

March, 2014, assuming “no excess occurrence [of thyroid cancer] in the first three years [after the Fukushima Dai-ichi nuclear accident in March 2011]”.¹ Regular thyroid examinations began in April, 2014, and will be compared with these baseline data.

We have some concerns about this approach. First, without a large control group, the present design (a before–after comparison) might not be able to accurately assess the health impact of radiation exposure. The Ministry of Environment conducted a similar ultrasonography examination of children in three prefectures not affected by the nuclear accident and identified only a single thyroid cancer.² However, the sample size (4365) was too small to conclude that the prevalence of thyroid cancer in these three prefectures was different from that in Fukushima.²

Second, over-diagnosis and over-treatment of thyroid cancer that might never progress are possible.³ The Fukushima baseline survey showed an unexpectedly high prevalence of thyroid cancer: 33 confirmed cases and 42 suspected cases among 269 354 children.⁴ The possibility of over-diagnosis in the study protocol was not mentioned.¹ Of these 75 children with thyroid cancer, 34 were operated on. According to Fukushima prefecture screening is their responsibility, but treatment plans are entirely the responsibility of hospitals, where the risk of overdiagnosis might not have been properly taken into account.

The apparent increase in thyroid cancer prevalence has caused public concern and fear about the effect of radiation, but Fukushima Prefecture and Fukushima Medical College, who manage this programme, are not yet willing to confirm an association between increased risk of thyroid cancer and radiation exposure based on the available data.⁵ It will be difficult to confirm any association without comparing thyroid cancer prevalence in Fukushima with that of

other prefectures not affected by the accident. A comparison of trends in prevalence between areas with high and low radiation exposure within Fukushima using a matched design should be considered, although the risk of over-diagnosis remains.

Without revisiting the protocol and informing doctors and populations about the risk of over-diagnosis, the present thyroid examination programme is not suitable to assess the effect of radiation and reduce the fear and anxiety of residents of Fukushima.

KS is a member of the Supervisory Panel for Thyroid Ultrasound Examination. SG and AO declare no competing interests.

*Kenji Shibuya, Stuart Gilmour, Akira Oshima
shibuyak@m.u-tokyo.ac.jp

Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo 113-0033, Japan (KS, SG); and Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan (AO)

- 1 Yasumura S, Hosoya M, Yamashita S, et al. Study protocol for the Fukushima Health Management Survey. *J Epidemiol* 2012; **22**: 375–83.
- 2 Hayashida N, Imaizumi M, Shimura H, et al. Thyroid ultrasound findings in children from three Japanese prefectures: Aomori, Yamanashi and Nagasaki. *PLoS One* 2013; **8**: e83220.
- 3 Ministry of Environment. Results of the thyroid cancer tracing project. (in Japanese). <http://www.env.go.jp/press/press.php?serial=17965> (accessed April 20, 2014).
- 4 Brito JP, Morris JC, Montori VM. Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours. *BMJ* 2013; **347**: f4706.
- 5 Fukushima Medical School. Information concerning implementation of the thyroid screening programme. (in Japanese). <http://fukushima-mimamori.jp/news/2014/03/000131.html> (accessed April 20, 2014).

Renal denervation for resistant hypertension—the Symplicity HTN-1 study

It must be seen as a regrettable coincidence that just a month after Medtronic (the sponsors of the Symplicity trials) announced that Symplicity HTN-3 had failed to meet its primary efficacy endpoint of a reduction of 10 mm Hg in systolic

blood pressure and that all further trials were being suspended,¹ *The Lancet* should see fit to publish the result of the Symplicity HTN-1 trial² and a largely laudatory commentary on renal denervation.³

When Henry Krum and colleagues published early data claiming efficacy for renal denervation in *The Lancet* in 2009,⁴ I asked: “How was an otherwise well designed interventional study approved by five ethics committees when the measurement technique on which the proof-of-principle would depend was clearly flawed but could so easily have been corrected had ambulatory blood pressure been measured on all patients at regular intervals?”⁵ Since then others have warned that reliance on conventional measurement would lead to fallacious conclusions.⁶ How is it that 4 years on and much money spent we are still calling in vain for the use of a methodology that has been proven to remove the white coat effect and other confounding factors in interventional trials?

I declare no competing interests.

Eoin O’Brien
eobrien@iol.ie

The Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin 4, Ireland

- 1 Medtronic. Medtronic Announces U.S. Renal Denervation Pivotal Trial Fails to Meet Primary Efficacy Endpoint While Meeting Primary Safety Endpoint. <http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&iid=1889335> (accessed Jan 16, 2014).
- 2 Krum H, Schlaich MP, Böhm M, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet* 2014; **383**: 622–29.
- 3 Johns EJ. Resistant hypertension and renal denervation: 3 years on. *Lancet* 2014; **383**: 583–84.
- 4 Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; **373**: 1275–81.
- 5 O’Brien E. Renal sympathetic denervation for resistant hypertension. *Lancet* 2009; **373**: 2109.
- 6 Persu A, Renkin J, Asayama K, O’Brien E, Staessen JA. Renal denervation in treatment-resistant hypertension: the need for restraint and more and better evidence. *Expert Rev Cardiovasc Ther* 2013; **11**: 739–49.

Henry Krum and colleagues¹ reported that the improvement in blood pressure control resulting from renal denervation persisted during 36 months of follow-up. However, because this was an open label study, several confounding factors could have affected the results.² A few factors were mentioned by the authors, but they failed to mention that the mean number of medications taken by patients was higher at 36 months than at 6 months. Similarly, more patients were receiving aldosterone antagonists at 36 months compared to baseline, and this treatment has been very effective in resistant hypertension.³

Furthermore, whether there were any differences in medication dosage at follow-up was not clear, which could have affected the result.⁴ Additionally, the progressive improvement in blood pressure control during the follow-up period is suggestive of a so-called healthy adherer effect resulting from participation in a clinical study.⁵ Therefore, it would have been helpful if the authors could have provided some data on changes in patient weight during the follow-up.

Finally, placebo-controlled, randomised clinical trials provide the best clinical evidence,² and the recently completed Symplicity HTN-3 study showed that renal denervation is no better than a sham procedure for reducing office blood pressure through 6 months. Thus, the apparent early and persistent improvement in blood pressure in the open label study by Krum and colleagues¹ is most likely due to the above-mentioned factors rather than renal denervation.

I declare no competing interests.

Rahman Shah
shahcardiology@yahoo.com

Veterans Affairs Medical Center, University of Tennessee, Memphis, TN 38104, USA

- 1 Krum H, Schlaich MP, Böhm M, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet* 2014; **383**: 622–29.
- 2 Barton S. Which clinical studies provide the best evidence? *BMJ* 2000; **321**: 255–56.

- 3 Chapman N, Dobson J, Wilson S, et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 2007; **49**: 839.
- 4 Brunner HR, Nussberger J, Waebler B. Dose-response relationships of ACE inhibitors and angiotensin II blockers. *Eur Heart J* 1994; **15S**: 123–28.
- 5 Chewning B. The healthy adherer and the placebo effect. *BMJ* 2006; **333**: 18–19.

The effect of renal denervation on renal artery stenosis was not well investigated in Henry Krum and colleagues' study.¹ Only 18 patients underwent angiography at 14–30 days, and 14 underwent magnetic resonance angiography at 6 months. Therefore, the rate of follow-up was very low in this cohort of 153 patients. How many patients underwent renal artery imaging at 12, 24, and 36 months was not reported; nor was the imaging method used at these timepoints. Ultrasonography has limitations in detecting renal artery stenosis.^{2,3}

It is of concern that estimated glomerular filtration rate (eGFR) decreased ($p=0.05$) and creatinine concentrations in serum progressively increased ($p=0.05$).¹ Additionally, the effect of renal denervation on renal function was not clearly described. 28 patients had a decrease in eGFR of more than 25% after renal denervation.¹ However, how many patients were followed up at each timepoint was not reported; nor was the extent to which eGFR decreased in each patient. It would be informative if authors could provide eGFR values for these 28 patients over this 3 year follow-up, and also how many patients had a clinically significant increase in creatinine concentrations at each timepoint. The authors can not conclude that renal denervation is safe.

I declare no competing interests.

Yutang Wang
yutangwang000@gmail.com

Vascular Biology Unit, Queensland Research Centre for Peripheral Vascular Disease, School of Medicine and Dentistry, James Cook University, Townsville, Queensland 4811, Australia

- 1 Krum H, Schlaich MP, Böhm M, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet* 2014; **383**: 622–29.

- 2 Zhang HL, Sos TA, Winchester PA, Gao J, Prince MR. Renal artery stenosis: imaging options, pitfalls, and concerns. *Prog Cardiovasc Dis* 2009; **52**: 209–19.
- 3 Lao D, Parasher PS, Cho KC, Yeghiazarians Y. Atherosclerotic renal artery stenosis—diagnosis and treatment. *Mayo Clin Proc* 2011; **86**: 649–57.

Authors' reply

First, we take this opportunity to clarify the purpose of our safety and proof-of-principle study published in 2009,¹ as there seems to be some misunderstanding of its aims. We did this initial 45 patients, 12 month uncontrolled assessment focused primarily on safety of the renal denervation procedure (both peri-procedural and longer-term) as well as to establish whether systemic sympathetic abrogation was actually being achieved, using both precise (noradrenaline kinetics, micro-neurography²) and crude (office blood pressure) clinical measures. We sought to determine whether the totality of the safety and efficacy data showed a signal to support further, more definitive studies focused on disease states associated with sympathetic activation. It is entirely appropriate that such a first-in-man study be uncontrolled to permit maximum exposure of individuals to the procedure for the above assessments.

This initial publication¹ and the subsequent 3 year follow-up paper³ clearly stated the caveats regarding interpretation of the results obtained in the absence of a proper control group, primarily regression to the mean and Hawthorne effect. The healthy adherer effect might also come into play with longer-term follow-up.

An ambulatory blood pressure monitoring substudy was done in our initial 45 patient study,¹ which also showed blood pressure lowering albeit of a lesser magnitude than that observed with office blood pressure recordings and in a much smaller cohort. Ambulatory blood pressure monitoring was not used as a primary efficacy endpoint in



Science Photo Library

Symplicity HTN-3 (although it was used as an entry criteria), on the basis of office blood pressure being the more widely accepted measure of blood pressure-lowering efficacy of therapeutic interventions (drug, device, procedure). Nevertheless, we agree that ambulatory blood pressure monitoring data might provide important complementary information in blood pressure-focused randomised controlled trials (RCTs) that could help overcome several important measurement biases, especially white coat hypertension.

Regarding background blood pressure medication use in the longer term follow-up of the expanded Symplicity HTN-1 cohort,³ we can only report on number of drugs (not dosing) beyond the initial 12 months of the study because, per-protocol, follow-up became more limited beyond that timepoint. Although use of background medications did not significantly increase during the trial, it certainly was not reduced, as would have been hoped for.

With respect to safety, Yutang Wang's data seem to refer to our 2009 paper¹ in which only 45 patients were denervated and only 26 had reached 6 months follow-up at the time of publication. Almost all of the expanded Symplicity HTN-1 cohort had follow-up imaging of their renal arteries post-procedure, with very low rates of stenotic or other local vascular complications noted.

Renal function in Symplicity HTN-1 declined over time, as would be expected on the basis of natural history. The observed reductions in estimated glomerular filtration rate over time might actually be less than anticipated on the basis of natural history (derived from historical controls) and the substantially increased starting blood pressure of our patients. However, the absence of a control group makes the rate of renal function decline observed somewhat difficult to interpret.

On the basis of these generally encouraging safety and efficacy

findings, we called in our 2009 paper¹ for well designed, prospective RCTs to formally test one of the hypotheses raised—ie, that renal denervation provides clinically meaningful blood pressure lowering in refractory hypertensive patients. Since then, several small RCTs, using differing denervation modalities, have generally supported our initial findings, albeit with most using office blood pressure as the primary efficacy measure. Additionally, emerging assessments of the effect of renal denervation on end-organ damage support a true blood pressure-lowering or sympathetic abrogation effect, or both.⁴

By contrast with these studies, the Symplicity HTN-3 trial investigators have recently reported that their primary (office) blood pressure endpoint was not met.⁵ This RCT had several design and logistic features that might have mitigated against a dramatic blood pressure-lowering effect of the active intervention. The type of catheter used by the US operators in Symplicity HTN-3 (Flex) differed from the first generation device used primarily in Symplicity HTN-1 and that could be relevant in achievement of adequate denervation and thus sympathetic abrogation. Also, the broad simultaneous rollout to many (88) US sites that had never done the procedure could be an issue. The level of procedural training and proctoring was considerably less than in Symplicity HTN-1. In Symplicity HTN-3, optimisation of background antihypertensive therapy was mandated but up-titration was allowed to continue potentially up to only 2 weeks before the procedure. In view of the fact that the peak blood pressure-lowering effect of antihypertensive drugs might occur up to 12 weeks' post-commencement, it is possible that blood pressure stability had not been achieved in a proportion of Symplicity HTN-3 patients at the time of the procedure. This might have contributed to the

significant blood pressure-lowering observed in the sham group, making a further increment achievable by renal denervation more difficult. Furthermore, patients from non-tertiary centres might not yet have exhausted all non-procedural treatment options for their refractory hypertension before entering the study.

Additional analysis of the Symplicity HTN-1 dataset, as well as longer term follow up of study patients, which is planned for up to 5 years, will provide important insight into potential reasons for the discrepancies discussed above.

We declare no competing interests other than those disclosed in the main Article.³

*Henry Krum, Paul Sobotka, Markus Schlaich, Michael Bohm, Murray Esler
henry.krum@monash.edu

Centre of Cardiovascular Research and Education in Therapeutics, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University/Alfred Hospital, Melbourne, VIC 3004, Australia (HK); Davis Heart and Lung Research Institute, Ohio State University, Columbus, OH, USA (PS); Neurovascular Hypertension and Kidney Disease Laboratory, Baker IDI Heart and Diabetes Institute and Heart Centre, Alfred Hospital, Melbourne, VIC, Australia (MS); Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Homburg, Germany (MB); and Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia (ME)

- 1 Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; **373**: 1275–81.
- 2 Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. *N Engl J Med* 2009; **361**: 932–34.
- 3 Krum H, Schlaich MP, Böhm M, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet* 2014; **383**: 622–29.
- 4 Mahfoud F, Urban D, Teller D, et al. Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multi-centre cardiovascular magnetic resonance imaging trial. *Eur Heart J* 2014; published online March 6. DOI:10.1093/eurheartj/ehu093.
- 5 Bhatt DL, Kandzari DE, O'Neill WW, et al, and the SYMPPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; **370**: 1393–401.