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INVESTIGATION

Ticagrelor doubts: inaccuracies uncovered in key studies for AstraZeneca's billion dollar drug

As generic versions of AstraZeneca's blockbuster drug ticagrelor prepare to enter the market, *The BMJ* raises fresh concerns over the integrity of the clinical trials that underpinned its approval. Peter Doshi reports

Peter Doshi *senior editor*

What we found

The multibillion dollar heart drug ticagrelor (Brilinta, Brilique) goes generic this year.

Last December, a BMJ investigation found serious data integrity problems in the landmark 18 000 patient PLATO study,[1] calling into question the drug's advantage over cheaper rivals.

In this article, *The BMJ* has expanded its investigation, looking at two key platelet studies that AstraZeneca claimed explained ticagrelor's ability to treat patients with acute coronary syndrome successfully. We found evidence of serious misreporting, however, raising doubts over the approval and decade long use of ticagrelor.

We found:

- The primary endpoint results for both clinical trials were inaccurately reported in *Circulation*
- More than 60 of 282 readings from platelet machines used in the trials were not present in US Food and Drug Administration datasets
- One active trial investigator never became a study author, while one author told *The BMJ* he was not involved in the trial. Most investigators, including the principal investigator, were unreachable or declined to be interviewed

For more than a decade, the multibillion dollar drug ticagrelor (Brilinta in the US and Brilique in Europe) has been recommended in the treatment of patients with acute coronary syndrome. As generic versions of the antiplatelet drug prepare to launch this year, *The BMJ* has investigated the evidence underpinning the drug's approval and continued use. In our first story we revealed serious data integrity problems in the PLATO study, the 18 000 patient randomised trial that brought ticagrelor to market.[1]

The BMJ now turns its attention to two key supporting AstraZeneca studies that convinced doctors of ticagrelor's ability to rapidly and consistently inhibit platelets—critical for managing patients following percutaneous coronary intervention. Our investigation was based on interviews with trial investigators and platelet experts and access to the underlying trial data submitted to regulators, as well as readouts from laboratory equipment used in the studies. We found evidence that the trials were inaccurately reported. In one instance AstraZeneca's trial failed to show statistical significance, but was published in a leading cardiology journal as significant. Extraordinarily, most investigators, including the principal investigator and the drug company, were unreachable or declined to be interviewed. The findings raise even deeper questions over the approval and decade long use of the drug.

Victor Serebruany, an adjunct faculty member at Johns Hopkins University and ticagrelor's most renowned critic, told *The BMJ* that "there are episodes of skyrocketing rebound and profound platelet inhibition after ticagrelor making patients prone to thrombosis or bleeding. If doctors had known what happened in these trials, they would never have started using ticagrelor."

The original oddity

Ticagrelor brings in more than a billion dollars in annual sales and is recommended globally.[2–4] Despite this, doubts over the PLATO trial's reliability have persisted.

But back in 2009, as AstraZeneca sought licensure for its new drug, interventional cardiologists were captivated by the drug's pharmacodynamics. Shortly after PLATO's publication in the *New England Journal of Medicine*, two AstraZeneca studies, known as ONSET/OFFSET and RESPOND, were published in *Circulation*, one of cardiology's leading journals, reporting the drug's effects on platelet function.[5,6]

ONSET/OFFSET was a 123 patient, randomised phase 2 trial that reported that ticagrelor provided faster and greater inhibition of platelets than clopidogrel (Plavix), a competitor P2Y12 inhibitor that was nearing patent expiration. Similar results were published in RESPOND, a 98 patient randomised trial that investigated ticagrelor's platelet inhibition in so called clopidogrel non-responders. With previous trials of anti-platelet therapy[7–9] linking early treatment with clinical benefit and evidence that the greater the platelet inhibition, the better the outcome, it stood to reason that using ticagrelor should lead to fewer fatal thromboses.

"The ONSET/OFFSET study, when it came out, caused incredible interest," says cardiologist Dan Atar, head of research at Oslo University Hospital. "I remember numerous discussion groups where people were asked to interpret these findings."

AstraZeneca was also pressing the message: PLATO had demonstrated a cardiovascular mortality benefit over clopidogrel, the company said, and the platelet

studies, reporting faster and greater platelet inhibition, explained why. Addressing advisers to the US Food and Drug Administration (FDA), an AstraZeneca vice president said, "We think this is important in the urgent management of patients with acute coronary syndromes."

But for the FDA doctor leading the review of AstraZeneca's application, the story was not adding up. Thomas Marciniak's careful look at PLATO revealed a curious wrinkle in the data: early clinical benefit was not seen. If the platelet trial data were correct, Marciniak reasoned, ticagrelor's faster and greater inhibition should have led to it beating clopidogrel on clinical outcomes in this population in PLATO—but it hadn't. In his review memo, Marciniak noted that "ticagrelor patients undergoing early percutaneous coronary intervention" for secondary prevention, the practice for most patients with acute coronary syndrome, "fare worse than clopidogrel patients."

"I would expect that patients with the very early invasive strategy would have the greatest need for good platelet inhibition, but ticagrelor fared worse [in PLATO] for short term outcomes in these patients," Marciniak wrote in his report.

Deepening doubts

While Marciniak's memo left the paradox unresolved, one of his colleagues outside the agency was also trying to make sense of the discrepancy. Victor Serebruany, who would later become ticagrelor's fiercest critic, originally had a stake in the drug's success.

In early 2010, when the platelet studies were published, he held a patent application related to ticagrelor and was in talks with AstraZeneca about a business relationship. But Serebruany, a pharmacologist with expertise in platelet function tests, thought the pharmacodynamic data were too good to be true. ONSET/OFFSET's study schedule, he reckoned, was almost impossibly intense, including a requirement for six blood tests in an eight hour period.

"6 !!!! blood draws at Day 1 … Can you confirm that it was really done with other investigators of the study," he emailed his contact at AstraZeneca in January 2010. Serebruany estimated that in a 24 hour period, 210 mL of blood would have to be drawn from study participants, patients with stable coronary artery disease (see box).

A lot of blood

Patients in AstraZeneca's pharmacodynamic studies would have to be unusually committed. Typical platelet studies involve one or two blood draws; AstraZeneca's required up to six per visit.

Trial consent forms seen by *The BMJ* inform patients that up to 429 mL (ONSET/OFFSET) and 604 mL (RESPOND) of blood would be taken across multiple study visits spanning weeks. And according to the forms, patients would not be paid for enrolling, increasing the difficulty investigators faced in recruiting volunteers.

Alan Michelson, director emeritus of the Center for Platelet Research Studies at Boston Children's Hospital, who was not involved in either AstraZeneca study, was surprised by the amount of blood taken. "If I was the subject, I think I'd probably be saying no just on that basis—even though I don't think it's a dangerous amount of blood to take. But it's a lot."

The BMJ's analysis found that two of ONSET/OFFSET's 10 study sites failed to recruit any patients. (RESPOND did not publish enrolment by site.) Others described recruitment as challenging. Drew Purdy, who operated a trial site in Rapid City, South Dakota, told *The BMJ*, "Our site is known for being able to get people to sign up for studies." But because of all the blood draws, he judged that only people living nearby would join. "I could see maybe seven of our best clients probably would have stuck around for it, knowing the importance of the trial."

But Robert Storey, a professor of clinical cardiology at the University of Sheffield who recruited 48 patients across the two studies according to AstraZeneca records, didn't recall participant retention being a problem. He told *The BMJ*, "It is indeed a testament to altruism that patients were willing to have multiple blood tests."

AstraZeneca told Serebruany that it looked into his concerns but found nothing. "We remain confident in the integrity and validity of the data."

But *The BMJ*'s investigation raises serious questions about data validity.

The investigators

The BMJ sought to interview more than 15 investigators from the two AstraZeneca trials, to understand their experience conducting the studies, and to verify trial records. But most were unreachable or not willing to be interviewed (see supplemental online table in Related content). Among them was Lars Hvilsted Rasmussen, dean of the faculty of medicine at Aalborg University in Denmark, who emailed *The BMJ* a statement: "I have no reason to doubt the proper conduct of the [RESPOND] study in relation to the protocol or the results. If you require further information about the study, please refer to the study's corresponding author Dr Paul A Gurbel or AstraZeneca."

Gurbel, the lead investigator for both ONSET/OFFSET and RESPOND, did not respond to multiple email requests, however.

One investigator *The BMJ* could reach was Tonny Nielsen, a co-author of RESPOND and principal investigator in Denmark, according to AstraZeneca documents. But Nielsen told *The BMJ* in a written response, "I did not participate in the RESPOND study," a statement further substantiated by two of his colleagues. And yet he was listed as an author of the *Circulation* paper despite not being involved.

Meanwhile, *The BMJ* found that one investigator, Alberto Yataco, operated an active study site in Baltimore, but never became an author despite enrolling 12 patients and ordering extra test kits. Yataco could not be located for this story.

The BMJ also found that several of the named authors of the *Circulation* studies apparently lacked relevant experience. Beyond ONSET/OFFSET and RESPOND, *The BMJ* could not locate any other platelet function study in which Cordel Parris, Vance Wilson, Gary Ledley, Dharmendra Patel, or Georges Sabe-Affaki were named authors.

Was training provided?

Both ONSET/OFFSET and RESPOND were multicentre studies, a characteristic that generally adds credibility to results. But experts told *The BMJ* that when it comes to platelet studies, integrating data from multiple study sites adds complexity that calls for special laboratory training—but it is unclear that such training occurred.

For technical reasons, platelet function studies tend to be conducted at a single centre. Platelet aggregation, measured using light transmittance aggregometry (LTA), must be performed within a few hours of blood draw. The time constraints dictate that assays be conducted on site.

"On the face of it, it's a simple test," explained Alan Michelson, director emeritus of the Center for Platelet Research Studies at Boston Children's Hospital, who was not involved in either AstraZeneca study. But, he said, LTA is also a "finnicky test, very prone to artefacts of various kinds. So quality control is particularly

important"—all the more so when combining data across different sites.

Both ONSET/OFFSET and RESPOND had 10 study sites, with locations across the US and in the UK, as well as Canada and Denmark for RESPOND.

Michelson said that "platelet aggregation is often referred to as a semi-quantitative test. People do not do platelet aggregation the same way." So for studies like ONSET/OFFSET and RESPOND, the question is "did they organise and train the sites to do these assays in such a way they could reliably get the same results at different sites?"

But *The BMJ* was unable to confirm that all sites received training.

Data integrity concerns

Following our investigation into the PLATO trial, which documented discrepancies between study site level records and data submitted to the FDA, *The BMJ* asked investigators on the ONSET/OFFSET and RESPOND studies to share original data. But of the three that spoke to *The BMJ*, all said they had no data, which they indicated had been archived in storage or destroyed.

The BMJ did, however, obtain trial datasets submitted to the FDA as well as documents sent by one of the platelet function test manufacturers to the FDA. One email, sent in response to a request from the FDA, detailed when machines and supplies were shipped to various trial sites. The information presented a confusing picture.

The AstraZeneca dataset shows that one ONSET/OFFSET site apparently began recording platelet levels the morning after a machine was shipped to that investigator. *The BMJ* made multiple unsuccessful attempts to interview the investigator, Cordel Parris, to understand how the machine could have been obtained and put to use so rapidly after shipment.

At another trial site, the test manufacturer had no record of supplying machines, although other distributors of machines and test kits exist. The manufacturer did supply test cartridges to this site, according to the email seen by *The BMJ*. FDA records indicate, however, that those cartridges were shipped after more than 200 tests had already been performed. *The BMJ* sought to understand where the investigator, Robert Storey, sourced the cartridges used for these 200 tests, but after more than a dozen back-and-forth emails about other aspects of the trial, Storey, without explanation, stopped communicating with *The BMJ*.

Some machines were also returned to the manufacturer for servicing with the most recent platelet activity readings still stored in the machines' memory. *The BMJ* was able to access readouts from machines used at the site of Paul Gurbel, the interventional cardiologist who led the two trials. Our analysis found more than 60 readings (or around one quarter of the total readings) were not present in either the ONSET/OFFSET or RESPOND datasets submitted to the FDA, and that the platelet activity levels not entered were significantly higher than those used in the *Circulation* papers and FDA datasets. It is unclear whose blood was sampled, and why those measurements did not contribute to data in either trial. In addition, trial subject numbers—unique identifiers essential for proper record keeping—were not used to identify patients in the machines from Gurbel's lab.

Through a spokesperson, Sinai Center for Thrombosis Research and Drug Development, which Gurbel leads, stated, "Any allegations of any research misconduct in the RESPOND and ONSET/OFFSET studies are baseless and erroneous." Gurbel declined to be interviewed, as did the chair of his hospital's institutional review board.

Our investigation also included a reanalysis of patient level data obtained under a freedom of information request submitted to the FDA last year. We began by reviewing data from the ONSET/OFFSET trial's primary endpoint—inhibition of platelet aggregation.

The BMJ found that at three of the study's eight active sites, staff apparently missed conducting the most important test: baseline platelet aggregation—again raising questions about the competence of site operations. Of the 26 patients enrolled at these sites, the dataset shows that tests were not performed at baseline for seven patients—yet blood was subsequently drawn from those same patients an average of 11 times. Why additional blood was taken from these patients is unclear because, owing to the missing baseline measurements, their data were excluded from the analysis.

Then, after removing the patients, authors of the *Circulation* paper labelled the remaining 116 participants the "intention-to-treat" population, a term widely understood to imply analysing all randomised patients.

The BMJ attempted to interview the principal investigators at these sites, to learn if they knew that their patients had been excluded from the intention-to-treat analysis. Despite multiple attempts, however, none could be reached for comment.

Our analysis also identified more than a dozen patients with baseline platelet aggregation levels recorded as under 50%—lower than what would be expected for stable, non-hospitalised patients. And for some of them, platelet aggregation dramatically increased after treatment, an improbable effect for an anti-platelet drug—and one that suggests an incorrect laboratory reading. *The BMJ* analysis determined that the implausible datapoints were incorporated into some analyses. However, for the primary endpoint analysis—a calculation of inhibition of platelet aggregation—they were first transformed through an unpublished data adjustment, obscuring the implausible datapoints.

Dan Atar, editor in chief of *Cardiology*, said that the data adjustment should have been reported in trial publications. "Whether the adjustment was reasonable or not can be debated. But either way it is something that absolutely should have been reported by the authors. Without that transparency, one cannot even evaluate its appropriateness."

The BMJ's review also found that the protocol specified primary endpoint results for RESPOND were statistically non-significant (P=0.157) but were subsequently reported in *Circulation* as significant (P=0.005) because of an undeclared change in primary endpoint definition. The study had aimed to test whether ticagrelor could convert so called clopidogrel non-responders into responders.

Circulation and AstraZeneca did not respond to a request for comment.

Serebruany told *The BMJ*, "It's been obvious for years that there is something wrong with the data. That the FDA's leadership could look past all these problems—on top of the many problems their own reviewers identified and are now being discovered by *The BMJ*—is unconscionable. We all need to know how and why that happened."

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Supplemental online table: *The BMJ*'s attempts to reach study investigators