



## Notes from the Editor - Lars H. Lindholm

Dear member!

It is a pleasure for me to present a new issue of Hypertension News, Opus 45. This is a comprehensive newsletter, and I hope you have time to read it during the summer. The next one (Opus 46-47) will be a double-issue, out in early November, after the ISH has changed president (Neil Poulter is taking office) and we can report on the outcome of the ISH meeting in Seoul in September.



As editor, I have picked out a few of the contributions in today's newsletter (see below). However, please look at the List of Contents since there may be other papers which interest you more!

One of the highlights in Seoul will be the presentation of The Lancet Commission on Hypertension, chaired by Michael Hecht Olsen from Denmark. In this issue of Hypertension News, Stuart Spencer from The Lancet (an honorary fellow of ISH) reports on the journal's different clinical commissions (page 25). In his text, Stuart Spencer states that "it is considered important that the majority of the commissioners are not the doyens of the field. They are selected from those with sufficient knowledge and experience, but who are 15-20 years from retirement. If they take ownership of the recommendations and calls to action.....they may be able to help implement required changes".

Anthony Rodgers and Emily Atkins from Sydney, Australia have been invited to comment on a review written by Bo Carlberg and Mattias Brunström from Umeå, Sweden (recently published in the BMJ) in the 'Hot Off the Press' section (pages 5-9). The authors showed that if systolic blood pressure in patients with diabetes is below 140 mm Hg, further treatment is associated with increased (!) risk of cardiovascular death, with no observed benefit. Rodgers and Atkins are critical and state that the authors have "thrown the baby out with the bathwater" and that studies including dual RAAS blockade should not have been included in the analyses. In a reply, Carlberg and Brunström cannot see why they should have handled the data differently and state that "there is no baby in the water". Finally, Rodgers and Atkins remain unconvinced and do not accept that vascular death is increased in this group of patients. We have decided to publish this 5-page debate uncut since there is a lot to learn for most of us!

An adequately powered, randomized controlled 12-week study of yoga to reduce blood pressure in hypertensive patients in primary care was

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## Notes from the Editor - Lars H. Lindholm - continued

carried out by Moa Wolff and co-workers in Malmö, Sweden and is published in Journal of Human Hypertension. It showed that the patients' self-rated health was improved but that there was no effect on blood pressure. In the 'Hot Off the Press' section (page 12) it is pointed out that previous randomized, controlled studies of yoga, conducted in India, have about 25 times higher odds of showing positive results.

The 'Institute Focus' in this issue is on Murray Esler (pages 15-18) and a single laboratory 'down-under', located in the Baker IDI Heart and Diabetes Institute in Melbourne, Australia, the **Human Neurotransmitters Laboratory**. I hope you will enjoy reading it as much as I did!

In a Council's Corner presentation (pages 25-26), Lewis Landsberg tries to answer his own question: Why does such a large proportion of the world's population suffer from hypertension?

Finally, we have asked Robert Brook from Ann Arbor (MI), USA to follow up on our previous paper (published by Jenny A. Bosson and Jeremy P. Langrish in Opus 41) on air pollution and risk of cardiovascular disease. He has done so in a paper entitled "Inhaling the Cardio-Metabolic-Syndrome" which was presented at the American Society of Hypertension (ASH) meeting in May this year (pages 19-23).

Have a good read!

Lars H Lindholm, Editor

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*"Working together for better  
BP control and CVD reduction"*

# Hypertension Seoul 2016

The 26<sup>th</sup> Scientific Meeting of the **International Society of Hypertension**

in collaboration with the 12<sup>th</sup> Congress of the Asian Pacific Society of Hypertension (APSH)  
the 25<sup>th</sup> Annual Scientific Meeting of the Korean Society of Hypertension (KSH)

**September 24(Sat)-29(Thu), 2016 Coex, Seoul, Korea**

## Key Date: July 31, 2016

### Submit your abstract and register by July 31, 2016!

There is still a **chance to receive a travel grant** for late-breaking abstracts.

Submit your abstract and grab the chance!

Register today and **benefit from saving up to USD 100 on your registration fee!**

## From the ISH President - Rhian Touyz



The past few months have been a busy and exciting time for ISH with activities spanning Africa, Asia, Europe and South America.

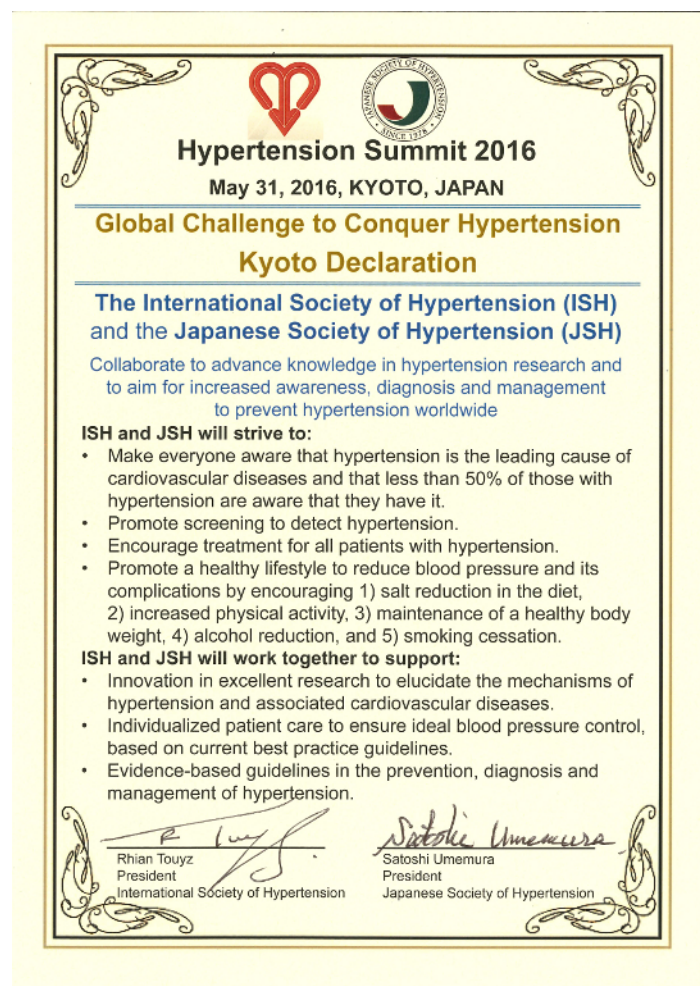
### ISH Teaching Seminar, Maputo, Mozambique - April



*Seminar Faculty members pictured*

In April, the Africa Regional Advisory Group, under the leadership of Professor Basden Onwubere, ran a very successful Hypertension Teaching Seminar in Maputo. This was hosted by a local organising committee chaired by Professor Albertino Damasceno in collaboration with the European Society of Hypertension (ESH), the Mozambican Heart Association (AMOCOR) and the International Forum for Hypertension Control and Prevention in Africa (IFHA). The event, which is highlighted in the current issue of the newsletter, attracted over 65 participants from over 11 African countries. In addition there was representation from the AstraZeneca Healthy Heart programme in Africa. The meeting was a great success and provided opportunities for young doctors and health care providers from across Africa to learn about hypertension.

### Hypertension Summit, Kyoto - May



On the 31<sup>st</sup> May, members of the ISH Executive and Council participated in a very exciting Hypertension Summit in Kyoto organised by the Japanese Society of Hypertension (JSH). This event, which brought together the leadership of ISH and JSH, provided a wonderful platform for the two societies to plan activities together to address the challenges of hypertension globally. The meeting culminated with the signing of the Kyoto Hypertension Declaration between the Societies, pledging to work together to advance knowledge in hypertension research and to aim for increased awareness, diagnosis and management to prevent hypertension worldwide.

### Mexico Declaration - June

In June, ISH signed another important declaration. On the 4<sup>th</sup> June in Mexico City, ISH, together with many other international cardiovascular organisations, participated in the World Heart Federation (WHF) Global Summit on Circulatory Health by signing The Mexico Declaration. The ISH is a proud supporter of the 2016 Mexico Declaration for Circulatory Health in its goals to tackle cardiovascular

disease worldwide. Considering that hypertension is the major preventable risk factor for cardiovascular disease, together with the fact that the mission of the ISH is to promote knowledge and awareness in the prevention and better management of hypertension globally, our Society is well placed to work with the WHF to achieve its goals.

### **ESH Meeting - June**

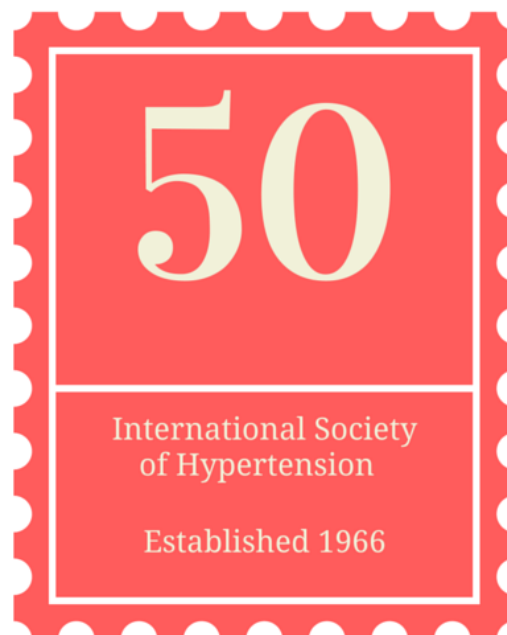
In June, ISH participated in the European Society of Hypertension (ESH) meeting, held in Paris. Many ISH leaders were invited to give special presentations at the Paris meeting and we had a strong presence through our ISH booth in the Exhibition Hall. It is important that ISH and ESH continue to work together to support common missions and we look forward to welcoming ESH members to our 2016 meeting later this year.

### **New Initiatives**

The ISH leadership is working hard to advance many new initiatives to better serve its members globally, such as the creation of a new Fellowship for low-middle-income countries, growth of the 'Women in Hypertension Research' portfolio, continued support of the NIC activities, and on-going liaisons with the local organising committee in Seoul in preparation for the 2016 Biennial Scientific Meeting.

**The meeting promises great science, networking opportunities, wonderful Korean hospitality and fun activities in celebration of 50 years of ISH.**

Please make every effort to join us in Seoul in September 2016. As always, I thank Helen Horsfield, Lars Lindholm and the Communications Committee for their tremendous efforts and hard work in the production of our regular newsletters, which ensures good communications between our global ISH community.



## **KEY EVENTS: HYPERTENSION SEOUL 2016 (ISH SCIENTIFIC MEETING), 24-29 SEPTEMBER**

### **ISH Women in Hypertension Research Launch Event**

**Monday 26<sup>th</sup> September, 12:30-14:00 hrs**

The ISH Women in Hypertension Research Network has been recently established to encourage, support and inspire women in science and medicine in the field of hypertension and related cardiovascular diseases. It aims to allow new avenues for communication, collaboration and education. Please email [secretariat@ish-world.com](mailto:secretariat@ish-world.com) should you be interested in attending this event.

### **ISH International Forum Meeting**

**Tuesday 27<sup>th</sup> September, 12:30-14:00 hrs**

The mandate of the Forum is to establish effective liaison between the ISH and National and Regional Societies of Hypertension or Councils of High Blood Pressure Research. All Forum members and their representatives are invited to attend this meeting.

### **ISH General Meeting**

**Wednesday 28<sup>th</sup> September, 12:30-13:30 hrs**

All individual Society members are encouraged to attend this meeting.



### Commentary on “Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses”

### Benefits of intensive blood pressure lowering in diabetes: throwing the baby out with the bathwater?

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Brunström and Carlberg published a review earlier this year<sup>1</sup> and concluded “antihypertensive treatment reduces the risk of mortality and cardiovascular morbidity in people with diabetes mellitus and a systolic blood pressure more than 140 mm Hg. If systolic blood pressure is less than 140 mm Hg, however, further treatment is associated with an increased risk of cardiovascular death, with no observed benefit.” Naturally the concluding sentence will get most attention. The fundamental basis of the paper’s conclusion was a significant increase in vascular death among trials under 140mmHg, and a linear trend leading from benefit above 140mmHg to harm below 140mmHg. How much does the conclusion stand up to scrutiny? The short answer is: not much. The key issue is that a single large trial of dual renin-angiotensin system (RAAS) blockade accounted for 32% of the statistical weight in the <140mmHg group in the Brunström and Carlberg analysis. Dual RAAS blockade is now contraindicated and recommended against in all major guidelines, so inclusion in the meta-analysis at all is highly questionable. Furthermore the BP difference in this trial was 1.3/0.6mmHg. So how can this be considered a trial of blood pressure lowering? The results for patients with SBP <140mmHg after excluding dual RAAS trials are shown in Figure 1 – clearly these are not compatible with Brunström and Carlberg’s eye-catching conclusion – there is a clear benefit for stroke, and no clear effect on other outcomes.

There are five possible reasons for a trial or meta-analysis to observe lower relative risk reductions at lower blood pressure levels:

1. A true biological phenomenon
2. Use of composite outcomes – using total cardiovascular events or deaths for example, as Brunström and Carlberg do, it is a mathematical inevitability that relative risk reductions will decrease at lower BP levels. Less BP-sensitive outcomes like CHD make up a bigger proportion of cardiovascular events at lower BP levels, while more BP-sensitive outcomes like stroke predominate at higher BP levels. Therefore even if the relative risk reduction in CHD and stroke per mmHg is constant at all BP levels, the relative reduction in cardiovascular events will be lower at lower BP levels
3. Lesser BP reductions at lower baseline BP levels is the norm with all BP interventions. Hence failure to account for this phenomenon with standardization, such as in this review, can lead to conclusions that lower relative risks at lower BP levels are evidence of some attenuation of effect rather than the low blood pressure reduction. Systematic reviews that standardize for blood pressure reduction will give very little statistical weight to trials such as ALTITUDE, and that is appropriate because they contribute very little to the question of assessment of effects of blood pressure reduction.

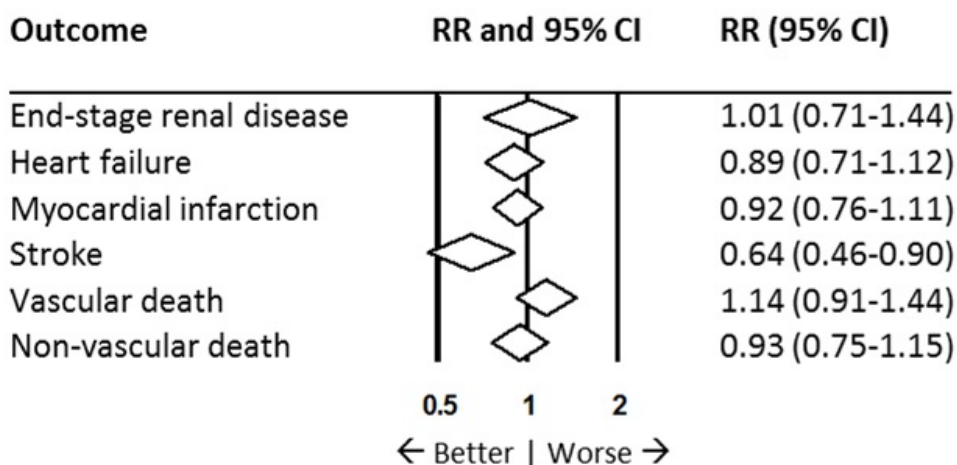
4. Subgroup analysis and chance is always a possibility.<sup>2</sup> The reduction of stroke, CHD, and heart failure by BP lowering across a wide range of patient groups and blood pressure levels (including non “hypertensives”) is a remarkably consistent finding.<sup>3</sup> Some variability in the size of effect is inevitable, especially in subgroups of subgroups (eg. diabetics with SBP <140mmHg)

5. Confounding – types of interventions being tested in non-hypertensives are different from those tested in hypertensives. This is the key issue here - dual RAAS is known to be harmful for reasons unrelated to BP lowering and most trials were done in diabetics with SBP under 140mmHg. So meta-analyses that include these trials run the risk of suggesting the issue is treatment effects in diabetics, or in those with SBP <140mmhg, when in fact it is dual RAAS. This issue can only be partly addressed by excluding dual RAAS trials, since in some of the ARB vs placebo trials some patients had background ACE-I use, for example in 70% of participants in the ORIENT trial.<sup>4</sup> Similarly, in some of the ACE-I vs placebo trials, some patients had background ARB use (for example, 10-13% patients in ADVANCE<sup>5</sup>). This would lead to an underestimation of the net benefits of treatment in these trials.

One further issue at hand is that Brunström and Carlberg did not report the relevant results from the ADVANCE trial,<sup>5</sup> which observed the largest number of events in a diabetic population in a blood pressure lowering trial. Figure 2 clearly shows no evidence of effect modification by baseline blood pressure levels. However, null findings are less newsworthy. We suspect an important issue at play is a well-described cognitive bias: possible risks tend to be more salient and motivating than possible benefits.<sup>6</sup>

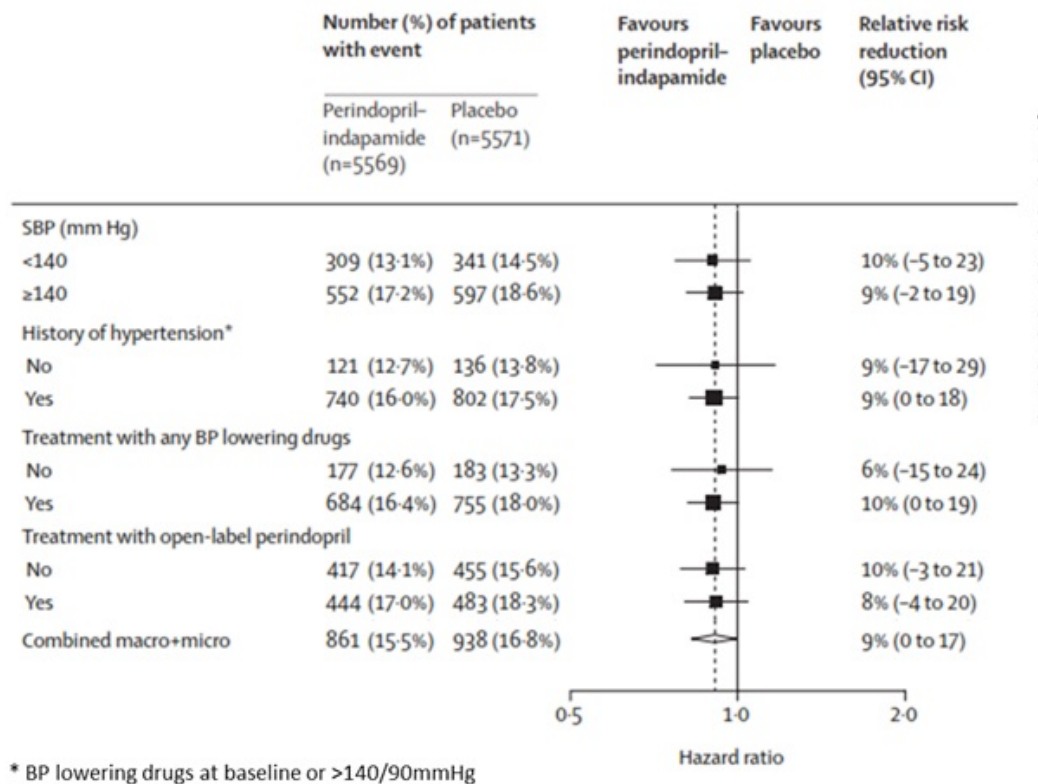
In conclusion, it appears that the Brunström and Carlberg review has “thrown the baby out with the bathwater”. A clinically appropriate analysis that does not include dual RAAS trials does not show a significant harm. Once dual RAAS trials are excluded, it is apparent that established blood pressure lowering interventions have clear benefits among non-hypertensive diabetics for stroke, plus the trends to reduction in CHD and heart failure are consistent with the effects seen in other patient groups. Furthermore a recent review<sup>7</sup> also demonstrated reductions in retinopathy and albuminuria in this patient group. It is possible that relative risk reductions per mmHg BP reduction are lower in diabetics compared to non-diabetics, but detailed individual participant data analyses will be required to confirm or refute this hypothesis. However, the net clinical benefits are also determined by absolute risk, and it is well established that diabetics are at such high risk of cardiovascular and renal events that even comparatively small relative risk reductions could be clinically worthwhile.

**Figure 1: Effects of blood pressure lowering in previous trials in diabetes with baseline SBP <140mmHg (excluding dual renin-angiotensin blockade trials)**



Legend: The data from Brunström and Carlberg<sup>1</sup> are replotted after exclusion of dual RAAS trials. RR = relative risk. Diamond width is proportional to 95% confidence intervals.

Figure 2: Effects of blood pressure lowering in ADVANCE, according to BP level and use of BP lowering drugs Data from ADVANCE trial<sup>5</sup>



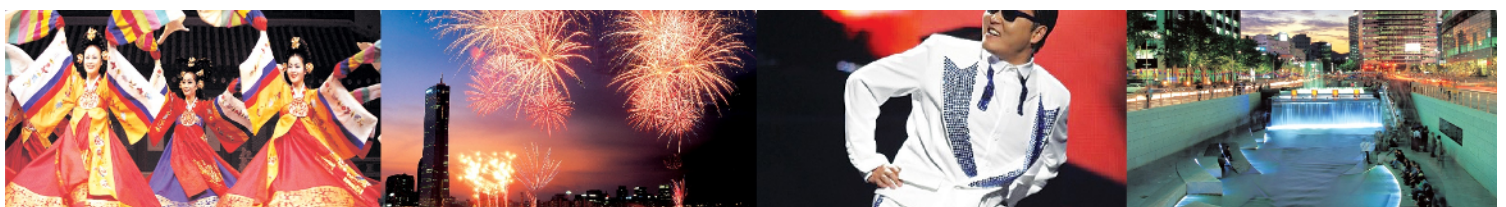
## References

1. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ*. 2016;352:i717.
2. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA*. 1991;266(1):93-8.
3. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *The Lancet*. 2016;387(10022):957-67.
4. Imai E, Chan J, Ito S, Yamasaki T, Kobayashi F, Haneda M, et al. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. *Diabetologia*. 2011;54(12):2978-86.
5. Patel A, Group AC, MacMahon S, Chalmers J, Neal B, Woodward M, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *The Lancet*. 2007;370(9590):829-40.
6. Kahneman D. *Thinking, fast and slow*: Macmillan; 2011.
7. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2015;313(6):603-15.

## Disclosures

George Health Enterprises, the social enterprise arm of The George Institute for Global Health, has received investment to develop combination products containing aspirin, statin and blood pressure lowering drugs.

-Anthony Rodgers and Emily Atkins

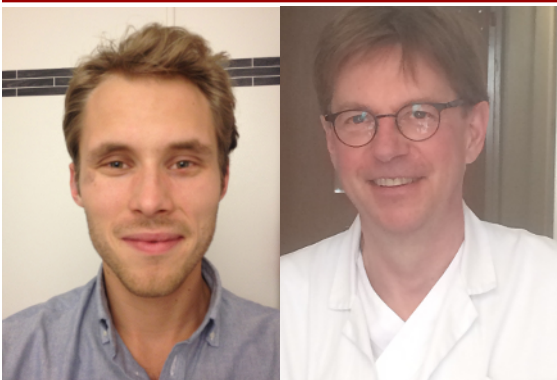


**Join us at the ISH Biennial Scientific Meeting in Seoul in September!**

### Reply to comment by Rodgers & Atkins

Mattias Brunström MD, and Bo Carlberg MD, PhD

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We conducted a systematic review and meta-analysis of the effect of blood pressure lowering at different blood pressure levels in people with diabetes, published in the *BMJ* in February this year.<sup>1</sup> We found a significant interaction between baseline systolic blood pressure and treatment effect on all-cause and cardiovascular mortality, as well as myocardial infarction.

This interaction was further supported by metaregression analyses showing that treatment effect was 12% worse on myocardial infarction and 15% worse on cardiovascular mortality, for each 10 mm Hg lower baseline systolic blood pressure ( $p=0.01$  for both). In people with diabetes and a systolic blood pressure < 140 mm Hg, treatment increased the risk of cardiovascular mortality by 15%.

In a comment in this issue of *Hypertension News*, Drs Rodgers and Atkins argue that these results do not stand up to scrutiny. Their main argument is that our analyses included the ALTITUDE trial, which tested Aliskiren against placebo in people with diabetes and chronic kidney disease, with RAAS-blocking background therapy.<sup>2</sup> They argue that because double RAAS inhibition is now contraindicated, the results of ALTITUDE can be discarded. This is erroneous for three reasons.

First of all, double RAAS treatment is contraindicated partly based on ALTITUDE, and hence excluding ALTITUDE is conditioning the outcome. This is a way to reach one's designated conclusions, and a known source of bias in epidemiology. Secondly, the adverse treatment effect in ALTITUDE has universally been interpreted as due to RAAS inhibition. We believe that this interpretation is poorly supported by data, however, noting that treatment in ALTITUDE increased the risk of cardiac, cerebrovascular and renal events, a combination of outcomes generally more related to blood pressure than RAAS specifically. Thirdly, and perhaps most importantly, we performed sensitivity analyses excluding ALTITUDE from the <140 mm Hg analyses, and found no sign of interaction. Thus, the statement by Rodgers and Atkins, that our results are

not compatible with results excluding double RAAS inhibition, is wrong.

Rodgers and Atkins give five potential explanations to our findings. We agree only to the first one:

2. *Composite outcomes.* In principle, the relative effect on composite outcomes can decrease if the proportion of individual outcomes is shifted towards an outcome on which treatment has less effect. However, it is impossible to find harm, as we do for cardiovascular mortality, if treatment reduces the risk of all components. We argue that the patient who dies from treatment does not care if it is from a stroke or myocardial infarction, and hence cardiovascular mortality is a highly relevant composite outcome even if internal proportions differ across blood pressure strata.

3. *Lesser BP reductions at lower baseline BP levels.* We agree that lesser blood pressure reduction is the norm at lower blood pressure levels.<sup>3</sup> This is one of two key reasons NOT to perform standardized meta-analyses. Unstandardized meta-analyses, as we did, reflect the actual treatment effect in the included trials. As clinicians, we want to know the effect of adding another agent, which is the situation you face in everyday practice.

Standardisation of study weights, as Rodgers and Atkins argue for, is even more prone to introduce bias than standardisation of results according to blood pressure reduction. The whole purpose of weighting is that each study should contribute to the overall estimate to the same extent as it contributes with patients and events. In a recent standardized analyses by Rodgers, Atkins and co-authors, the EWPHE trial, with 162 deaths in 840 participants, is given as much weight as 32 trials, including 5,611 deaths in 107,693 participants, combined (page 23, web appendix).<sup>4</sup> This does not make sense.

4. *Subgroup analysis.* Our findings were consistent



across several outcomes, in both interaction analyses and metaregression analyses, and for both baseline and attained systolic blood pressure. We think this speaks strongly against chance findings. Rodgers and Atkins state that the reduction of stroke, coronary heart disease and heart failure by blood pressure lowering across a wide range of patient groups and blood pressure levels is a remarkably consistent finding. They refer to an analysis using standardisation as described above, however, with the remarkable consistency being an effect of standardisation rather than trial results.<sup>4</sup>

5. As mentioned above, treatment effect was not different in ALTITUDE compared to other trials. Since all trials in people with diabetes and a systolic blood pressure < 140 mm Hg are trials of RAAS-inhibitors with various degrees of background therapy, it is impossible to separate RAAS effect from blood pressure lowering effect. To assume that all harm comes from RAAS inhibition and state that the effect of blood pressure lowering differs to the results of the included trials is not appropriate.

ADVANCE was included in our analyses. We cannot see why we should have handled it differently compared to other studies.

Rodgers and Atkins conclude that we are throwing the baby out with the bathwater, presumably referring to treatment benefit as the baby, however, there is no baby in the water.

**- Mattias Brunström and Bo Carlberg**

#### REFERENCES

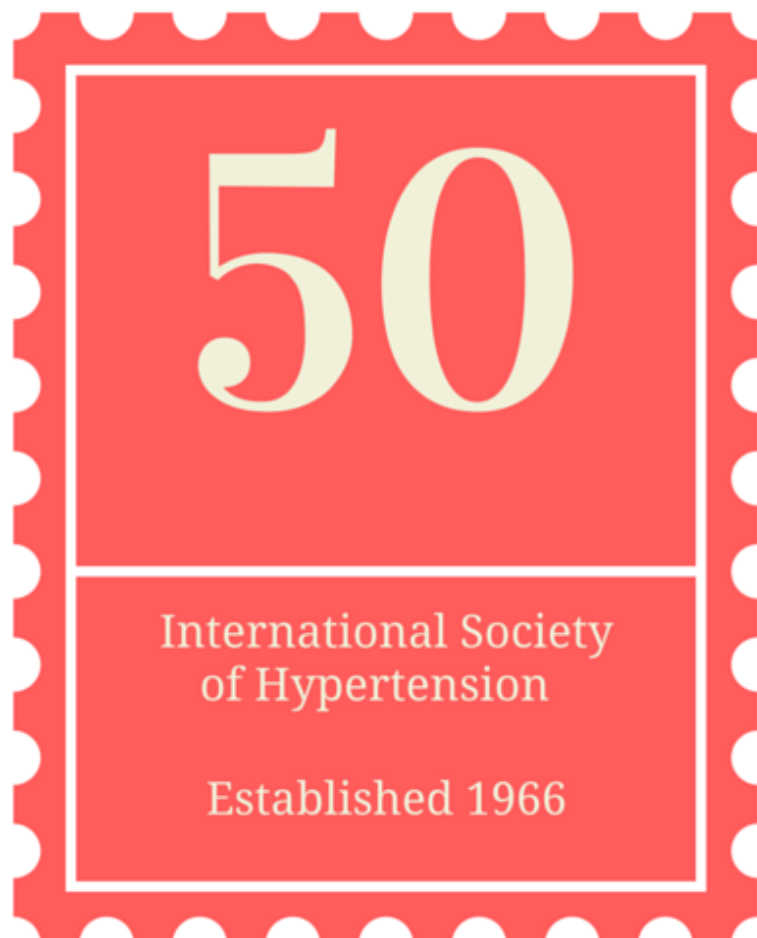
1. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ* 2016; **352**: i717.
2. Parving HH, Brenner BM, McMurray JJV, et al. Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes. *New England Journal of Medicine* 2012; **367**(23): 2204-13.
3. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *British Medical Journal* 2009; **338**: 34.
4. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; **387**(10022): 957-67.

## Reply to Brunström MD, Carlberg MD

We thank Drs Brunström and Carlberg for their response. The essence of the argument is whether a meta-analysis assessing blood pressure lowering should give large statistical weight to a trial in which BP was reduced by only 1.3/0.6mmHg using dual RAAS inhibition. For any clinicians considering using dual RAAS inhibition among the treatment regimens provided to their patients with diabetes, then the Brunström and Carlberg findings are the most relevant and an increase in cardiovascular death can be expected.

**For clinicians who plan only to use other BP lowering regimens, then the revised analysis we presented is the most relevant; there is no evidence that vascular death is increased and there is clear evidence that important outcomes such as stroke are reduced.**

**-Anthony Rodgers and Emily Atkins**



### Thomas Kahan

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### More HOPE in the treatment of hypertensive patients

**A multifactorial approach in primary prevention of high-risk people to prevent future cardiovascular disease is recommended [1]. Both blood pressure and cholesterol levels show associations with cardiovascular disease. Thus, combined lowering of blood pressure and cholesterol can potentially offer a greater protection for future cardiovascular events than either intervention alone.**

Some studies suggest that lipid lowering therapy for primary prevention [2,3] or antihypertensive therapy in prehypertension [4,5] may offer benefit. However, the efficacy of treatment with different drugs and their combinations in primary prevention has not been well studied. The recently presented results of the Heart Outcomes Prevention Evaluation (HOPE) -3 trial extend our knowledge, and provide evidence to influence future recommendations in the primary prevention of people at low-to-intermediate cardiovascular risk [6-8].

HOPE-3 was a two-by-two factorial design randomized controlled study in 21 countries of 12075 intermediate-risk men (55 years or above) and women (60 years or above) with no previous cardiovascular disease. The participants were randomized to receive blood pressure lowering therapy with a fixed combination of an angiotensin receptor blocker and a diuretic (candesartan 16 mg and hydrochlorothiazide 12.5 mg od) or placebo, and a statin (rosuvastatin 10 mg od) or placebo for a median of 5.6 years. The mean age in the four study groups was 66 years, 46% were female, body mass index 27 kg/m<sup>2</sup>, blood pressure 138/82 mm Hg, LDL-cholesterol 3.3 mmol/L, and high sensitive CRP 2.0 mg/L. The first co-primary composite endpoint was cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, and the second composite endpoint also included revascularization, heart failure, and resuscitated cardiac arrest.

As compared to placebo, statin treatment reduced LDL-cholesterol levels by 26%, and reduced the co-primary endpoint (3.7 vs 4.8% by placebo) by 26%

(95% confidence interval 9 to 36%); with similar results for the second primary endpoint [6]. The benefit was similar in participants with CRP levels below or above a median of 2 mg/L. Blood pressure lowering treatment decreased blood pressure by 6/3 mm Hg compared to placebo but did not reduce the co-primary endpoint (4.1 vs 4.4% by placebo), ie by 7% (95% confidence interval -21 to 10%); the results for the second primary endpoint were similar [7]. In a pre-specified analysis of the outcome by baseline systolic blood pressure tertiles, blood pressure lowering treatment in the highest tertile (above 143.5 mm Hg) reduced both co-primary outcomes significantly more than placebo. Finally, compared to placebo, statin and blood pressure lowering therapy combined reduced the first co-primary endpoint (3.6 vs 5.0% by placebo) by 29% (95% confidence interval 10 to 44%); again with similar results for the second primary endpoint [8]. The numbers needed to treat to prevent one event of the primary and secondary co-primary outcome were 72 and 63, respectively. Muscle weakness and dizziness were more common by active treatment but discontinuation rates were similar in the two study groups.

These findings have implications for primary prevention of cardiovascular disease. The results suggest that primary prevention with statin treatment provides benefit in intermediate-risk people, and the decision to treat should be based on cardiovascular risk, rather than on LDL-cholesterol levels alone. The combination of an angiotensin receptor blocker and a diuretic reduced cardiovascular events in people with an initial systolic blood pressure above 143.5 mm Hg, in support of several previous studies showing a benefit of antihypertensive treatment in patients with a systolic blood pressure of 140 mm Hg or above. Antihypertensive therapy in patients with a systolic blood pressure below approximately 140 mm Hg, however, appears to offer little benefit. Whether the use of other blood pressure lowering drug combinations and/or doses to achieve a greater reduction in blood pressure provides other results remains to be studied. Recent results have suggested benefit of

antihypertensive treatment in high-risk cardiovascular patients with lower blood pressure values [9]. In contrast, the participants in HOPE-3 had an intermediate cardiovascular risk, with a 5% risk of cardiovascular death, non-fatal myocardial infarction or stroke over a period of 5.6 years. Thus, as for statin treatment, the decision to treat should be based on cardiovascular risk, rather than blood pressure values levels alone. In summary, the results of HOPE-3 support primary prevention in intermediate-risk people with a combination of a fixed combination of an angiotensin receptor blocker and a diuretic, and a statin. However, in people with a 5 year cardiovascular event risk below approximately 5% and a systolic blood pressure below approximately 140 mm Hg blood pressure lowering treatment does not seem to be useful.

- Thomas Kahan

## REFERENCES

1. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016 [Epub ahead of print June 8, 2016]
2. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in

- men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7
3. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195-207
4. Julius S, Nesbitt SD, Egan BM, Weber MA, Michelson EL, Kaciroti N, et al. Trial of Preventing Hypertension (TROPHY). *New Engl J Med* 2006;354:1685-9
5. Lüders S, Schrader J, Berger J, Unger T, Zidek W, Böhm M, et al. The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure: a prospective, randomized, controlled prevention trial of the German Hypertension League. *J Hypertens*. 2008 J;26:1487-96
6. Lönn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;374:2009-20
7. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;374:2021-31
8. Yusuf S, Lönn E, Pais P, Bosch J, López-Jaramillo P, Zhu J, et al. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. *N Engl J Med* 2016;374:2032-43
9. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103-16

## ISH Funding for Mentors and Organisations to Train Research Scholars in Hypertension: **DEADLINE 27 JULY 2016**

### **PURPOSE:**

There is a critical need to establish and support high quality training programs within low/middle income countries that can enhance the early careers of researchers in the basic science, clinical and public health areas of hypertension. To help meet this need the Society is offering awards to mentors in these countries who have the expertise and resources to offer fellowship training in hypertension disciplines to young investigators.

### **WHO IS ELIGIBLE?**

Applications are invited from established basic scientists, clinicians or public health experts with experience in mentoring early career scientists in hypertension research. Mentors should be located in low/middle income countries Mentors should be able to identify and attract suitable candidates for training from within their own low/middle income geographic region, although if needed ISH can provide help in finding eligible fellows for the training programme. Mentors should ideally be ISH members.

**View the ISH website for further information.**

Thomas Kahan

Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine, Stockholm, Sweden; and Department of Cardiology, Danderyd University Hospital Corporation, Stockholm, Sweden

### No benefit of yoga in the treatment of hypertension

**Life style intervention is a key factor for cardiovascular risk prevention, including hypertension [1].**

**Psychological stress is increasingly being recognised as a modifiable cardiovascular risk factor. Thus, stress management and behaviour may be one way to reduce blood pressure and cardiovascular risk [2]. Although small studies have suggested that yoga may reduce blood pressure, larger confirmatory studies of yoga in the management of hypertension have been awaited [3].**

A recent study by Wolff and collaborators aimed to study the effects of a home-based yoga programme in patients with prehypertension or mild-to moderate hypertension [4]. The authors screened electronic health records of patients attending Swedish primary health care aged 30 to 80 years with a diagnosis of hypertension and the most recently recorded blood pressure of 130-160/85-100 mm Hg. Out of 1020 patients assessed for eligibility, 191 with a systolic and diastolic blood pressure of 130-160 and/or 85-100 mm Hg and stable medication for at least four weeks were eventually randomized to either yoga or usual standard care treatment. The yoga programme offered was a form of Kundalini yoga with two exercises, taking about 15 min, twice daily for 12 weeks. The primary outcome was a between-group difference in office systolic blood pressure, and the study had an *a priori* calculated 80% power to detect a 5 mm Hg difference with a two-sided significance level of 5%.

The mean age of the participants was 65 years, 50% were female, and body mass index was 28 kg/m<sup>2</sup>. Baseline office blood pressure was 149/88 mm Hg and 90% were on medication with an average of 1.5 antihypertensive drugs. The reductions by week 12 (mean values and 95% confidence intervals) in systolic blood pressure in the intervention and control groups were -3.8 (-6.5; -1.2) and -4.5 (-7.0; -1.9) mm Hg, and in diastolic blood pressure -1.7 (-3.3; -0.2) and -3.0 (-4.6; -1.4) mm Hg, respectively; the difference between the groups in systolic and diastolic blood pressure were 0.5

(-3.0; 3.9) and 1.4 (-0.7; 3.4) mm Hg. Self-rated health satisfaction and depression score improved in the yoga group ( $P < 0.001$  and  $P = 0.001$ , respectively, vs the control group), whereas self-rated quality of life was unchanged by treatment in both groups.

Thus, this adequately powered randomized controlled study of yoga to reduce blood pressure in hypertensive patients attending primary health care shows that yoga during 12 weeks improves self-rated health satisfaction but does not have an impact on blood pressure. The results extend previous smaller studies [3] and provide little evidence in favour of yoga for the treatment of hypertension. However, other types of yoga interventions might provide different results on blood pressure. Also, cultural and geographical background may influence the results. Of note, randomized controlled studies of yoga conducted in India have about 25 times higher odds to show positive results [5]. In conclusion, non-pharmacological interventions to reduce blood pressure in hypertensive patients could be of great value. However, yoga may not be the way to go for further studies.

- Thomas Kahan

#### REFERENCES

1. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016 [Epub ahead of print June 8, 2016]
2. Hjemdahl P, Rosengren A, Steptoe A (eds). *Stress and cardiovascular disease*. Springer-Verlag London 2012, pp 1-390
3. Cramer H, Haller H, Lauche R, Steckhan N, Michalsen A, Dobos G. A systematic review and meta-analysis of yoga for hypertension. *Am J Hypertens* 2014;27:1146-51
4. Wolff M, Rogers K, Erdal B, Chalmers JP, Sundquist K, Midlöv P. Impact of a short home-based yoga programme on blood pressure in patients with hypertension: a randomized controlled trial in primary care. *J Hum Hypertens* 2016. [Epub ahead of print January 21, 2016]
5. Cramer H, Lauche R, Langhorst J, Dobos G. Are Indian yoga trials more likely to be positive than those from other countries? A systematic review of randomized controlled trials. *Contemp Clin Trials* 2015;41:269-72



Alissa A Frame and Richard Wainford

Boston University, Boston, USA

### Interleukin-17A Regulates Renal Sodium Transporters and Renal Injury in Angiotensin II-Induced Hypertension

Allison E. Norlander, Mohamed A. Saleh, Nikhil V. Kamat, Benjamin Ko, Juan Gnecco, Linjue Zhu, Bethany L. Dale, Yoichiro Iwakura, Robert S. Hoover, Alicia A. McDonough, Meena S. Madhur / *Hypertension* 2016; 68:167-174

**Hypertension and renal sodium handling are intrinsically linked: impairment of sodium excretion contributes to an increase in blood pressure, and chronically increased blood pressure leads in turn to renal end-organ damage that can impair sodium excretion. The pathogenic mechanisms underlying hypertension, and those linking hypertension with alterations in renal sodium transport, remain largely unknown. Recent evidence implicates IL-17A as an important player in the development of high blood pressure and impaired natriuresis in animal models of deoxycorticosterone acetate-salt hypertension<sup>1</sup> and angiotensin II-induced hypertension,<sup>2</sup> and increased levels of IL-17A have been observed in human prehypertension.<sup>3</sup>**

In a recent study published in *Hypertension*, Norlander et al. identified a novel role for interleukin-17A (IL-17A) in the regulation of several key renal sodium transporters. Using IL-17A knockout mice, the authors demonstrate that the absence of IL-17A completely abrogates angiotensin II-induced activation of the distal convoluted tubule sodium-chloride cotransporter (NCC) and proximal tubule sodium hydrogen exchanger (NHE3) and upregulation of NCC expression. Angiotensin II-induced activation of sodium and glucocorticoid-regulated kinase 1 (SGK1) was also reduced in IL-17A knockout mice. In vitro studies using distal convoluted tubule and proximal tubule cell lines revealed IL-17A-driven increases in NCC activity and NHE3 expression are accompanied by an increase in SGK1 activity and abolished by an SGK1 inhibitor. A reduction in IL-17A-induced NCC activation following lentiviral knockdown of Nedd4-2, a ubiquitin ligase downstream of SGK1, provides further evidence that IL-17A mediates angiotensin II-induced increases in NCC and NHE3 expression and activity via an SGK1-dependent mechanism. In relation to the attenuation of end-organ hypertensive damage, the

absence of IL-17A in vivo protects knockout mice against angiotensin II-induced glomerular and tubular injury. In contrast, and highlighting the specific impact of IL-17A, angiotensin II-induced renal injury and changes in NCC and NHE3 expression and activity were preserved in IL-17F knockout animals. Importantly, the protective effects of IL-17A deficiency were observed after four weeks of angiotensin II infusion, a time point at which IL-17A deficiency also protects against angiotensin II-induced hypertension and impaired fluid and electrolyte homeostasis.

Norlander et al. have provided evidence for an IL-17A-SGK1-Nedd4-2 pathway mediating increases in renal sodium transporter activity and expression in angiotensin II-induced hypertension. The protective effect of IL-17A deficiency against increased renal sodium reabsorption, coupled with previous observations that IL-17A deficiency protects against angiotensin II-mediated increases in blood pressure,<sup>2</sup> makes a strong case for the novel application of therapeutics targeting IL-17A in hypertension. It is important to highlight that IL-17A deficiency does not merely reduce, but rather completely abolishes, angiotensin II-induced changes in NCC and NHE3 abundance and activity and renal tubular and glomerular injury. As noted by the authors, an anti-IL-17A therapeutic approach that would reduce sodium retention at both the NHE3 and NCC would likely prove more clinically efficacious than NCC-specific thiazide diuretics, the current first line mainstay of antihypertensive therapy. The development of a more effective therapeutic approach targeting multiple sodium transporters simultaneously could also reduce the need for combination drug therapy, thereby improving issues with patient compliance that continue to hinder blood pressure control.<sup>4</sup> This delineation of the potential therapeutic utility of targeting IL-17A in hypertension by Norlander et al. is particularly timely given the 2015 FDA approval of the IL-17A antagonist secukinumab for

plaque psoriasis<sup>5</sup> and the recent clinical evidence from the PATHWAY-2 Trial, which suggests a primary role of sodium retention in resistant hypertension.<sup>6</sup>

**-Alissa A. Frame and Richard Wainford**

## REFERENCES

1. Amador CA, Barrientos V, Pena J, Herrada AA, Gonzalez M, Valdes S, Carrasco L, Alzamora R, Figueroa F, Kalergis AM, Michea L. Spironolactone decreases DOCA-salt-induced organ damage by blocking the activation of T helper 17 and the downregulation of regulatory T lymphocytes. *Hypertension*. 2014;63(4):797-803.

2. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik TJ, Harrison DG. Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction.

*Hypertension*. 2010;55:500-507.

3. Yao W, Sun Y, Wang X, Niu K. Elevated serum level of interleukin 17 in a population with prehypertension. *Journal of Clinical Hypertension*. 2015;17(10):770-4.

4. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. 2009;119:3028-3035.

5. Sanford M, McKeage K. Secukinumab: first global approval. *Drugs*. 2015;75(3):329-38.

6. Williams B, MacDonald T, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salisbury J, Mackenzie I, Padmanabhan S, Brown MJ, for The British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomized, double-blind, crossover trial. *Lancet*. 2015;386:2059-68.

## KEY EVENTS: HYPERTENSION SEOUL 2016 (ISH SCIENTIFIC MEETING), 24-29 SEPTEMBER

### ISH Women in Hypertension Research Launch Event

**Monday 26<sup>th</sup> September, 12:30-14:00 hrs**

The ISH Women in Hypertension Research Network has been recently established to encourage, support and inspire women in science and medicine in the field of hypertension and related cardiovascular diseases. It aims to allow new avenues for communication, collaboration and education. Please email [secretariat@ish-world.com](mailto:secretariat@ish-world.com) should you be interested in attending this event.

### ISH International Forum Meeting

**Tuesday 27<sup>th</sup> September, 12:30-14:00 hrs**

The mandate of the Forum is to establish effective liaison between the ISH and National and Regional Societies of Hypertension or Councils of High Blood Pressure Research. All Forum members and their representatives are invited to attend this meeting.

### ISH New Investigator Mentorship and Networking Event

**Tuesday 27<sup>th</sup> September, evening - time to be confirmed**

A perfect opportunity for new investigators (PhD students, post-docs or clinical research fellows) to mingle with their peers and senior ISH Faculty in a relaxed environment. These events play an important part in developing networking opportunities for young members of the ISH and promoting their long-term collaborations with established investigators. Please email [secretariat@ish-world.com](mailto:secretariat@ish-world.com) should you be interested in attending this event.

### ISH General Meeting

**Wednesday 28<sup>th</sup> September, 12:30-13:30 hrs**

All individual Society members are encouraged to attend this meeting.

## Institute Focus



### The Human Neurotransmitters Laboratory of the Baker IDI Heart and Diabetes Institute

Murray Esler

*ISH Hypertension News* commonly presents signature reports from large cardiovascular centres or university departments. The invitation has gone out because these are places which shine like a beacon in our discipline of hypertension. And the published report does them full justice; discoveries abound and research metrics overflow. In contrast, this month's report is in miniature, an account of a single laboratory "down under", resident in the Baker IDI Heart and Diabetes Institute, the *Human Neurotransmitters Laboratory*.

### Antecedents

This laboratory provided a personal journey in cardiovascular neuroscience for its founder, Murray Esler. Esler took postdoctoral employment in the Hypertension Division of the University of Michigan Medical Centre, Ann Arbor Michigan, working with Professor Stevo Julius. Julius pioneered the investigation of borderline hypertension, which he recognised as the progenitor of more severe, sustained hypertension. He rightly believed that the developmental pathophysiology of essential hypertension could be best studied in this early phase. Julius used the measurement of hypertension haemodynamics, and its modification by pharmacological autonomic blockade as his investigative tools to study neural mechanisms in hypertension. In Ann Arbor, Esler set up a new research initiative which applied plasma noradrenaline measurements in parallel with the existing research techniques.

Despite successes achieved with this program (1), deficiencies of plasma noradrenaline measurements in quantifying human sympathetic nervous system activity were evident. Esler developed the idea that isotope dilution methodology, with radiolabelled noradrenaline, might be applied to establish a more valid technique for measuring the release rate of the neurotransmitter from sympathetic nerves. The response of the University of Michigan Medical Center administrators was that this could not be done without 2 years full time training in nuclear medicine! Given this depressing news Esler made plans to return to Australia in early 1977, to the Baker Research Institute, where the regulatory controls might be less burdensome. Faced with the loss of his young protégé, Julius spoke with an Australian colleague, Professor Austin Doyle - - - **Julius:** "What do they do at the Baker Institute"? **Doyle:** "They bake".

### Early Years of the Human Neurotransmitters Laboratory

The then director of the Baker Institute, Professor Paul Korner, provided a nurturing home for the fledgling laboratory. At its commencement it ran on a shoe string; Esler's salary came from an NHMRC (governmental) fellowship, a research grant provided salary support for the sole research assistant, and the adjacent Alfred Hospital provided generous, if at times unwitting support, prior to the days of meticulous hospital unbundling of expenses. The research goal was the development of better ways of studying the human sympathetic nervous system. Circa 1980 this was a "black hole". Development of the



**Figure 1 (left)**

*Measurement of whole body noradrenaline plasma spillover in a patient with pure autonomic failure, tilted head-up to disclose the impaired sympathetic circulatory reflex. An informally dressed Gavin Lambert and young Murray Esler, circa 1985, are conducting the procedure.*

isotope dilution technique for measuring the overall appearance rate of the sympathetic neurotransmitter in plasma filled this need at first. It was Paul Korner who coined the term, "noradrenaline spillover" for the plasma noradrenaline appearance rate. This research tool was applied in the investigation of the sympathetic neural physiology of circulatory control (Figure 1) aging, exercise and mental stress responses, and the neural pathophysiology of cardiac failure and essential hypertension (2).

## Regional Sympathetic Activity in Humans

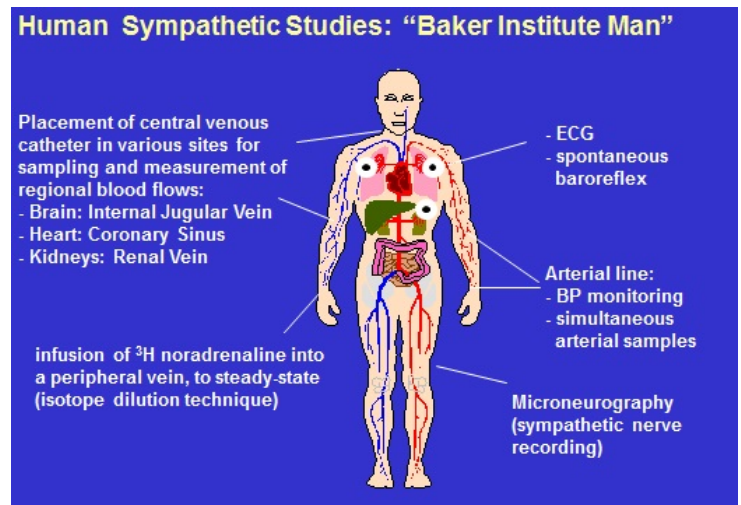


**Figure 3 (right)**

*Representation of a full complement of research procedures conducted on a participating volunteer patient.*

**Figure 2 (left)**

*Assessment of regional sympathetic activity, using organ-specific noradrenaline spillover measurements in a patient (circa 1989). Blood sampling for measurement of noradrenaline and tritiated noradrenaline plasma concentrations is being done simultaneously via a central venous catheter and a brachial artery cannula (2). The infusion pump in the left foreground is infusing intravenously tritiated noradrenaline, for the isotope dilution measurement of noradrenaline spillover, and para-aminohippurate (PAH) as the indicator substance to measure renal plasma flow, needed for the renal noradrenaline spillover measurement. The proceduralist at the catheter laboratory table is Ian Meredith. The doctors watching on are Garry Jennings and Peter Friberg.*



Information conveyed by measurements of the overall rate of release of noradrenaline to plasma, however, has one substantial deficiency. The sympathetic nervous system is not organised as an all-or-nothing system, since the sympathetic outflow to all organs is not uniform, and local, organ-specific increases or decreases in sympathetic activity can occur with different reflexes, and in diseases. A biochemical index of overall sympathetic activity represents the algebraic sum of the changes in regional noradrenaline release, and has very restricted physiological meaning, since the pattern of sympathetic nervous activation is not delineated. For more penetrating analysis, techniques allowing study of regional, organ-specific sympathetic nervous function were developed (Figure 2)(2).

To these measurements of regional noradrenaline release was grafted sympathetic nerve recording, using clinical microneurography. Professor Gunnar Wallin, visiting from Gothenburg on a mini-sabbatical, provided the expertise. Organ-specific sympathetic nervous activity could now be studied, most importantly in the heart and kidneys as it turned out, with re-positioning of a central venous sampling catheter giving the necessary access to the draining veins of multiple organs, in the one sitting, this being done in tandem with sympathetic nerve recording. Now the "Baker Institute Man" (Figure 3) was complete, and the Human Neurotransmitter Laboratory began to sing. A high level of chronic activation of the cardiac sympathetic outflow was demonstrated in patients with heart failure, this providing the theoretical backdrop for the evaluation of beta-adrenergic blockers in this condition (3). More recently, the earlier demonstration of activation of the renal sympathetic outflow in essential hypertension (4) was a stimulus for the development of the new treatment for difficult to control patients, radio-frequency ablation of the renal

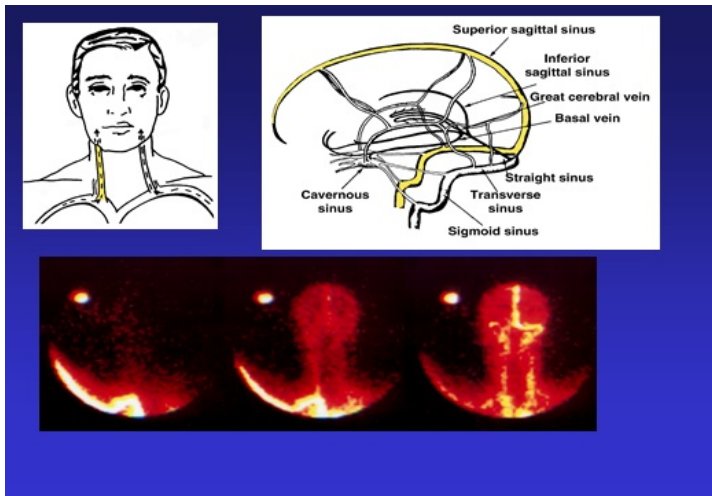


sympathetic nerves with purpose-designed renal artery catheter (5). The renal noradrenaline spillover method developed in 1982 (6) is now a test for renal denervation in 2016. But everyone in hypertension, of course, knows that renal denervation is an unfinished story!

## Other Neuroscience Methods, Other Research Targets

The regional monoamine kinetics method was also applied to the brain, allowing the laboratory to “trespass” on neuropsychiatry (Figure 4). It turned out, for example, that in depressive illness and panic disorder, which are often comorbid conditions, CNS turnover of serotonin was elevated (7,8), not what you would expect, given the therapeutic efficacy or selective serotonin reuptake blocking drugs, which are said to increase brain serotonin turnover. Accepting this research result would have been a paradigm shift for psychiatry, but psychiatry has not paradigm-shifted!

Application of the method in patients with essential hypertension demonstrated that noradrenaline turnover is increased in suprabulbar subcortical brain regions, this being a driver of the sympathetic activation present (Figure 4)(9). Now this earlier finding takes on new meaning, with the demonstration in renal denervation studies that renal afferent nerves in hypertension project to the CNS, demonstrably increase central noradrenaline turnover in experimental hypertension (10), and cause sympathetic nervous activation.



**Figure 4 (left)**

*Blood sampling from the internal jugular vein, to determine brain monoamine turnover, with the catheter tip placed beyond the angle of the jaw, to exclude blood draining from the face and scalp. The bottom panel shows a sequence of images of the cerebral venous sinuses during injection of the patient's own technetium 99 labelled red cells. Viewed from the back in this patient, sagittal venous sinus drainage is seen to be predominantly to the right. Knowing this, bilateral internal jugular venous sinus sampling allows discrimination between monoamine turnover in the cortex, and in suprabulbar cortical regions (9), in this patient the left vein providing subcortical measurements, and the right vein cortical measurements. Application of this methodology allowed demonstration that subcortical noradrenaline turnover was markedly increased, and a driver of sympathetic activation in essential hypertension (9).*

**Figure 5 (right)**

*Performing a subcutaneous vein biopsy to access tissue for sympathetic nerve molecular studies. Subcutaneous veins have dense sympathetic innervation. Proteins are extracted for Western blot analysis. The biopsy is being done by Garry Jennings. The vein belongs to Gavin Lambert, who kindly acted as the first volunteer for the procedure.*

**Vein Biopsy: Sympathetic Nerve Proteins for Western blot Studies**



Deviating a little from its high blood pressure remit were studies done by the laboratory on circulatory control disorders characterised by orthostatic intolerance and postural syncope. Pivotal in this work was the development of a biopsy method to study human sympathetic nerve proteins (Figure 5). Subcutaneous veins, which served as the biopsy sample, have a dense sympathetic innervation. Western blot analysis allows abundance of critical sympathetic nerve proteins to be determined. It turned out that this analysis can sometimes provide a “molecular signature” of the autonomic neural disability in orthostatic intolerance (OI) disorders. One phenotype delineated was characterised by low BP while supine (and lower still while standing), low tyrosine hydroxylase content in

sympathetic nerves, lowered rates of noradrenaline spillover under gravity and increased, presumably compensatory sympathetic nerve firing (11). The noradrenaline pro-drug, LDOPS, has been successfully trialled in this OI variant, to overcome the deficiency in the noradrenaline-synthesizing enzyme.

## Structure and Personnel of the Human Neurotransmitter Laboratory

The structure of the laboratory has been fluid, ebbing and flowing according to the research needs (and of course funding). And staff and students have flowed in and out, according to their own personal and career needs. But some have been permanent, most notably Gavin Lambert, who was recruited as a young research assistant in 1985, and is now graced by the titles of "Professor" and "Laboratory Head". Alex Bobik and Graeme Jackman provided indispensable assistance in the laboratory start-up. At the coal face throughout have been faithful research assistants; Paul Leonard, Dianne Kelleher and Flora Socratous. Many PhD students toiled, some of whom are now celebrated; Ian Meredith, David Kaye. Some postdoctoral students actually arrived distinguished, and are now eminent; Graeme Eisenhofer, Peter Friberg, Claudia Ferrier, HansPeter Brunner-LaRocca and Markus Schlaich. Long-serving staff made their mark; Elisabeth Lambert, Jane Thompson, Ling Guo, Nina Eikelis, Carolina Sari and Nora Straznicky. Colleagues within the Institute collaborated, most notably Garry Jennings, as a partner-in-research, cardiac proceduralist for central venous catheterisations, informally as plastic surgeon for vein biopsies, and latterly, as Institute Director. And the contribution of those on sabbatical leave was crucial; Gunnar Wallin, Guido Grassi, Oleg Medvedev and Bob Mazzeo. At centre stage were our research volunteers, who participated selflessly, and bravely, in what were often invasive studies. The laboratory, and medicine, is in their debt.

**These are the people who made the Human Neurotransmitter Laboratory for two decades the engine room of the Baker Institute. And the laboratory has been under notice throughout, with receipt of awards from the International Society of Hypertension (2000), European Society of Hypertension (2012), US High Blood Pressure Research Council (2013) and the American College of Cardiology (2014). But the discoveries made, and any contribution to human health are our real reward.**

- Murray Esler

### REFERENCES

1. Esler M, Julius S, Zweifler A, Randall O, Harburg E, Gardiner H, DeQuattro V. Mild high-renin essential hypertension: a neurogenic human hypertension? *New Engl J Med* 1977;296:405-411.
2. Esler M, Jennings G, Lambert G, Meredith I, Horne M, Eisenhofer G. Overflow of catecholamine neurotransmitters to the circulation: Source, fate and functions. *Physiological Reviews* 1990;70: 963-985.
3. Hasking G, Esler M, Jennings G, Burton D, Johns J, Korner P. Norepinephrine spillover to plasma in congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation* 1986;73:615-621.
4. Esler M, Jennings G, Korner P, Willett I, Dudley F, Hasking G, Anderson W, Lambert G. The assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension* 1988;11:3-20.
5. Krum H, Schlaich MP, Whitbourn R, Sobotka P, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009;373:1275-1281
6. Esler M, Blombery P, Leonard P, Jennings G, Korner P. Radiotracer methodology for the simultaneous estimation of total, and renal, sympathetic nervous system activity in humans. *Clin Sci* 1982;63:285S-287S.
7. Barton DA, Esler MD, Dawood T, Lambert EA, Hailerwal D, Brenchley C, Socratous F, Hastings J, Guo L, Wiesner G, Kaye DM, Bayles R, Schlaich MP, Lambert GW. Elevated brain serotonin turnover in patients with depression: Effect of genotype and therapy. *Archives of General Psychiatry* 2008;65:1-9.
8. Esler M, Lambert E, Alvarenga M, Socratous F, Richards J, Barton D, Pier C, Brenchley C, Dawood T, Hastings J, Guo L, Haikerwal D, Kaye D, Jennings G, Kalff V, Kelly M, Wiesner G, Lambert G. Increased brain serotonin turnover in panic disorder patients in the absence of a panic attack: Reduction by a selective serotonin reuptake inhibitor. *Stress* 2007;10:295-304.
9. Ferrier C, Jennings GL, Eisenhofer G, Lambert G, Cox HS, Kalff V, Kelly M, Esler MD. Evidence for increased noradrenaline release from subcortical brain regions in essential hypertension. *J Hypertension* 1993;11:1217-1227.
10. Campese VM, Kogosov E. Renal afferent denervation prevents hypertension in rats with chronic renal failure. *Hypertension*. 1995;25:878-882.
11. Vaddadi G, Guo L, Esler M, Socratous F, Schlaich M, Chopra R, Eikelis N, Lambert G, Trauer T, Lambert E. Recurrent postural vasovagal syncope: Sympathetic nervous system phenotypes. *Circulation Arrhythmia* 2011;4:711-718.

# Inhaling the Cardio-Metabolic Syndrome: The Global Epidemics of Air Pollution, Hypertension and Diabetes



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### ABSTRACT

Growing evidence supports that fine particulate matter (PM<sub>2.5</sub>) air pollution, a leading cause of global morbidity and mortality, plays a role in elevating BP. Recent studies demonstrate that long-term exposure to ambient concentrations of PM<sub>2.5</sub> is further capable of promoting the development of chronic hypertension as well as other aspects of the metabolic syndrome including diabetes mellitus (DM). While PM<sub>2.5</sub> levels are improving across most of North America and Western Europe, much of the developing world (e.g., China and India) faces an unprecedented increase in air pollution. The co-epidemics of PM<sub>2.5</sub> and the metabolic syndrome, particularly among developing regions, are together colluding to present one of the world's leading threats to public health. Continued efforts to improve air quality are urgently needed in the comprehensive effort to combat cardio-metabolic diseases.

### AIR POLLUTION AND CARDIOVASCULAR DISEASE

Air pollution is a complex mixture of gases (e.g., ozone) and particles. While there are numerous natural (e.g., fires, sand) and anthropogenic sources (e.g., traffic, industry, agriculture), the combustion of fossil fuels (e.g., coal, oil, gas, diesel) accounts for a major portion of pollution across the modern world. Fine particle matter < 2.5 microns in diameter (PM<sub>2.5</sub>) is itself a complicated amalgam of compounds (e.g., elemental and organic carbon species, metals, nitrates, sulfates) many of which are capable of instigating pro-oxidant and inflammatory responses upon inhalation (1,2). This plays a direct role in exacerbating a variety of lung diseases (e.g., asthma). However, evidence accrued over the past few decades illustrates that it is in fact cardiovascular diseases which represent the largest portion of PM<sub>2.5</sub>-induced morbidity and mortality (1-4).

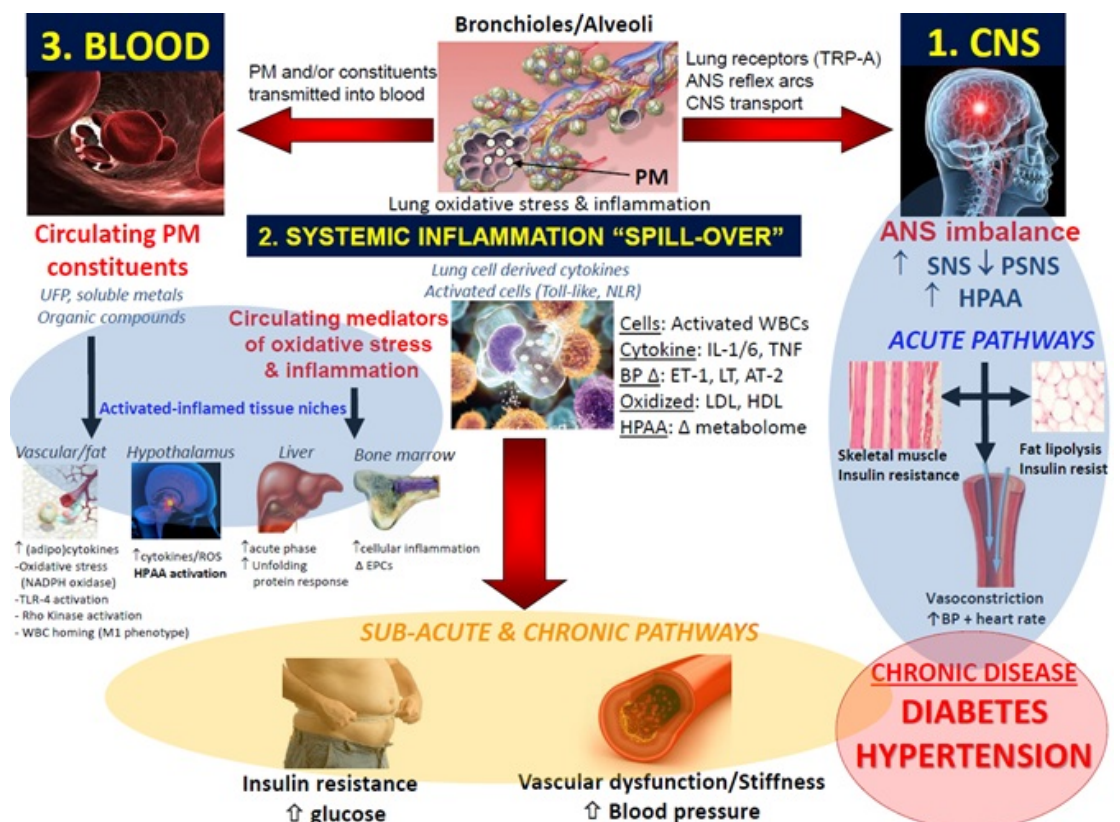
Both the American Heart Association and European Society of Cardiology acknowledge the critical importance of PM<sub>2.5</sub> as a cause of cardiovascular diseases (1,2). A wealth of epidemiological studies demonstrate that a 10 µg/m<sup>3</sup> elevation (~1 standard deviation in day-to-day levels) in ambient PM<sub>2.5</sub> concentration over the prior few days promotes an increase in myocardial infarctions (5), heart failure (6), strokes (7) and cardiovascular death by 1-2% (1,2). A host of pathological mechanisms have been implicated including vasoconstriction, endothelial dysfunction, heightened coagulation and thrombosis potential, instigation of arrhythmias, and atherosclerotic plaque instability (1,2). Broadly speaking, three pathways have been demonstrated whereby the inhalation of PM<sub>2.5</sub> into the lungs is capable of triggering remote adverse cardiovascular responses. These include the "spill-over" of pro-inflammatory mediators (activated cells, cytokines, oxidized lipids, hemodynamically-active molecules) from the lungs into the systemic circulation, autonomic imbalance favoring sympathetic nervous system (SNS) activity prompted by particles interacting with a variety of pulmonary receptors, and the direct action of inhaled nanometer-sized compounds reaching cardiovascular tissues (1,2). While acute PM<sub>2.5</sub> exposures trigger a 1-2% increase in cardiovascular events, a variety of prospective cohort studies have shown that longer-term exposures over several years synergistically promote an even greater increase in risk (approximately 10%) (1,2,8). A leading explanation for this phenomena is that repetitive exposures play a causal role in potentiating chronic disease-states, thereby heightening the underlying vulnerability of the population (1). Indeed, several studies have shown that PM<sub>2.5</sub> enhances the progression of atherosclerosis (coronary artery calcium, carotid intima-media thickness) (9,10). However, our work, along with that of other investigators during the past decade, have elucidated an additional pathway that is also at least partially responsible - PM<sub>2.5</sub> raises arterial blood pressure (BP).

## AIR POLLUTION AND HIGH BLOOD PRESSURE

A growing body of studies from across the world have demonstrated that PM<sub>2.5</sub> is capable of increasing BP (11,12). The average effect is typically modest (1-2 mm Hg per 10 µg/m<sup>3</sup> elevation in PM<sub>2.5</sub>); however, susceptible individuals can suffer a more robust response (i.e., 8-10 mm Hg) (11,13). We have conducted a series of studies among varying populations and air pollution levels in numerous real-world environments (Table). The totality evidence from our studies (13-18), the published literature (11), and a recent meta-analysis (12) conclusively demonstrates that short-term PM<sub>2.5</sub> exposures over hours-to-several days can prompt higher BP levels. In support of these observations we and others have performed randomized double-blind filtered air controlled exposures to concentrated ambient PM<sub>2.5</sub> and diesel particles (19, 20). The inhalation of these particulate pollutants led to a rapid increase in BP by 2-5 mm Hg within minutes. While vascular dysfunction occurred the following day, the totality of our experimental findings suggest that SNS activation is the principal mechanism responsible for the acute BP elevation (19). PM<sub>2.5</sub> is known to stimulate a variety of pulmonary receptors (e.g., transient receptor potential channels) and thereby instigate autonomic reflex arcs ultimately leading to vagal withdrawal and/or SNS activation (1,2). Other pathways (e.g., release of endothelin, activation of the hypothalamic pituitary adrenal axis, blunted natriuresis) likely contribute to the more sustained hypertensive responses over several days (11).

The acute BP-raising effect of short-term PM<sub>2.5</sub> exposure is clinically-important as it may play a role in promoting a range of cardiovascular events including myocardial infarctions, strokes, and heart failure exacerbations (1,2). Emergency room visits specifically for hypertension have also been shown to be increased days following higher levels of ambient PM<sub>2.5</sub> (21, 22). However, the long-term impact is perhaps of even greater health importance. Results from a meta-analysis show that year-long exposure to higher PM<sub>2.5</sub> levels causes an amplified pro-hypertensive response (BP elevation of 8-10 mm Hg per 10 µg/m<sup>3</sup>) (12). Our studies show that living in more polluted environments actually promotes the development of overt hypertension (23,24). Hypertension-related mortality rates are also increased by chronic exposures (25). We recognize that not all studies have been positive (11). However, supporting the underlying biological plausibility, our animal experiments corroborate the pro-hypertensive actions of PM<sub>2.5</sub> (26-28). One unifying pathway appears to be that components within PM<sub>2.5</sub> and/or secondarily oxidized endogenous phospholipids (from free radicals generated by metals/organic species) are recognized by a variety of innate immune receptors (e.g., toll-like receptors) thus activating a variety of host cells (e.g., macrophages) which thereafter propagate a systemic pro-inflammatory response generating oxidative stress in various cardiovascular, adipocyte and neural tissue niches. This culminates in central SNS activation via hypothalamic inflammation, endothelial dysfunction due to reduced nitric oxide and increased endothelin bioavailability, and vascular hyper-reactivity (e.g., to angiotensin II) as a consequence of NADPH oxidase-induced oxidative stress and rho-kinase activation (**Figure**).

**Figure:**  
*Mechanisms Linking Air Pollution Exposure with Hypertension and Diabetes Mellitus*



## GLOBAL PERSPECTIVE

Mounting epidemiological and animal studies further show that air pollution also promotes insulin resistance and DM (29,30). We have posited that PM<sub>2.5</sub> may be an important risk factor intrinsic to modern societies contributing to the burgeoning growth of the global metabolic syndrome epidemic (29). Clearly, obesity, lack of exercise, and diet are the major culprits. However, it may not be an innocent geographical coincidence that the rates of DM and hypertension are exploding across India and China (31,32), the locals also suffering from by far the highest global air pollution levels (4,33). Indeed, we (16,17) and others (34-36) have shown that the extreme air pollution levels in China and Asia are also capable of increasing BP and insulin resistance.

PM<sub>2.5</sub> levels have markedly improved across the U.S. resulting from a multi-faceted effort following the instigation of National Ambient Air Quality Standards in the early 1970s (33). Most of the population (80%) currently faces PM<sub>2.5</sub> levels meeting annual World Health Organization Air Quality Guidelines (10 µg/m<sup>3</sup>). However, recent evidence suggests that even in Canada very low levels of PM<sub>2.5</sub> (5-10 µg/m<sup>3</sup>) are still associated with excess cardiovascular risks (37). Our studies in Ontario also demonstrate that even very low ambient air pollution levels can promote the chronic development of hypertension (23) and DM (38). In this regard, it is important to stress that the global importance of maintaining the trending improvements in air quality across North America and Europe. At the same time enhanced strategies to help reduce exposures at a personal level (e.g., air purifiers, facemasks) (39) need to be validated and implemented on a large scale among regions facing extraordinarily high levels (e.g., China) while we await reductions in PM<sub>2.5</sub> (which may be a decade's long process) via national-level efforts to meet WHO guidelines.

**Table: Human studies from our Group Demonstrating Higher BP and/or Insulin Resistance in Association with Ambient Air Pollutants**

Location	Subjects	Exposures	Outcome/results
<b>Blood Pressure Study Results.</b> SBP=Systolic blood pressure; DBP=diastolic blood pressure			
Detroit-area (13)	N=347 mixed population	Community PM <sub>2.5</sub> monitors Mean: 15.0 ± 8.2 µg/m <sup>3</sup>	Higher SBP (3.5-8.6 mm Hg) per 10 µg/m <sup>3</sup> ; lag days 2-5; p<0.05
Detroit-area (14)	N=65 mixed population	5-day personal-PM <sub>2.5</sub> Mean: 21.9 ± 24.8 µg/m <sup>3</sup>	Higher SBP (1.4 mm Hg per 10 µg/m <sup>3</sup> ); lag day 1; p<0.001
Michigan (15)	N=2087 cardiac patients	Community PM <sub>2.5</sub> monitors Mean: 12.6 ± 8.2 µg/m <sup>3</sup>	Higher SBP and DBP (2-4 mm Hg per 8.5 µg/m <sup>3</sup> ); lag days 4-6; p<0.05
Beijing (16)	N=64 with Metabolic syndrome	5-day personal-BC monitors Mean: 4.7 ± 2.9 µg/m <sup>3</sup>	Higher SBP/DBP (0.53/0.37 mm Hg) per 1 µg/m <sup>3</sup> of BC prior 10 hours; Higher low/high frequency ratio 5.1% (lag 10 hours; p<0.05) in HRV
Beijing (17)	N=64 with Metabolic syndrome	Community PM <sub>2.5</sub> monitors Mean: 99.5 ± 67.2 µg/m <sup>3</sup>	Higher SBP (2-2.7 mm Hg; p<0.05) per standard deviation (67.2 µg/m <sup>3</sup> ); lag 1-7 day cumulative average; p<0.05
<b>Metabolic IR Study Results.</b> HOMA-IR=homeostasis model assessment of insulin resistance			
Southeast Michigan (18)	N=25 healthy population	Community PM <sub>2.5</sub> monitors on Mean: 9.7 ± 3.9 µg/m <sup>3</sup>	Higher blood glucose, insulin, and HOMA-IR (0.7 units; p=0.023) per 10 µg/m <sup>3</sup> increase in 5-day mean PM <sub>2.5</sub> . Lower heart rate variability (-13.1 msec/10 µg/m <sup>3</sup> 5-day PM <sub>2.5</sub> ; p=0.04)
Beijing (17)	N=64 with Metabolic syndrome	Community PM <sub>2.5</sub> monitors Mean: 99.5 ± 67.2 µg/m <sup>3</sup>	Higher HOMA-IR (0.18 to 0.22 units) per standard deviation (67.2 µg/m <sup>3</sup> ); lag days 4 and 5; p<0.05
<b>Human controlled exposure studies</b>			
Ann Arbor and Toronto (19)	N=50 healthy population	2-hour exposure to concentrated ambient PM <sub>2.5</sub> around 150 µg/m <sup>3</sup>	Exposure to PM <sub>2.5</sub> promoted a 2-3 mm Hg increase in SBP and DBP compared to filtered air during 2-hour long exposure period. The response was associated with reduced heart rate variability

-Robert Brook

## REFERENCES

- 1) Brook RD, Rajagopalan S, Pope CA III, Brook JR, Bhatnagar A, Diez-Roux A, Holguin F, Hong Y, Luepker, RV, Mittleman M, Peters A, Siscovich D, Smith SC Jr, Whitsett L, Kaufman JD. Particulate matter air pollution and cardiovascular disease. An update to the scientific statement from the American Heart Association. *Circulation* 2010; 121: 2331-78.
- 2) Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, Forastiere F, Franchini M, Franco OH, Graham I, Hoek G,

Hoffmann B, Hoylaerts MF, Künzli N, Mills N, Pekkanen J, Peters A, Piepoli MF, Rajagopalan S, Storey RF. Expert position paper on air pollution and cardiovascular disease. *Eur Heart J* 2015; 36: 83-93b.

3) Lim, S.S., et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2224-2260.

4) Lelieveld J, Evans JS, Fnais M, Giannadaki D, Pozzer A. The contribution of outdoor air pollution sources to premature mortality on a global scale. *Nature* 2015; 525: 367-71.

5) See comment in PubMed Commons below Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M, Périer MC, Marijon E, Vernerey D, Empena JP, Jouven X. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. *JAMA* 2012; 307: 713-21. See comment in PubMed Commons below

6) Shah AS, Langrish JP, Nair H, McAllister DA, Hunter AL, Donaldson K, Newby DE, Mills NL. Global association of air pollution and heart failure: a systematic review and meta-analysis. *Lancet* 2013; 382: 1039-48.

7) Shah AS, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, Langrish JP, Newby DE, Mills NL. Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ* 2015; 350: h1295.

8) Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, Kaufman JD. Long-term air pollution exposure and cardio-respiratory mortality: a review. *Environ Health* 2013; 12: 43.

9) Provost EB, Madhloum N, Int Panis L, De Boever P, Nawrot TS. Carotid intima-media thickness, a marker of subclinical atherosclerosis, and particulate air pollution exposure: the meta-analytical evidence. *PLoS One* 2015; 10: e0127014.

10) Kaugman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, Daviglius ML, Diez Roux AV, Gassett AJ, Jacobs DR, Kronmal R, Larson TV, Navas-Acien A, Olives C, Sampson PD, Sheppard Lianne, Siscovick DS, Stein JH, Sapiro AA, Watson KE. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. *Lancet* 2016 (published online May 2016)

11) Giorgini P, Di Giosia P, Grassi D, Rubenfire M, Brook RD, Ferri C. Air pollution exposure and blood pressure: An updated review of the literature. *Curr Pharm Design* 2015; 22: 28-51.

12) Liang R, Zhang B, Zhao X, Ruan Y, Lian H, Fan Z. Effect of exposure to PM<sub>2.5</sub> on blood pressure: a systematic review and meta-analysis. *J Hypertens* 2014; 32: 2130-40. <![if !supportLists]>13) <![endif]>Dvonch JT, Kannan S, Schulz AJ, Mentz G, House J, Benjamin A, Max P, Keeler JG, Brook RD. Acute Effects of Ambient Particulate Matter on Blood Pressure: Differential effects across urban communities. *Hypertension* 2009; 53: 853-859.

14) Brook RD, Bard RL, Burnett RT, Shin HH, Vette A, Croghan C, Phillips M, Rodes C, Thornburg J, Williams R. Differences in blood pressure and vascular responses associated with ambient fine particulate matter exposures measured at the personal versus

the community level. *Occup Environ Med* 2011; 68: 224-30.

15) <Giorgini P, Rubenfire M, Das R, Gracik T, Wang L, Morishita M, Bard RL, Jackson EA, Fitzner CA, Ferri C, Brook RD. Particulate matter air pollution and ambient temperature: Opposing effects on blood pressure in high risk cardiac patients. *J Hypertens* 2015; 33: 2032-8.

16) Zhao X, Sun Z, Ruan Y, Yan J, Mukherjee B, Yang F, Uan F, Sun L, Liang R, Lian H, Zhang S, Fang Q, Gu D, Brook JR, Sun Q, Brook RD, Rajagopalan S, Fan Z. Personal black carbon exposure influences ambulatory blood pressure. Air pollution and cardiometabolic disease (AIRCMD-China) study. *Hypertension* 2014; 63: 871-7.

17) Brook RD, Sun Z, Brook JR, Zhao X, Ruan Y, Yan J, Mukherjee M, Rao X, Duan F, Sun L, Liang R, Lian H, Zhang S, Fang Q, Gu D, Sun Q, Fan Z, Rajagopalan S. Extreme Air Pollution Conditions Adversely Impact Blood Pressure and Insulin Sensitivity. The Air Pollution and Cardiometabolic Disease (AIRCMD-China) Study. *Hypertension* 2016; 67: 77-85.

18) Brook RD, Xu X, Bard RL, Dvonch JT, Morishita M, Kaciroti N, Sun Q, Harkema J, Rajagopalan S. Reduced metabolic insulin sensitivity following sub-acute to low levels of ambient fine particulate matter air pollution. *Sci Total Environ* 2013; 448: 66-71.

19) Brook RD, Urch B, Dvonch JT, Bard RL, Speck M, Keeler G, Morishita M, Kaciroti N, Harkema J, Corey P, Silverman F, Wellenius G, Mittleman MA, Rajagopalan S, Brook JR. Insights into the Mechanisms and Mediators of the Effects of Air Pollution Exposure on Blood Pressure and Vascular Function in Healthy Humans. *Hypertension* 2009; 54: 659-667.

20) Cosselman KE, Krishnan RM, Oron AP, Jansen K, Peretz A, Sullivan JH, Larson TV, Kaufman JD. Blood pressure response to controlled diesel exhaust exposure in human subjects. *Hypertension* 2012; 59: 943-8.

21) Brook RD, Kousha T. Air pollution and emergency department visits for hypertension in Edmonton and Calgary, Canada: A case crossover study. *Am J Hypertension* 2015; 28: 1121-6.

22) Szyszkowicz M, Rowe BH, Brook RD. Even low levels of ambient air pollutants are associated with increased emergency department visits for hypertension. *Can J Cardiol* 2012; 28: 360-6.

23) Chen H, Burnett RT, Kwong JC, Villeneuve PJ, Goldberg MS, Brook RD, van Donkelaar A, Jerrett M, Martin RV, Kopp A, Brook JR, Copes R. Spatial associations between ambient fine particulate matter and incident hypertension. *Circulation* 2013; 129: 562-9.

24) Coogan PF, White LF, Jerrett M, Brook RD, Su GC, Seto E, Burnett RT, Palmar JR, Rosenberg L. Air pollution and incidence of hypertension and diabetes in African American women living in Los Angeles. *Circulation* 2012; 125: 767-772.

25) Pope CA, Turner MC, Burnett R, Jerrett M, Gapstur SM, Diver WR, Krewski D, Brook RD. Relationships between fine particulate matter air pollution, cardiometabolic disorders, and cardiovascular mortality. *Circ Res* 2015; 116: 108-115.

26) Ying Z, Xu X, Bai Y, Zhong J, Chen M, Liang Y, Zhao J, Lio D, Morishita M, Sun Q, Spino C, Brook RD, Harkema JR, Rajagopalan S. Long-term exposure to concentrated ambient PM<sub>2.5</sub> increases mouse blood pressure through abnormal activation of the sympathetic nervous system: A role for hypothalamic inflammation. *Environ Health Perspect* 2014; 122: 79-86.

27) Sun Q, Yue P, Ying Z, Cardounel AJ, Brook RD, Devlin R, Hwang J-S, Zweier JL, Chen LC, Rajagopalan S. Air pollution exposure potentiates hypertension through reactive oxygen species-mediated activation of Rho/ROCK. *Arterioscler Thromb Vasc Biol* 2008; 29: 1760-66.

28) Kampfrath T, Moiseev A, Shah Z, Ying Z, Deiuliis JA, Kongara RM, Kherada N, Pature NP, Chen LC, Moffatt-Bruce S, Parthasarathy S, Sun Q, Morawietz H, Brook RD, Rajagopalan S. Chronic Fine Particulate matter Exposure Induces Systemic Vascular Dysfunction via NADPH Oxidase and TLR4 Pathways. *Circulation Research* 2011; 108: 716-26.

29) Rao X, Montresor-Lopez, Puett R, Rajagopalan S, Brook RD. Ambient air pollution: An emerging risk factor for diabetes mellitus. *Curr Diabetes Rep* 2015; 15: 33.

30) Eze IC, Hemkens LG, Bucher HC, Hoffmann B, Schindler C, Künzli N, Schikowski T, Probst-Hensch NM. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. *Environ Health Perspect* 2015; 123: 381-9.

31) Xu Y, Wang L, He J, Bi Y, Li M, Wang T, Wang L, Jiang Y, Dai M, Lu J, Xu M, Li Y, Hu N, Li J, Mi S, Chen CS, Li G, Mu Y, Zhao J, Kong L, Chen J, Lai S, Wang W, Zhao W, Ning G. Prevalence and control of diabetes in Chinese adults. *JAMA* 2013; 310: 948-59. <![if !supportLists]>32) <![endif]>Rahimi K, Emdin CA, MacMahon S. The epidemiology of blood pressure and its worldwide management. *Circ Res* 2015; 116: 925-36.

33) Van Donkelaar A, Martin RV, Brauer M, Boys BL. Use of satellite observations for long-term exposure assessment of

global concentrations of fine particulate matter. *Environ Health Perspect* 2015; 123: 135-43.

34) Dong GH, Qian ZM, Xaverius PK, Trevathan E, Maalouf S, Parker J, Yang L, Liu MM, Wang D, Ren WH, Ma W, Wang J, Zelicoff A, Fu Q, Simckes M. Association between long-term air pollution and increased blood pressure and hypertension in China. *Hypertension* 2013; 61: 578-84.

35) Chen SY, Wu CF, Lee JH, Hoffmann B, Peters A, Brunekreef B, Chu DC, Chan CC. Associations between Long-Term Air Pollutant Exposures and Blood Pressure in Elderly Residents of Taipei City: A Cross-Sectional Study. *Environ Health Perspect* 2015; 123: 779-84.

36) Chen L, Zhou Y, Li S, Williams G, Kan H, Marks GB, Morawska L, Abramson MJ, Chen S, Yao T, Qin T, Wu S, Guo Y. Air pollution and fasting blood glucose: A longitudinal study in China. *Sci Total Environ* 2016; 541: 750-5.

37) Pinault L, Tjepkema M, Crouse DL, Weichenthal S, van Donkelaar A, Martin RV, Brauer M, Chen H, Burnett RT. Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian community health survey cohort. *Environ Health* 2016; 15: 18. <![if !supportLists]>

38) Chen H, Burnett RT, Kwong JC, Villeneuve PJ, Goldberg MS, Brook RD, van Donkelaar A, Jerrett M, Martin RV, Brook JR, Copes R. Risk of incident diabetes in relation to long-term exposure to fine particulate matter in Ontario, Canada. *Environ Health Perspect* 2013; 121: 804-10.

39) Morishita M, Thompson KC, Brook RD. Understanding air pollution and cardiovascular diseases: Is it preventable? *Curr Cardiovasc Risk Rep* 2015; 9: 30.



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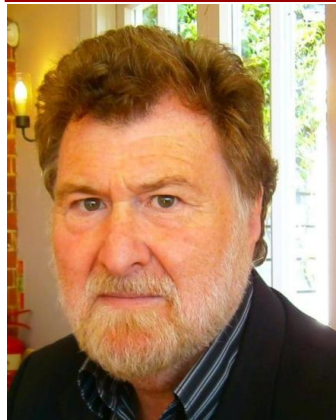
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# The Lancet Global Health Commissions



Stuart Spencer

Senior Executive Editor, The Lancet

As readers will be aware, *The Lancet* has established a commission on hypertension.

What's this about? What are the aims? Why is this important? Is this just a large review? How are commissioners chosen? These are questions that have been asked. Here are some answers.

*The Lancet* has initiated and organised a number of global health commissions (<http://www.thelancet.com/global-health/commissions>). They focused on elucidating public health issues and inspiring change by suggesting initiatives. Such commissions were often in partnership with other organisations: A UNAIDS–Lancet Commission on Defeating AIDS, The Lancet—University of Oslo Commission on Global Governance for Health, The Rockefeller Foundation–Lancet Commission on Planetary Health. These were followed by a new programme of clinical commissions.

The first clinical commission was on liver disease and reported in November 2014. Commissions on asthma and on adolescent health have followed. The commission on hypertension is another in the vanguard of clinical reports and is expected this year.

*The Lancet* commissions are not just big Cochrane-like reviews. They engage experts to look critically at the field and pose questions such as: What are the blocks to progress? What radical changes could improve the situation? The commissions should have a central message, should have original findings or thoughts; they should have forward vision and make recommendations for change. Commissions are not aimed at endorsing or criticising current guidelines. Guidelines have been carefully and responsibly prepared using the best available data. The Commission might, however, question whether the premise and scientific background underlying guidelines is as strong as we might like.

Finally, Commissions are expected to have an after-life. Writing a report then sitting back and waiting for change is not sufficient. There needs to be a campaign to disseminate the messages, engage in debate, foster change at all levels, and to continue to update the findings of the commission as new research, practices and policies become available. There is a Public Health aspect as well as the hope of improving treatment for patients.

It is not possible to have everybody on a commission. It is inevitable that the conclusions of a commission will not meet with the approval of everybody in the field. *The Lancet* has chosen commissioners with care. It is desirable to have commissioners from around the world. There also needs to be a balance of clinical expertise with public health and basic science skills.

Finally, for a raft of reasons, it is considered important that the majority of the commissioners are not the doyens of the field. They are selected from those with sufficient knowledge and experience but who are 15-20 years from retirement. It is hoped that such mid-career commissioners will have experience but also be open-minded. If they take ownership of the recommendations and calls to action, and they become active leaders in their fields, they may be able to help implement required changes.

Inevitably, not everyone will be happy with the report. It is not possible to make an omelette without breaking eggs. However, the commission does not aim to criticise, but to question whether current approaches are the optimum, or simply the best available. It is only by challenging our current thinking that we move forward. The aim of the commissions is to better the lives of patients, clinicians and researchers by accelerating improvements in healthcare.

-Stuart Spencer



# Council's Corner: Hypertension Issues - a personal view



**Lewis Landsberg**

Northwestern University, Feinberg School of Medicine,  
Chicago, USA

**Why does such a large proportion of the world's population suffer from hypertension? There are several answers to this question, which may be addressed at the level of genetics, of physiology, and the interplay of these factors with the external environment.**

## **Role of the sympathetic nervous system and the renin-angiotensin-aldosterone system**

First of all, mammals are hard-wired to maintain the adequacy of the circulation. This is priority number one since without an adequate circulation life ends. Mechanisms have evolved, therefore, to defend the circulation at all costs. Defense of the circulation in the face of external perturbations includes maintenance of plasma volume, perfusion pressure, and cardiac output in situations involving hemorrhage, trauma, and volume depletion from vomiting and diarrhea, to name a few exigent circumstances. These mechanisms to defend the circulation are deeply embedded in our genome. The sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) are the major defenders of the circulation. These two systems are also the major factors in the pathogenesis of hypertension. The inherent activity of these two systems varies among different individuals; those individuals at the higher end of the activity distribution for these two traits would defend the circulation better under external challenge but would be liable to the development of hypertension under the right circumstances.

Since hypertension is associated with adverse effects on the cardiovascular system why have these traits persisted in populations? Because the adverse effects of hypertension are generally played out over the course of decades and manifest themselves in the post-reproductive years.

## **Regulation of blood pressure and the pressure natriuresis relationship**

Secondly, blood pressure is not a tightly controlled variable. Throughout the course of a 24-hour period BP varies widely depending on the activity of the subject. During exercise, for example, blood pressure increases markedly and during sleep, on the other hand, pressure falls significantly. Cardiac

output, plasma volume, and tissue perfusion, by way of comparison, are much more closely regulated. In a related fashion the relationship between blood pressure and sodium excretion demonstrates the primacy of extracellular fluid volume over pressure. All things being equal, as the BP rises sodium excretion increases. The kidneys, therefore, have an infinite capacity to correct for hypertension. This pressure natriuresis relationship explains the interplay between volume and pressure and is critical to understanding how hypertension develops and is sustained. As noted above an important component of the defense of the circulation is the maintenance of the circulating volume in the presence of hemorrhage or fluid loss. Both the SNS and the RAAS increase renal sodium reabsorption. This increased avidity for salt operates to preserve volume in the face of diminished extracellular fluid thereby helping to maintain an adequate circulation. In the sodium replete state, however, renal avidity for sodium shifts the pressure natriuresis relationship to the right; this rightward shift in the relationship means that to excrete the day's salt intake higher BPs are required, as pointed out by Arthur Guyton decades ago. The increased renal avidity for salt, therefore, creates a "natriuretic handicap" whereby the increase in BP is the compensatory mechanism recruited to maintain plasma volume in the face of enhanced renal sodium reabsorption.

## **The environment**

The two major environmental factors that interact with genetic background and the associated physiological traits are salt intake and caloric intake. Since the propensity for hypertension is associated with renal avidity for salt, it follows that this propensity will not be expressed on very low sodium diets, as has been amply demonstrated in populations that have habitually low salt intakes. On high sodium diets, in contrast, the conservative trait of enhanced sodium reabsorption necessitates an increase in blood pressure to maintain normal extracellular fluid balance. Increased caloric intake, with associated obesity, is also related to the development of hypertension, again through stimulation

of the SNS and RAAS by leptin and insulin.

## The moral of the story

Although we are not able to modify our conservative genetic endowment we can beneficially effect the expression of our inherited traits by altering the circumstances that bring them into play: consuming less salt and less calories.

## Council's Corner: Hypertension Issues - a personal view



### Jiguang Wang, MD, PhD

Centre for Epidemiological Studies and Clinical Trials, The Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

President Elect of the Chinese Hypertension League (CHL).

**In 2008, I participated in the bidding for the 2016 ISH biennial meeting on behalf of the CHL. Although our bidding for an ISH meeting in Beijing was not successful, we, the CHL, soon reached an agreement with the ISH to initiate an educational programme in the western part of China.**

For several decades, western China has been less focused on educational programmes for the management of hypertension, even though the disease burden of hypertension is no smaller, and possibly greater, than in the eastern part of China. West China is economically far behind east China. This explains why physicians from west China participate in national meetings much less than those from east China. It may also explain why pharmaceutical companies are less interested in the organization of promotional activities in west China. Pharmaceutical companies often invite experts from Europe and North America to give lectures in their educational and promotional meetings in China. However, those meetings are often organized in Beijing, Shanghai, Guangzhou and other major cities in east or south east China, but very rarely in cities in west China.

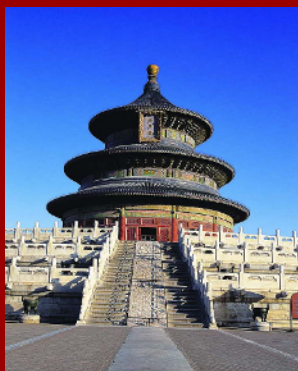
In 2009, at the invitation of the CHL, the ISH decided

to help organize teaching seminars on the management of hypertension in west China in collaboration with the Asian Pacific Society of Hypertension (APSH). Every year there were two seminars in two different cities of west China. Each seminar would be a whole day programme including several lectures on the latest advances in hypertension. Lecturers were jointly appointed and supported by the ISH, APSH and CHL.

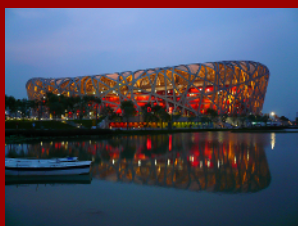
In the past seven years, the teaching seminar has been to most of the capital cities of west and central China. All the ISH sitting presidents (Anthony Heagerty, Stephen Harrap, Ernesto Schiffrin and Rhian Touyz) and Secretary General of the APSH, Trefor Morgan, participated in the seminar. The CHL president, Zhaosu Wu, chaired these meetings over the years. Probably because of the impact of these international and national organizations, the seminars were well-attended, with hundreds of participants each. The total number of participants of the 14 seminars exceeded a few thousands.

In China, the prevalence of hypertension increased substantially from about 5% in the late 1950s to about 25% in 2012 (Figure). The control rate of hypertension remained less than 10% in the China National Blood Pressure Survey in 2012 and was even lower in west China.

# China will host the 2018 ISH Biennial Scientific Meeting in Beijing.



At this meeting, China should not only present the scientific achievements in hypertension research, but also show improvements in fighting hypertension.



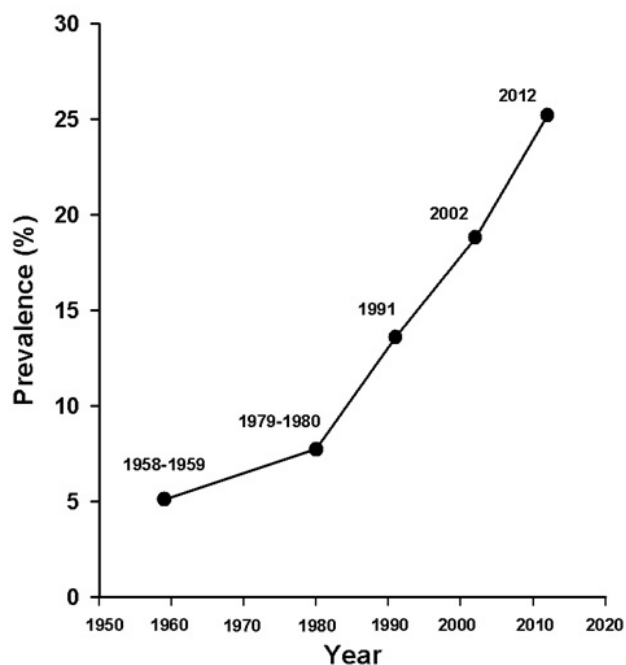
The Chinese government is establishing a nationwide health insurance system. Controlling hypertension is a major task of primary care physicians for chronic disease management in community health centres. I believe that with these joint forces, the management of hypertension will be improved to a much higher level in the coming years. The contribution of the ISH teaching seminar in west China must be appreciated. In the 21st century, the lecturers from other countries should be acknowledged, just as Dr Norman Bethune\* [1890-1939] was.

\*Norman Bethune was a Canadian surgeon who worked in China from January 1938 to November 1939. [https://en.wikipedia.org/wiki/Norman\\_Bethune](https://en.wikipedia.org/wiki/Norman_Bethune).

**Pictures taken at China Workshops - below and right**



**Figure :** Prevalence of hypertension in five Chinese national surveys from 1958 to 2012



-Jiguang Wang



**PUBLIC HEALTH FOUNDATION OF INDIA**



# Certificate Course in Management of Hypertension (CCMH)

**Cycle-I (July 2016 – April 2017)**

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## Registration Open\*

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Course starts on **24<sup>th</sup> July 2016**

**Course Fees**  
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For Application Forms and Program Brochure, please contact:

**Program Secretariat-CCMH**

**Public Health Foundation of India**

Plot No. 47, Sector 44, Institutional Area, Gurgaon -122002, India

Tel: +91-124-4781400 Ext: 4514 Fax: 0124-4722971

Email: [ccmh@phfi.org](mailto:ccmh@phfi.org), Web: [www.ccmh.org.in](http://www.ccmh.org.in), [www.phfi.org](http://www.phfi.org)

**Disclaimer:** PHFI, CCDC, ISH & BHS hereby declare that this jointly designed "Certificate Course in Management of Hypertension" is not a recognized medical qualification, under section 11(1) of the Indian Council Act, 1956. PHFI, CCDC, ISH & BHS offering this course hereby declare that they are not a medical college or a university and are not offering this course in accordance with the provisions of the Indian Medical Council Act/ University Grants Commission Act

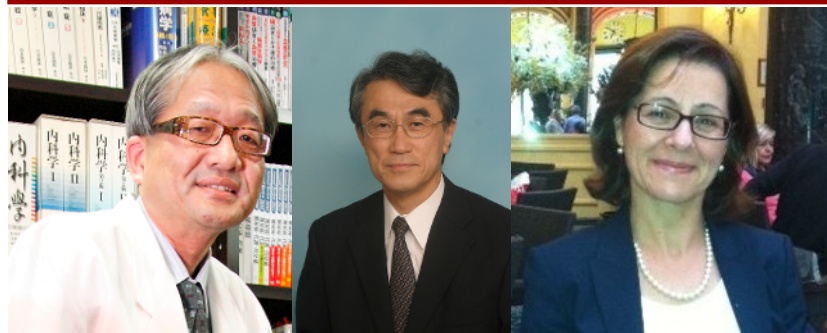
\*Decision taken by PHFI for selection and enrolment of participants will be final.

\*\*Course fee to be paid in the form of Demand Draft (DD) for INR 10,000/- drawn in favour of Public Health Foundation of India, payable at New Delhi.



Supported by educational grant from **SUN PHARMA**

# Kyoto Hypertension Summit 2016



From left to right:  
Prof. Hiroshi Itoh, Satoshi Umemura  
and Rhian Touyz

Ten years have passed since the Fukuoka Statement for overcoming high blood pressure was signed at the ISH Scientific Meeting in 2006. Since the number of ISH members from the Japanese Society of Hypertension (JSH) has increased to 135 (12.2% of the total number), JSH has made a commitment to contribute more to the ISH activities for global hypertension care and education.

The Hypertension Summit 2016 was held on May 31 at Hotel Granvia, Kyoto, Japan. Prof. Hiroshi Itoh (Keio University School of Medicine), Chair of the Hypertension Summit, organized this meeting to strengthen the collaborations and interactions between the ISH and JSH. Kyoto was chosen by the JSH because it has been an ancient capital for more than ten centuries, with traditional artisan techniques and culture, and is an academic city of Japan that has gained worldwide renown for 17 UNESCO World Heritage Sites and 9 Nobel laureates. In addition, Kyoto has been ranked the most popular tourist destination worldwide, and is one of the safest cities in the world.

The following ISH committee members attended the Summit .

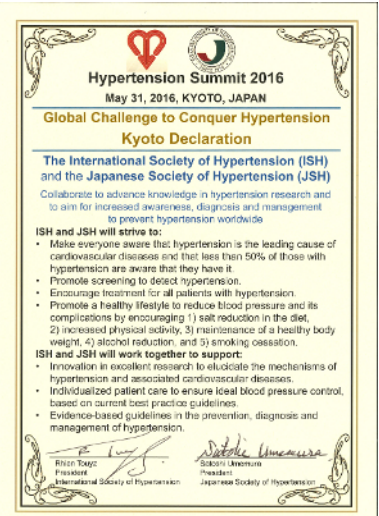


**ISH Executive Council members:** Rhian Touyz (President), Louise Burrell (Treasurer and Corporate Liaison Officer), Masatsugu Horiuchi (Secretary), Dorairaj Prabhakaran (Ex-Officio - International Development), Agustin Ramirez (Vice President), Ernesto Schiffrin (Immediate Past President), Alta Schutte (Chair, Membership Committee and New Investigators Liaison Officer), Ji-Guang Wang (Global Outreach and Promotion Officer)





After the meeting, the participants adopted a joint declaration, the **Kyoto Declaration 2016**, which was signed by Drs. Touyz and Umemura, pictured left



**ISH Scientific Council members:** Guido Grassi, Cheol-Ho Kim, Yoshihiro Kokubo, Basden Onwubere, Markus Schlaich, Naftali Stern, Roland Schmieder, Maciej Tomaszewski, Richard Wainford

**Ex-Officio Members of the Scientific Council:** Trefor Morgan (APSH Representative), Fadi J Charchar

**JSH:** Dr. Satoshi Umemura (Yokohama Rosai Hospital), President of the JSH, most of the core members and leadership of the JSH, as well as young Japanese investigators attended the summit. The total number of attendees was approximately 100.

In order to decide the next mission of the JSH under the leadership of the ISH, the meeting sought to understand the global activities of both these organizations and discuss their future collaboration. In addition, young investigators attended this meeting to present their outstanding research activities to the ISH core members.

The program was comprehensive and included sessions on:

1. Ongoing JSH activities and challenges after the Fukuoka Statement in 2006
2. Recent outstanding research by Japanese young investigators
3. Disaster and hypertension
4. Regional activities of ISH: past, present and future
5. Where are we going?
6. Workshop: Brainstorming for future collaboration between the ISH and JSH: Council Members of the ISH and JSH.

The brainstorming session was especially important and was an interactive dialogue between the panel members and audience. After much discussion a number of activities were highlighted for future JSH-ISH interactions and action points were defined

so that JSH and ISH could work together to achieve the mutual mission of reducing the burden of hypertension globally.

Fourteen young investigators (under 40 years of age) presented poster presentations, which were scored by ISH members. A report follows in this regard.

Following the official day of the meeting (June 1), the JSH invited the ISH participants to a city tour, which included a number of beautiful temples, the iPSC Center, Kyoto University, the Miyako Messe and Kyoto International Conference Centers. Thus, the 2-day 2016 Kyoto Hypertension Summit was a great success. It provided a wonderful opportunity for the leadership of the ISH and the JSH to share thoughts about common missions of the respective Societies and it provided a great opportunity for young investigators and trainees in Japan to learn more about the New Investigator activities and programmes of the ISH.

Finally, the Summit provided a platform for the signing of the Kyoto Declaration between the ISH and JSH, the goal of which is to conquer hypertension globally through education, awareness, prevention and better diagnosis and management.

- **Hiroshi Itoh** (Keio University School of Medicine),  
Chair of the Hypertension Summit / **Satoshi Umemura**  
(Yokohama Rosai Hospital), President of the JSH /  
**Rhiann Touyz**, ISH President



## Kyoto Summit – a report from the ISH New Investigator Committee (NIC)

### Fadi Charchar

#### NIC Member Lead for Mentorship and Networking

Robert HT Smith Personal Chair in Cardiovascular Genomics Federation Uni., Ballarat Australia

Honorary Research Fellow, Universities of Melbourne & Leicester



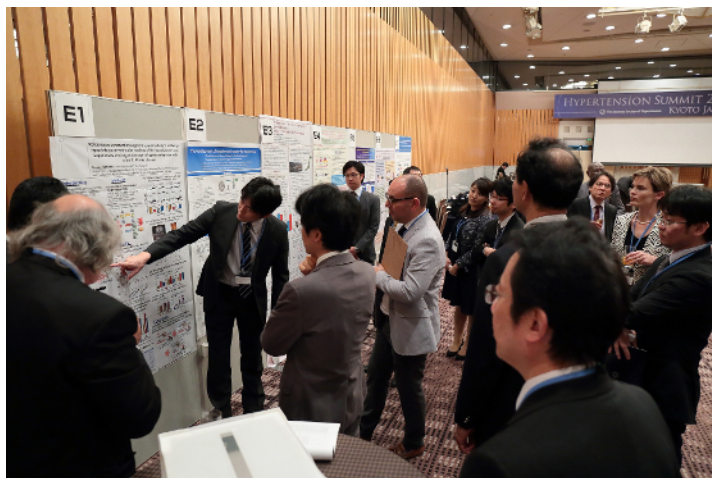
The Kyoto Hypertension Summit, hosted by the Japanese Society of Hypertension (JSH), was held between May 30 and June 1 2016. Scientific highlights of the summit were the oral and poster presentations from Japanese young investigators.



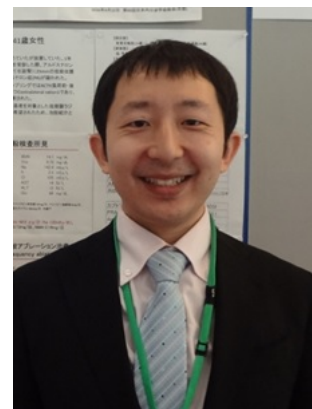
There was some outstanding research presented by young investigators on topics in hypertension and related cardiovascular disease. The poster session consisted of fourteen posters and was a showcase for the highest quality of science by the youngest generation of scientists from Japan.

The President, members of the Scientific Council of ISH, the chair of ISH NIC and the ISH lead for mentorship were actively involved in discussion around the posters and contributed to the judging of the presented posters. There were two winners, Dr. Hiroyuki Inoue (Keio Univ.) and Dr. Akiko Tanino (Ehime Univ.). They both received awards from the Japanese Society of Hypertension, will be awarded the ISH New Investigator of the month status, and featured on the Society website. Importantly for the ISH is that the winners and other young investigators will now become members of the ISH.

We were delighted to learn that the JHS has already dedicated support for young and new scientists from Japan in the form of the JSH Young Investigator Committee, which is chaired by Dr Tatsuo Shimomura. We very much look forward to working with our new colleagues and would like to thank them for helping us find our 'inner pop star' at Japanese-style karaoke.



*Hiroyuki Inoue (pictured right) was one of the winners from the Itoh group with a presentation entitled "Epigenetic modulation of renal arterioles induced by DOCA-salt loading in mice."*



**Congratulations to the winners and the organizers of this successful meeting in Japan.**

**-Fadi Charchar**

### ISH New Investigator Mentorship and Networking Event

**Seoul, Korea**

**Tuesday 27<sup>th</sup> September, evening - time to be confirmed**

A perfect opportunity for new investigators (PhD students, post-docs or clinical research fellows) to mingle with their peers and senior ISH Faculty in a relaxed environment. These events play an important part in developing networking opportunities for young members of the ISH and promoting their long-term collaborations with established investigators.

Please email [secretariat@ish-world.com](mailto:secretariat@ish-world.com) should you be interested in attending this event.

## What's your Brand? Preparing for professional careers

ISH NIC / AHA TAC 2016 Collaboration, Orlando, USA, September 2016



### Praveen Veerabhadrappe

Member of the International  
Society of Hypertension New  
Investigator Committee

Penn State Berks, Reading,  
PA, USA

**Being competitive for professional careers within and outside of academia requires more than technical skills - communication and social networking skills count. New investigators likely have these skills, but may lack the strategy for communicating and marketing these talents.**

To fulfill this need, the flourishing collaboration between the International Society of Hypertension New Investigator Committee and the Trainee Advocacy Committee of the Council on Hypertension of the American Heart Association has led to the organization of a special pre-conference workshop - 'Preparing for professional careers: What's your Brand?' for early career investigators and student attendees. The event, hosted by Randall Ribaldo (Co-founder, CEO, SciPhD) will take place on Tuesday, September 13, 2016 at the Dolphin Hotel, Orlando, Florida USA



during the Council on Hypertension Scientific Sessions. The workshop will focus on 24 critical skills that potential employers look for. Workshop attendees will learn to: communicate effectively, analyze a job advertisement, identify the technical, business and social skills required for the job, use that information to build a targeted résumé, expand their professional network, develop an elevator pitch to initiate conversations, and finally, manage the behavioral-based interview process. To learn about *your brand we encourage you to attend this session*. A pre-registration is required. To register for this event, please email your name, institution and email address to [TACWorkshop@heart.org](mailto:TACWorkshop@heart.org), prior to August 22, 2016.

**-Praveen Veerabhadrappe**

## Follow ISH New Investigator Network activities on social media



[www.twitter.com/ISHNIN](http://www.twitter.com/ISHNIN)



[www.facebook.com/ISHNIN](http://www.facebook.com/ISHNIN)

You can also find us on [YouTube](#) and [LinkedIn](#)



## World Hypertension Day 2016: By the WHL Global Office

# WORLD HYPERTENSION DAY

*Initiated by the World Hypertension League*

**WHL Global Office** - pictured above from left to right

**Daniel T Lackland (WHL President), Mark L. Niebylski (Chief Executive Officer), Kimbree Redburn (Population Health and Economics Specialist)**

This year, the World Hypertension League (WHL) celebration of World Hypertension Day (WHD) took place between May 17<sup>th</sup> and May 24<sup>th</sup>. For WHD 2016, the World Hypertension League in close partnership with the International Society of Hypertension (ISH) and the American Heart Association (AHA) promoted the theme of 'Know Your Numbers' with the goal of increasing awareness of high blood pressure and the risk for hypertension-related non-communicable diseases (NCDs). The campaign included member outreach, social media, and member events (blood pressure screenings, media events, calls to action and community awareness campaigns). And the celebrations were some of the most successful to date!

### **Blood Pressure Screenings:**

This year, in addition to raising awareness on NCDs, WHL set a goal of 3 million individual blood pressure screenings. While not all of our members and regional offices have reported yet, we are pleased to say that so far there have been 5,129,562 independent blood pressure screenings that took place between April 17<sup>th</sup> 2016 and May 24<sup>th</sup> 2016. We are thrilled that we were able to surpass our 3 million BP screenings goals, and we are happy to report that this is also higher than our 2,446,193 obtained during WHD 2015!

This success is due solely to the support of our partners, members, and other supporting organizations. The reports so far include measurements and campaigns from 18 different countries including Argentina, Barbados, Bulgaria, Cameroon, Canada, Croatia, Cuba, Ghana, India, Mexico, Nepal, Romania, Serbia, South Africa, Sudan, Thailand, the United States, and the United Kingdom. Thanks to all who participated and are making a difference. A list of teams/groups/organizations who have reported thus far can be found in the **table overleaf**.

For a view of how WHD 2016 was celebrated in specific areas throughout the world please visit:

<http://www.whleague.org/index.php/features/world-hypertension-day/world-hypertension-day-activities-2016>.

We also know that our Regional Office in China has been very busy with WHD celebrations and cannot wait to see what their office has accomplished! If any other members, partners, or organizations completed WHD 2016 celebrations, please e-mail us at [CEO@whleague.org](mailto:CEO@whleague.org) to report your activities. We would love to hear from you.

### **WHD 2016 in Pictures:**



*Dances and Education Events Held in Cuba*



*Blood Pressure Screenings Held In Ghana*



*Blood Pressure Screenings Held in India*



*Blood Pressure Screenings Held at Meijer in the United States*

## Results: Blood Pressure Screenings reported to WHL

Country/Region	Organisations Involved	Screenings/Activities
Argentina	Instituto Cardiovascular Lezica	577 Screenings conducted
Barbados	Heart & Stroke Foundation of Barbados, Inc.	263 Screenings conducted,
Bulgaria		2,300 Screenings
Cameroon		6,424 Screenings
Croatia	Pharmacies	101 Screenings conducted
Cuba		Held Dances and Education
Ghana	Life from 30	626 Screenings conducted
India	Team Tazloc (A division of USV Private Limited, BSD Marg), Max Super Speciality Hospital, USV and WHL Collaboration BP Camps, Dr. Verma, Dr. Maheshwari, Dr.	13,874 Screenings conducted
Mexico	Cardiovascular Research Institute, University of	90 Screenings conducted
North America	In Canada: Highland Crest home, Harbourstone Enhanced Care, Colchester East Hands Health Centre In United States: St. Louis Department of Public Health, Caseway NRa, Meijer, Kaiser Permanente, American Heart Association, Wayne State University In Both Canada and the US: Pharmasmart	5,101,870 Screenings conducted
Nepal	Hospital	493 Screenings conducted
Romania	Romanian Society of Hypertension	Press conferences in 4
Serbia	Institute for Cardiovascular disease "Dedinje"; HISPA	156 Screenings conducted
South Africa	Ganyese District Hospital, HART	1,313 Screenings
Sudan	Sudanese Society of Hypertension	800 Screenings conducted
Thailand	Thai Hypertension Society	Media releases and health
United Kingdom	Bristol CardioNomics	177 Screenings conducted

## WHD 2016 in Pictures:



*Blood Pressure Screenings Held at Wayne State University in the United States)*



*Blood Pressure Screenings Held in Nepal*



*Blood Pressure Screenings and Education Conducted in Nepal*

## Media Campaign:

One thing that was different and exciting about WHD 2016 was the presence it developed on both social media and at news outlets worldwide. On social media, the WHL and others celebrated WHD 2016 with the hashtags #knowyournumbers and #WorldHypertensionDay.

Elsewhere, WHD 2016 was found in several publications on or around May 17<sup>th</sup> 2016. To view these publications visit: <http://www.whleague.org/index.php/features/world-hypertension-day/world-hypertension-day-in-the-news>



In honor of WHD 2016 Niagara Falls was lit up blue and red on May 16<sup>th</sup> from 10:00 pm to 10:15 pm ET (USA). This lighting was a collaboration between WHL and the American Heart Association (AHA). It was done in the hopes of raising awareness for hypertension and other NCDs.

## WHL Awards:

In alliance with World Hypertension Day 2016, the WHL proudly announces the recipients of this year's Distinguished Service, Excellence, and Notable Achievement Awards in the categories of: Hypertension Control at the Population level, Dietary Salt Reduction at the Population level, and inaugural Rising Star Award in Promotion of Public Health for Cardiovascular Disease Risk and Hypertension Prevention & Control. All of these awards were developed to provide recognition to individuals, organizations and interventions that make tangible progress towards WHL's Mission & Mandate on the prevention and control of hypertension at the population level.

**To this year's well-deserving awardees, CONGRATULATIONS!**

### World Hypertension League Award Recipients – 2016

#### Excellence in Dietary Salt Reduction at the Population Level

##### Professor Bruce Neal, MD

Senior Director, Food Policy Division - The George Institute, Chair of the Australian Division of World Action on Salt and Health, Professor of Medicine - University of Sydney, Sydney, Australia

#### Excellence in Hypertension Prevention and Control at the Population Level

##### Dr. Paul Whelton, MB, MD, MSc

Show Chwan Professor of Global Public Health, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA

#### Notable Achievement in Hypertension Prevention and Control at the Population Level

Professor Anuj Maheshwari, The Indian Society of Hypertension, Vikas Nagar, India

#### Notable Achievement in Dietary Salt Reduction at the Population Level

The Portuguese Society of Hypertension, Lisboa, Portugal, <http://www.sphta.org.pt/pt/default.asp>

#### Rising Star Award in Promotion of Public Health for Cardiovascular Disease Risk and Hypertension Prevention & Control

##### Professor Narsingh Verma

The Indian Society of Hypertension, Tamilnadu, India

## What's Next: WHD 2017:

Building on the success of WHD 2016, we are already starting to plan for WHD 2017. We do not know the exact dates and have yet to set our next blood pressure screening goal. As we do we will keep you updated. But one thing is for sure, we will work to build on our momentum from this year and make WHD 2017 our best celebration yet!

NOTE: In our next Newsletter issue, we will include an update with additional screenings reported and more on planning 2017.

-WHL Global Office

Click here to view further World Hypertension Day reports and videos from ISH members

(Pictured right: Hypertension in Africa Research Team and Vietnamese Society of Hypertension initiatives)




## Please find below a poster to help promote HYPERTENSION AWARENESS.

Please distribute widely. This was produced in collaboration with the International Federation for Pharmaceutical Manufacturers and Associations (IFPMA) and is now also available in Spanish.

# COMBATING HYPERTENSION

THE LEADING CAUSE OF PREVENTABLE DEATH WORLDWIDE



Hypertension, or high blood pressure, may be symptomless but it kills **9.4 million** people worldwide every year

If untreated, hypertension can cause death or serious health consequences in a number of ways:

- HEART ATTACK
- STROKE
- DEMENTIA
- KIDNEY FAILURE
- VISION LOSS

**2/3** of those with hypertension are in developing countries

### PREVENTION IS KEY!



- Eat healthily and reduce salt consumption
- Eat more fruit and vegetables
- Limit alcohol intake
- Don't smoke
- Be physically active
- Maintain a healthy body weight

### KNOW YOUR NUMBERS!

Only 50% of those with hypertension are aware they have it

- Check your blood pressure regularly – whether at home, at a clinic, a pharmacy or elsewhere
- If you are being treated for hypertension, take your medicine even when you feel good – follow treatment advice of healthcare professionals

For more information: <http://ish-world.com/news/a/WHL-and-ISH-Hypertension-Fact-Sheet/>



# ISH Hypertension Teaching Seminar, Maputo, Mozambique

## Teaching Seminar organized by the ISH Africa Regional Advisory Group

B Onwubere, A Coca, A Damasceno, S Kadiri, R Kruger, D Lemogoum, JR M'Buyamba-Kabangu, I Okpechi, N Poulter, B Rayner, YK Seedat, AE Schutte, and R M Touyz.



**In line with the mission of the International Society of Hypertension (ISH) to promote and encourage the advancement of scientific research and knowledge and its application in the global prevention and management of heart disease, stroke and related cardiovascular diseases of hypertension the Africa Regional Advisory Group (RAG) of ISH (created in 2010), organised an education program reaching out to young doctors across Africa.**

A similar program, run through the Committee on Low and Middle Income Countries of ISH, had previously organized seven Hypertension Teaching Seminars in various parts of Africa since 2006. The eighth ISH Hypertension Teaching seminar was organised by the ISH Africa RAG in Maputo, Mozambique on 18–19 April, 2016 under the direction of Prof. B Onwubere and the local host, Prof. A Damasceno and in collaboration with the European Society of Hypertension (ESH), the Mozambican Heart Association (AMOCOR) and the International Forum for Hypertension Control and Prevention in Africa (IFHA). There were over 65 participants at the meeting from many countries across Africa. Apart from the Seminar Directors, other faculty members included: A Coca (Spain), S Kadiri (Nigeria), D Lemogoum (Cameroon), JR M'Buyamba-Kabangu (Congo DR), N Poulter (UK), B Rayner (S Africa), YK Seedat (S Africa), AE Schutte (S Africa), and RM Touyz (UK). Seminar coordinators were Drs. I Okpechi and R Kruger both from South Africa. The seminar was attended by participants from eleven African countries, including Cameroon, Democratic Republic of Congo, Ethiopia, Kenya, Malawi, Mozambique, Nigeria, South Africa, Sudan, Tanzania, and Uganda. The participants were selected from various medical and health-care professionals,



and included mainly doctors, but also representatives from nursing, clinical pharmacy and clinical psychology. This participation represented true multidisciplinary, highlighting the importance of the health-care team approach in the management of patients with hypertension.

The 2-day intensive program comprised eight sessions including a 'Guidelines' and Abstracts Session, where participants presented abstract-based talks. The topics of hypertension covered were: **Hypertension epidemiology, prevalence and mechanisms (pathogenesis) of hypertension in Africa** (Lectures given by: A. Damasceno, AE Schutte, YK Seedat, R Touyz), **Hypertension diagnosis, prevention, screening and blood pressure measurement in Africans** (Lectures given by: B Rayner, S. Kadiri, D. Lemogoum, JR M'Buyamba-Kabangu, N. Poulter), **Hypertension complications** (Lectures given by A Coca, S Kadiri, B Onwubere), **Hypertension treatment and control in Africa** (A Coca, D Lemogoum, J-R M'Buyamba-Kabangu, B Onwubere, N Poulter, B Rayner, AE Schutte, YK Seedat) **Review of hypertension guidelines and Panel discussions** (S. Kadiri, D. Lemogoum, N Poulter, B Rayner, YK Seedat, R Touyz).

YK Seedat gave an overview of hypertension in the African perspective outlining the immense burden of hypertension in the African region. The lectures variously reviewed mechanisms of blood pressure elevation in Africa including the important role of unhealthy lifestyle on vascular reactivity and the rising prevalence and burgeoning burden of hypertension as risk factor for various cardiovascular diseases in urban and rural Africans. Concerning vascular mechanisms in hypertension, R M Touyz reiterated that vascular injury in hypertension was associated with increased CV events and maintaining vascular health is important in the prevention of hypertension-related complications and target organ damage. AE Schutte highlighted the fact that hypertension occurs at a younger age and is often more severe in terms of BP levels in black patients than in whites and the disturbing situation that black

patients with hypertension are particularly vulnerable to strokes and kidney disease. Hypertension has also become more common in lower-income populations with increasing urbanisation.

On the topic of hypertension diagnosis, prevention, screening and blood pressure measurement in Africans, JR M'Buyamba-Kabangu discussed approaches on how to measure blood pressure in the office and out-of office. There was extensive discussion about the relative absence of ambulatory blood pressure monitoring devices in many centres in Africa and the need for validation and re-certification of existing devices when used for clinical practice and for research. AE Schutte stated that recent statistics show that cardiovascular disease (CVD) is likely to overtake infectious diseases as the greatest threats to health in Africa, and that cardiovascular risk factors, especially high blood pressure, are on an increasing trajectory that will be highly challenging to reverse. D Lemogoum pointed out that because of the large number of hypertensive individuals in Sub-Saharan Africa, treatment should be implemented at the primary health care level and a strategic approach to prevent and control hypertension was critically needed. B Rayner elucidated the need for proper evaluation, stratification of risks, and treatment based on current recommended guidelines, particularly related to the African context.

With regards to hypertension complications, B Onwubere focused on the more severe complications of hypertension especially in the black African population. A Coca stated that 'improvement of BP control in African countries is the current challenge to reduce stroke mortality'. S Kadiri discussed the likely renal origins of hypertension, the worse kidney effects in Blacks and the roles of renin-angiotensin system blockade and aldosterone antagonists in reducing proteinuria.

Concerning hypertension treatment and control, the cost of medications were highlighted as a factor that may be contributing to low BP control in Africa. YK Seedat stressed the importance of social factors impacting the

growing prevalence of hypertension in South Africa including increased slums/urbanisation, social differences in terms of crime, civil strife, poverty and drought, and short lifespan. N Poulter talked about the benefits of Single Pill Combinations (SPCs) as being more effective and rapid in blood pressure control than monotherapy and 2 'free' drugs. Other benefits are reduced side effects, enhanced adherence, improved cardiovascular protection, and increased cost effectiveness. B Rayner asserted that treatment of hypertension in low resource settings is yet to be well documented and currently largely observational rather than based on randomized clinical trials. B Onwubere discussed the impediments and challenges on controlling hypertension in most African settings, and highlighted poor availability of healthcare facilities, poverty, low awareness levels and clinical inertia as major factors. He stressed that policy makers should be made more aware of the importance of controlling hypertension at the population level and that there should be more pro-active input from opinion leaders and policy-makers.

During the Hypertension Guidelines Session, RM Touyz reiterated the hypertension paradox: the concept of pseudo-hypertension as a result of poor compliance and adherence to therapy. Guidelines should be user-friendly, practical, short, and should have widespread application. The current ASH/ISH guidelines have these qualities, according to RM Touyz. B Rayner stated that the South African Hypertension Guidelines should serve as a model for Africa and implementation thereof could make substantial impact even in low resource settings. S Kadiri highlighted the merits of the second Hypertension Guideline in Nigeria in providing details for local hypertension management and also mentioned a major weakness of limited available local literature. He stated that the current review process and the third Guidelines would address these areas since more local literature were now available in the country since the last Guideline release. D Lemogoum mentioned that the International Forum for Hypertension control and prevention in Africa (IFHA) in its first year of existence released a Hypertension Management Guideline for Sub-Saharan Africa published in 2003 in the Journal of Hypertension. He said that a revised Guideline would soon be released by the Society.

Fifteen oral presentations of submitted abstracts on hypertension studies in Africa were presented by participants from Nigeria (4), Kenya (4), South Africa (3), Uganda (2), Cameroon (1) and Democratic Republic of Congo (1). Some of the first data derived from the 2014

Astra Zeneca Healthy Heart Africa project based in Nairobi, Kenya were presented, stressing the endeavours to tackle a silent killer in parts of the world where access to healthcare is at its lowest. One study from Kenya (J Makoyo-Onyiego) assessed the role of task shifting towards sustainable management of hypertension while another from T Bello (Nigeria) reported on the high prevalence of pre-hypertension and hypertension in Ibadan, Nigeria from a World Kidney Day Programme. Five posters were presented of submitted abstracts on hypertension studies in Africa from Cameroon (1), DR Congo (1), Kenya (1), Nigeria (1), and Uganda (1).

A post-seminar test comprising the same questions administered at the beginning of the seminar was administered to participants. The average score at the end of the seminar rose from a pre-seminar score of 53% to a post-seminar score of 70.6%, marking a huge increase in the audience participation and learning and highlighting the importance of these teaching seminars especially in Africa. Moreover, the improved test scores reflected that the teaching was successful and that participants gained new knowledge and information about hypertension.

Two new academic initiatives arose from the Maputo Seminar: a proposal to submit a review on Hypertension in Africa - co-authored by all speakers, to the Journal of Hypertension; and also the availability of the slide presentations to the participants and ISH members through the Society's website as learning kits.

**The eighth ISH Hypertension Teaching Seminar received support from the European Society of Hypertension, the Mozambican Ministry of Health, Astra Zeneca through the Healthy Heart Africa project, and some pharmaceutical industries in Mozambique. Overall the Seminar was a great success. The goals and objectives were achieved and there was tremendous enthusiasm for the program to continue. It was suggested that the next Teaching Seminar be organised in a French-speaking African country, possibly Democratic Republic of Congo.**



## ISH Corporate Members

The ISH would like to acknowledge the support of our Corporate Members - as follows.



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