

高血圧症治療薬の臨床研究事案を踏まえた対応及び再発防止策について
(中間とりまとめ・抜粋)

別紙 5 : 東京慈恵会医科大学における本事案研究責任者に対するヒアリング概要

実施日 : 平成 25 年 9 月 18 日 (水)

担当チーム : 東京慈恵会医科大学担当チーム

ヒアリング対応者 :

- 本事案研究責任者 (A 氏) 及びその弁護士
- 桑島委員、竹内委員 (主査)、田島委員、藤原委員、森下委員
- 厚生労働省及び文部科学省関係者

4. その他

- 学会誌からのデータの疑義について

京都大学の医師による疑義指摘前の 2011 年に、Lancet に匿名投書があり、京大医師と同様の指摘をされた。 Lancet からの照会に対しては、論文共著者が回答し、Lancet から了解したとの返事がきた。

【京都大学由井医師から Lancet への投書】

From: Yoshiki Yui [mailto:]

Sent: Wednesday, October 12, 2011 4:17 PM

Subject:

Editor of the Lancet

Please find the attached files.

Yoshiki Yui, MD

Kyoto University Hospital
[Redacted]

(添付ファイルは別添資料参照)

To the Editor of Lancet & European Heart Journal

-Regarding the identical value of mean/SD (standard deviation) of achieved SBP (systolic blood pressure) in clinical trials of valsartan vs non-ARB)-

As shown in the attached table, in Jikei Heart Study (Lancet 369; 1431, 2007), and Kyoto Heart Study (European Heart Journal 30; 2461, 2009), the achieved SBP between valsartan and non-ARB group is identical in each trial. Moreover, in Kyoto Heart Study, baseline value of SBP and DBP is also equal. These results seem quite strange to me.

In Jikei Heart Study, the probability of coincidence among two groups at 132.0/14 is considered as follows.

□□□.□/□□

1 st place: fixed as 1	: 1
2 nd place: fixed as 3	: 1
3 rd place: 0-9	:10
4 th place: 0-9	:10
5 th place: 1-3	: 3
6 th place: 0-9	:10

Therefore, the probability of coincidence is $1/(1 \times 1 \times 10 \times 10 \times 3 \times 10) \times 1/(1 \times 1 \times 10 \times 10 \times 3 \times 10) \times (1 \times 1 \times 10 \times 10 \times 3 \times 10) = 1/(3 \times 10^3)$, and this means the achieved SBP becomes same once a 3×10^3 trials.

In Kyoto Heart Study, the probability is $1/(1 \times 2 \times 10 \times 3 \times 10) \times 1/(1 \times 2 \times 10 \times 3 \times 10) \times (1 \times 2 \times 10 \times 3 \times 10) = 1/(6 \times 10^2)$. Moreover, in this study, baseline SBP and DBP is also identical. Thus, if considering the baseline coincidence, the probability comes close next to zero.

As far as I know, among the hypertensive trials, in only these two studies, achieved SBP is equal. For example, many trials employed in


BPLTTC (including my JMIC-B trial), there are no trials whose achieved mean value of achieved SBP is same (of course, SD is not).

From the different point of view, in Jikei Heart Study, the coincidence of mean and SD suggests that normal distribution of two groups is same, because the normal distribution is determined by mean and SD. This is very odd. In other words, randomized but inhomogeneous population becomes homogeneous after 3 year drug intervention. This is the other way round. Also, in Kyoto Heart Study, the identical normal distribution still exists after 3 year drug intervention.

I'm very happy if you consult with your statistician and check whether my concern is meaningless or not. There have been many criticism and bad rumors (including fabrication) in Japan in these two trials. Many cardiologists suspect results of trials, because results of these trials were different from other ARB trials and daily clinical practices. Especially, significant effectiveness for angina pectoris of valsartan is considered to be strongly dubious.

PS: This letter was sent to both editors.

Sincerely yours,

Yoshiki Yui, MD
Department of Cardiology,
Kyoto University Hospital


Jikei Heart Study Lancet (369; 1431. 2007) Table 3, P.1435			
		baseline	achieved
Valsartan	SBP	139.2(mean) (11SD) mmHg (n 1541)	132.0 (14) (n 433)
	DBP	81.4 (11)	76.7(8)
Non-ARB	SBP	138.8 (11) (n 1540)	132.0 (14) (n 454)
	DBP	81.4 (11)	76.6(9)
Kyoto Heart Study European Heart J (30,2461, 2009) P 5 of 9 Figure 3			
		baseline	achieved
Valsartan	SBP	157(mean) (14SD) mmHg (n 1517)	133 (14)
	DBP	88 (11)	76(11)
Non-ARB	SBP	157 (14) (n 1514)	133 (14)
	DBP	88(11)	76(10)

② Lancet 誌 Editor から由井医師への返答

From: Spencer, Stuart (ELS-CAM) [mailto:]
Sent: Friday, October 28, 2011 8:21 PM
To: [redacted]
Subject: JIKEI

Dear Dr Yui,

We are seeking a response from the authors. We will let you know when we have heard back.

Best regards

Stuart

Elsevier Limited. Registered Office: The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB,
United Kingdom, Registration No. 1982084 (England and Wales).

③ Lancet 誌 Editor から由井医師へ疑念点について Letter への投稿依頼

From: Spencer, Stuart (ELS-CAM) [mailto:]
Sent: Monday, November 21, 2011 7:40 PM
To: [redacted]
Subject: JIKEI

Dear Dr Yui,

We have asked our stats advisors and the authors about the JIKEI trial.

It might be useful for readers to have access to the concerns and replies and we would be happy to consider a suitable letter from you for publication in The Lancet. We would then have a response from the authors. If you wish to take this opportunity please send a letter (300 words maximum) outlining your concerns. We would not publish the calculations, just the concerns.

Please submit through <http://ees.elsevier.com/thelancet> as Correspondence as soon as possible.

Best wishes

Stuart

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United Kingdom, Registration No. 1982084 (England and Wales).

Retraction—Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study

The *Lancet* published the Jikei Heart Study in April, 2007.¹ On July 31, 2013, we were informed by Professor Kazuhiro Hashimoto (Jikei University) that there had been a press conference on July 30 reporting an interim conclusion from an internal investigation into this research. The report considered that "The data on blood pressure are not reliable...". Given this finding, we now wish to retract the Jikei Heart Study on the grounds that we no longer have confidence in the published results.

When the Jikei Heart Study was first published, Staessen and Richart² congratulated the investigators on their report. But we soon became aware that there was concern in Japan about the trial. Indeed, there was not only concern about the Jikei Heart Study, but also the Kyoto Heart Study, which was published in the *European Heart Journal* in 2009.³ Both reports were about valsartan and had several authors in common. In October, 2011, we received correspondence expressing concern about the similarity of the standard deviations of the mean blood pressure measurements in the two studies, and we invited the authors to comment. Although we were initially satisfied with their response, in 2012 we published a letter from Dr Yui reporting further concerns.⁴

The retraction of the Kyoto Heart Study⁵ in February, 2013 led to an investigation into the conduct of the Jikei Heart Study. An investigating committee headed by Professor Hashimoto from Jikei University was established. We became aware of this development on April 29, 2013, and on May 2 we wrote to Jikei University asking for details of the investigation and requesting that we be kept informed. We wrote again on June 4 and June 19 asking when the investigation might be completed. We wrote again on July 31 after we were made aware that a press conference had been held. By return we received a synopsis of the investigation's findings. The report identifies concern over the reliability of the blood pressure data: "We believe, therefore, that the data were intentionally altered." The report goes on to say: "We suspect that the data were altered during their statistical analysis."

The report also comments on the affiliation of the person entrusted with the statistical analysis,

Nobuo Shirahashi. Mr Shirahashi's affiliation, as provided to *The Lancet*, was: "Clinical epidemiology, Osaka City University Graduate School". In April of this year, *The Lancet* received a letter from a professor at Osaka City University Graduate School of Medicine informing us that there has never been a Department of Clinical Epidemiology in the university, that Osaka City University "has never had the statistical analysis group for Jikei Heart Study", and that Mr Shirahashi "has never been staff of our university" but was employed by Novartis Pharma Japan.

Our attempts to obtain a response from Mr Shirahashi were hindered by his recent retirement from Novartis, but the Global Head of Medical Affairs, Dr Usman Azam, did share with *The Lancet* that Mr Shirahashi had been employed by Novartis throughout the period of the trial and its publication. Dr Azam also told us: "In addition, it appears Mr Shirahashi obtained an unpaid position in about 2001 with the Osaka City University Graduate School's Medical Research Faculty as a part-time lecturer in the Department of Medicine. He held the position until 2011." Dr Azam further acknowledges "...that Mr Shirahashi should have requested the studies' authors to identify him as a Novartis Pharma K.K. employee".

Taken together, these findings indicate that there is now sufficient doubt as to the integrity of the Jikei Heart Study and the obfuscation over affiliation of the study statistician for *The Lancet* formally to retract the paper from the scientific record.

The Lancet Editors

The Lancet, London NW1 7BY, UK

- 1 Mochizuki S, Dahlöf B, Shimizu M, et al. Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. *Lancet* 2007; 369: 1431-39.
- 2 Staessen JA, Richart T. Sum and substance in the Jikei Heart Study. *Lancet* 2007; 369: 1407-08.
- 3 Sawada T, Yamada H, Dahlöf B, Matsubara H. Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: Kyoto Heart Study. *Eur Heart J* 2009; 30: 2461-69.
- 4 Yui Y. Concerns about the Jikei Heart Study. *Lancet* 2012; 379: e48.
- 5 Retraction of: Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study [*Eur Heart J* (2009) 30: 2461-69, DOI:10.1093/eurheartj/ehp363]. *Eur Heart J* 2013; 34: 1023.