrel."[33]

As Serebruany's initial optimism transformed into deep suspicion over the integrity of the trial data, he began contacting PLATO site investigators around the world, requesting their assistance in verifying the death data. Many cooperated—some, such as in Mexico and Canada, even shared original trial documents. But records did not always match.[38]

At one site in South East Asia, a PLATO investigator wrote Serebruany, in an email seen by *The BMJ*, saying, "There were no deaths from our PLATO patients. That is almost certain." But according to data submitted to FDA and reviewed by *The BMJ*, four deaths occurred at this site (three in the clopidogrel group), raising questions about the accuracy of reporting to FDA. *The BMJ* also saw site level records where the date of patient death did not match the date in FDA's dataset.

In Canada, *The BMJ* spoke with Jean-François Tanguay, professor of medicine at Université de Montréal, who was not involved in PLATO but says what was reported to FDA is inaccurate. Tanguay obtained trial records, seen by *The BMJ*, that describe the death of a PLATO patient that was "clearly a vascular death." But according to the database AstraZeneca provided FDA, site investigators classified it as a death from cancer. Tanguay said it did not resemble a late stage cancer death. The idea that the site investigators would have labelled the death as being from cancer, he said, was "quite a stretch."

The BMJ's analysis also found omissions in PLATO's landmark publication. The paper, published in *NEJM* and reported as an intent-to-treat analysis, reports 905 total deaths from any cause among all randomised patients.[17] An internal company report states, however, that 983 patients had died at this point. While 33 deaths occurred after the follow-up period, the *NEJM* tally still leaves out 45 deaths "discovered after withdrawal of consent." *The BMJ* obtained some records for patients whose deaths were not reported in *NEJM* (see table 1) and asked the journal for a response.

The *NEJM* did not dispute the error, but said it was uncertain about publishing a correction. Citing new (but not yet public) guidelines from the International Committee of Medical Journal Editors (ICMJE), *NEJM* editor in chief Eric Rubin told *The BMJ* that "for older manuscripts, correction is not necessarily appropriate unless there would be an effect on clinical practice," concluding that "it does not appear that correcting this 15-year-old article is going to have any impact." (Current ICMJE guidance states: "Corrections are needed for errors of fact.") Rubin added, "In fact, the FDA, using the data that you [BMJ] provide, approved the drug."

Nonetheless, Rubin said he would attempt to contact the authors. "But, if we are unable to reach them or they are unable to access the data, we would most likely not proceed with corrections.

"We have written to [PLATO trial co-chair] Dr Harrington and await a reply. We will then decide how to move forward."

Resolution

Fifteen years after PLATO, Serebruany continues to publish critiques. Since 2016, many of these have been coauthored by Marciniak, now retired from the FDA. The PLATO investigators, however, appear largely to have stopped responding.

In an interview with *The BMJ*, Serebruany expressed little hope that scientific levers will resolve questions about data integrity in PLATO. The only way forward, in his opinion, is re-engagement from the Department of Justice.

"There are many good people in the justice department and we need to give them another chance to look at the case, issue new civil investigative demands, and stop the flirting, dealing, and wheeling in exchange for future high profile jobs in big pharma. Then the American people will receive justice."

Table 1 | Deaths included and excluded from analyses in *NEJM*

Population	Number of deaths in ticagrelor group	Number of deaths in clopidogrel group	Data favours	Included or excluded in analysis
Deaths in patients who did not receive any study drug	10	15	Ticagrelor	Included in *NEJM*
Deaths in patients who started study drug ≥1 day after being randomised	1	17	Ticagrelor	Included in *NEJM**
Deaths after withdrawal of consent	25	20	Clopidogrel	Excluded from *NEJM*
Deaths after intended treatment period	19	14	Clopidogrel	Excluded from *NEJM*

* At least 17 of 18 deaths were included in the NEJM report. One death occurred 266 days after randomisation but at a point in the study when AstraZeneca had commenced patient phase out.

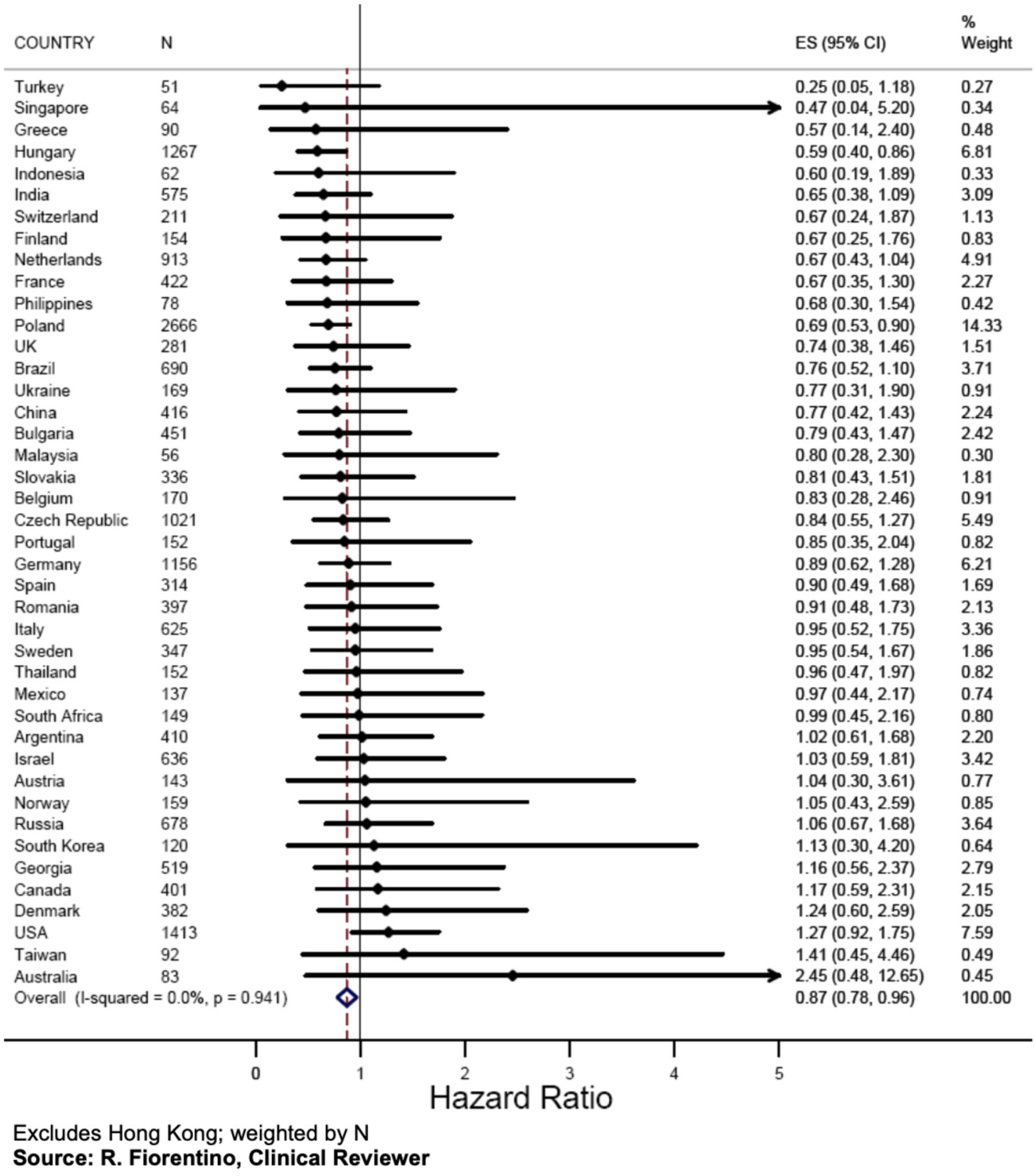

Fig 2 | Primary endpoint results by country (Source: June 2010 FDA review memo)[39]

This feature has been funded by the BMJ Investigations Unit. For details see bmj.com/investigations

Competing interests: See www.bmj.com/about-bmj/editorial-staff/peter-doshi for full disclosures.

Provenance and peer review: Commissioned; externally peer reviewed.

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