



JAPAN

Tampered Data Cast Shadow on Drug Trial

TOKYO—In a scandal reverberating across Japan's biomedical research landscape, a university in Kyoto last week acknowledged data manipulation in a university-run clinical trial for a blockbuster hypertension drug, valsartan. Japanese media have turned the episode into a cause célèbre; the *Yomiuri Shimbun*, one of Japan's biggest newspapers, labeled it a "serious betrayal" for patients. Repercussions could extend beyond valsartan, marketed under the trade name Diovan by the Swiss pharmaceutical giant Novartis.

"This incident is causing a loss of confidence in Japan's research internationally and making Japanese patients skeptical [about treatments]," says Yoshiki Yui, a medical doctor at Kyoto University. Health minister Norihisa Tamura has vowed to appoint a committee that would propose measures to prevent a recurrence.

Sold worldwide, valsartan was approved in Japan in 2000 and has become the country's best-selling drug, pulling in roughly \$1 billion last year, according to analysts. A clinical trial claiming that valsartan also reduces angina and stroke risk helped boost its popularity in Japan. That claim has fallen apart, in the process raising concerns about cozy ties between researchers and drug companies and about impediments to investigating research misconduct in Japan.

At the heart of the scandal are data from the Kyoto Heart Study, launched in 2003 by Hiroaki Matsubara, a cardiologist at Kyoto Prefectural University of Medicine (KPUM).

The 4-year study followed 3000 patients given valsartan or alternative medications. A main outcome, reported on 31 August 2009 in the *European Heart Journal*, was that valsartan, which reduces blood pressure by blocking the receptor for the hormone angiotensin, "prevented more cardiovascular events" in high-risk patients than did drugs that lower blood pressure through another mechanism.

In late 2011, bloggers started raising questions about alleged image manipulation in Matsubara's papers. Then, in an April 2012 letter to *The Lancet*, Yui expressed concerns about Kyoto Heart Study's statistics and conclusions, writing that the effectiveness in preventing angina was not seen in other trials of valsartanlike drugs or in clinical practice. Responding to requests from journals, KPUM started its own investigation. Matsubara resigned from KPUM in February, after the *European Heart Journal*, citing "[c]ritical problems ... with some of the data," retracted the heart study paper.

"Data were manipulated," KPUM President Toshikazu Yoshikawa bluntly stated at an 11 July press conference. According to the university's investigative report, which *Science* has obtained, in the Kyoto Heart Study there were 34 discrepancies between the clinical medical records and the data set used for analysis; these overstated adverse cardiovascular events in the nonvalsartan group and missed such events in the valsartan

Chagrined. KPUM President Toshikazu Yoshikawa (center) and other officials apologize after reporting fraud.

group. Once anomalous data were corrected, the claim that valsartan reduces the incidence of cardiovascular events such as angina or stroke by about half "is not supported," the report says. Eight papers authored by Matsubara have been retracted.

In an e-mail to *Science*, Matsubara writes that he "was not involved in and gave no instructions" for the event data analysis, which he said was the responsibility of a Novartis employee. Novartis headquarters in Basel declined to comment on KPUM's findings, stating in an e-mail to *Science* that "we are unfamiliar with how the university conducted its review." But the company has confirmed that employees of its Japanese subsidiary participated in the Kyoto Heart Study and several similar studies at other Japanese institutions without noting their affiliation on resulting papers. In a statement posted to its website on 12 July, Novartis blamed the disclosure failures on a lack of guidelines and a misunderstanding of the appropriate level of involvement in such trials. "Preventive and corrective measures have been implemented," the statement said.

The debacle raises troubling questions about research oversight. KPUM officials said that they could not probe more deeply into who manipulated data because they cannot compel cooperation from Novartis employees. Universities in Japan have no authority to question people outside their institution, says Tetsuya Tanimoto, a physician at the University of Tokyo who studies pharmaceutical regulatory issues. Japan needs something like the U.S. Office of Research Integrity, he says.

Japan's medical research establishment could come in for broad scrutiny. KPUM confirmed in an e-mail to *Science* that since 2008, Matsubara received about \$1.4 million for his research from Novartis. Such grants to clinical researchers are not unusual, but they highlight inadequate public support for clinical research in Japan, Tanimoto says. The revelations could also erode public support for emerging plans to shake up medical research by establishing an outcome-focused version of the U.S. National Institutes of Health. In the wake of the scandal, the Japanese public may question whether the money will be well-spent and the results trustworthy.

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—TOSHIKAZU YOSHIKAWA
KPUM PRESIDENT

—DENNIS NORMILE