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## The BMJ Press Release

### Drug company withheld information about faulty device in key trial of best selling anti-clotting drug

- *Concerns about faulty device raised by some trial investigators*
- *Company instigated safety checks but did not disclose data prior to approval*
- *Can we trust this evidence at all, asks The BMJ?*

An investigation published by **The BMJ today** reveals that Janssen, the pharmaceutical arm of Johnson and Johnson, withheld data from the US Food and Drug Administration (FDA) about a faulty blood testing device used in a key trial during approval of their blockbuster anti-clotting drug, rivaroxaban (Xarelto).

The trial, known as the ROCKET AF trial was published in the New England Journal of Medicine (NEJM) in 2011. It compared rivaroxaban with the older anti-clotting drug warfarin for preventing strokes in patients with irregular heartbeat (non-valvular atrial fibrillation).

The investigation, led by The BMJ's Associate Editor, Dr Deborah Cohen, shows that Janssen executives knew, early on in this trial, of concerns about device malfunction - and launched a safety programme (the Covance recheck programme) to check

the accuracy and reliability of blood test readings against laboratory results.

But Janssen failed to share these data with the trial's data safety monitoring board, Bayer (co-developer of rivaroxaban), and the FDA prior to drug approval, despite the safety of trial participants potentially being compromised.

Rivaroxaban is a new type of oral anticoagulant. It works by preventing blood from clotting and is marketed as a better alternative to warfarin because patients don't need regular tests to check if they have the right amount of drug in their bloodstream.

In February 2016, The BMJ raised concerns about the ROCKET AF trial results after the blood testing device (INRatio) was recalled for giving falsely low readings.

Doctors and researchers called for the data to be independently checked, but both Janssen and Bayer said an "independent reanalysis" - published as a letter to NEJM - showed the device had not affected trial outcomes.

Both the European Medicines Agency (EMA) and the FDA have not changed their recommendations regarding the use of Xarelto.

But Markku Kaste, one of the trial investigators and former head of the Clinical Stroke Research Group at Helsinki University General Hospital told The BMJ that the data from the Covance recheck programme should have also been shared with investigators as "it's vital for the ongoing ethical approval for the trial."

He added: "I now have some doubts about the validity of ROCKET AF trial. It possibly skews the data in favour of rivaroxaban."

Thomas Marciniak, a former FDA official who was a drug reviewer on Janssen's application to use rivaroxaban in acute coronary syndrome, told The BMJ that the company's analyses that they submitted to drug regulators are "worthless" because the "innaccuracies are not limited to the recall patients."

EMA's review, published in February 2016, seems to reflect Marciniak's concern. Its analysis of samples - taken from participants at weeks 12 and 24 of the trial - found "discrepancies of potential clinical relevance" in about 35% of cases.

Further analyses found that the larger the difference between the INRatio and laboratory readings, the higher the rate of major bleeding.

Carl Heneghan, professor of evidence based medicine at Oxford University, believes patients in the trial may have been put at undue risk of harm. He told The BMJ that the INR device errors "are worrying" as there is "a near exponential increase in bleeding risk with increasing INR."

Despite all this, the EMA report stated that "there was sufficient evidence to conclude that the benefit/risk balance remains unchanged and favourable for treatment with rivaroxaban in the prevention of thromboembolism in non-valvular atrial fibrillation."

Meanwhile, the FDA says it is still investigating.

Marciniak described EMA's review as a "whitewash," alleging that the regulator has ignored "the serious device inaccuracies that those analyses reveal."

Some are also questioning how "independent" the NEJM reanalysis actually is, particularly since employees of both Janssen and Bayer are members of the executive committee that carried it out, Cohen writes.

“The implications are we still do not know whether this is a safe drug,” says Carl Heneghan. “We need a trial to assess the safety and efficacy of rivaroxaban. Just one caveat - it should be run independently.”

In an editorial, Heneghan and colleague Dr Kamal Mahtani argue that independent replication of trials, data transparency, and detailed analysis of clinical study reports are needed “to increase our confidence in new oral anticoagulants.”

Meanwhile, they say, patients and clinicians “must, for now, live with the uncertainty left by the evidence currently available.”

In a linked commentary, Harlan Krumholz, Professor of Medicine at Yale University, and colleagues call on regulators to review performance standards for diagnostic devices used in research studies, especially those intended to inform regulatory approval.

People who have concerns regarding their treatment are urged to consult their doctor and not to discontinue taking their medication.

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### **Note to Editors**

Feature: Manufacturer failed to disclose faulty device in rivaroxaban trial

<http://www.bmj.com/content/354/bmj.i5131>

Editorial: Novel oral anticoagulants for atrial fibrillation

<http://www.bmj.com/content/354/bmj.i5187>

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