



Notes from the Editor - Lars H. Lindholm

The Biennial ISH Meeting in September 2016 in Seoul - what a success!

Dear member,

I am sure that most - if not all - of us who attended the recent ISH meeting in Seoul agree that it was one of the best hypertension meetings in many years.



More than 3500 delegates (about 2000 from outside South Korea) met to discuss high blood pressure, its risks, and prevention for almost a week at a wonderful venue, where we received a very warm welcome and fantastic hospitality by professors Kim, Kim, and Kim and their many co-workers under the leadership of Ms Jay Moon.

The city in itself was a pleasant surprise, with its very well-functioning Metro service. In this double issue of Hypertension News, you can read the New Investigators' reports from the meeting on pages 22-26.

This year ISH celebrated its 50th anniversary and it was time for our Society to change President and part of the Scientific Council. Neil Poulter (London, UK) took over from Rhian Touyz (Glasgow, UK) as President and you will find their addresses on pages 3-4 and 6, respectively.

We thank Rhian Touyz for all she has done for the Society and wish Neil Poulter good luck for the coming years. As a Past President of the Society, I know how time-consuming this pro-bono undertaking is, with a lot of international travelling involved. The new Council members (elected for 2016-20) are presented on page 5, together with their fields of interest.

Hypertension News will continue as before with me as Editor and with Thomas Kahan (Sweden), Dylan Burger (Canada), and Maciej Tomaszewski (UK, new) as members of the Editorial Board. Maciej is also Secretary of the Society and a member of the Executive Committee. We owe Neil Poulter much gratitude for his work on the Board during 2014-16. The Board is now an independent sub-committee under the Communication Committee, chaired by Rafael Castillo (The Philippines), whose views on hypertension you can find on pages 33-34.

One of the highlights at the Seoul meeting was the release of the first report from The Lancet's Commission on Hypertension (Lancet 2016,

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Notes from the Editor - Lars H. Lindholm - continued

published on 22 September) under the leadership of Professor Michael Hecht Olsen (Denmark).

On pages 11-13 you will find the background, aim, structure, and plans (with ten key action points) for the Commission's work.

On page 14, there is also an invitation to **ISH members to contribute** to this initiative by submitting 'published success stories on methods to improve blood pressure control in low-income settings' to Michael Hecht Olsen. If you can help here, I strongly recommend you to do so.

The results of The SPRINT study have started discussions around the world on whether it is necessary to reassess blood pressure targets.

As first (!) reported in Hypertension News in 2015, Opus 43 - shortly after the presentation of the study - blood pressure was recorded in a way which results in lower values than regular office recordings. In this issue of HT News there is a report under 'Hot Off The Press' (pages 8-9) by Thomas Kahan on several recent studies showing a 10/5 mm Hg difference. At the recent meeting of the American Heart Association in New Orleans, there was a similar discussion in a session organised by our Society and the World Hypertension League. Ernesto Schiffrin (Canada) - one of the five speakers - has kindly written a report from that session, held only two weeks ago (!) which you will find on pages 30-32. The final conclusion was that we need to intensify blood pressure lowering and improve the quality of the blood pressure measurements.

Have a good read!

Lars H Lindholm, Editor

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The ISH would like to thank all those who contributed to the great success of the Hypertension Seoul (ISH) 2016 Meeting in September.

Including: Professors Cheol-Ho Kim, Chong-Jin Kim and Soon-Kil Kim and their hard-working and dedicated committee members, InSessions - Jay Moon and her fantastic conference organising team, the speakers, industry supporters, our Affiliated Society members, the ISH Council and Committee members and most of all the event attendees.

From the new ISH President - Neil Poulter



It is a real honour and pleasure to address you as the incoming President of ISH. After 50 prestigious years of existence, it appears that the society is going from strength to strength in terms of increasing membership, innovative activities and global involvement and influence.

Before looking forward to the Society's plans for the next 2 years, I would, on your behalf like to thank **Rhian Touyz**, our outgoing President for all her hard work over the last 2 years. Luckily, Rhian stays on the Executive for another 2 years as outgoing president! However, I will say farewell and thank you (at least in terms of Committee involvement) to:

- **Louise Burrell (Australia)** - ISH Council member 2008-2016, Treasurer 2008-2012 and 2014-2016, Vice President 2012-2014 and Chair, Corporate Liaison Committee 2010-2016. Louise will still be contributing to the ISH in her role as leader of the International Forum and Regional Advisory Groups (see below).
- **Guido Grassi (Italy)** - ISH Council member 2008-2016.
- **Cheol-Ho Kim (South Korea)** - ISH Council member 2012-2016 and President of the ISH Seoul 2016 Meeting Local Organising Committee
- **Basden Onwubere (Nigeria)** - ISH Council member 2008-2016 and Chair of the ISH Africa Regional Advisory Group 2014-2016

- **Ernesto Schiffrin (Canada)**, an instrumental and long-standing member of the ISH Executive Committee who has played a number of pivotal roles over the last 10 years (Officer at Large 2006-2010, Vice President 2010-2012, President Elect 2011-2012, President 2012-2014 and Immediate Past President 2014-2016). An impressive record, by anyone's standards!
- **Naftali Stern (Israel)** - ISH Council member 2008-2016

Meanwhile a few minor changes to the structure and committees responsible for the administration of the Society are being introduced.

In an effort to strengthen and broaden ISH activities around the world, the International Forum and five Regional Advisory Groups (RAGs) will be brought closer together by co-ordinating their activities through a common leader, Louise Burrell, who brings extensive ISH experience to this role having served on the ISH Council for 8 years.

In addition, three new sub-committees (with representation on the Executive) will be formed to enhance current activities.

Firstly, the '**Scientific**' **Research and Education Committee** will be responsible for responding on our behalf for the various research/or scientific issues on which the Society is frequently asked to comment, advise or endorse. This group will coordinate all/any future ISH guideline Involvement.

Secondly, the **Mentorship and Training Committee** whose activities were introduced in 2014 by the New Investigator Committee will have Fadi Charchar as their representative on the Executive. This group has gone from strength to strength in their management of the ISH Mentorship Scheme and organisation of annual networking and mentorship events. Both initiatives have been designed to bring together new investigators and more experienced investigators and to promote long-term collaborations.

Thirdly, in order to build on the success of the 2016 ISH Scientific Meeting in Seoul, a **2018 Beijing Liaison Committee** will work alongside the local Organising

Committee in Beijing with the aim of delivering a massively successful event.

Over the next 2 years, I hope that ISH can continue to evolve as the pre-eminent global society responsible for tackling the horrendous burden on society which raised BP currently imposes. To achieve that, we must encourage the already increasing global membership of the Society (particularly among the younger representatives of those whose work relates to hypertension) and the global involvement and outreach of the Society, which the RAGs encourage through various outstanding activities. With that background, I hope to encourage the Society to focus on 3 key issues over the next 2 years. They are:

- (1) In order to encourage improved BP control among those treated for hypertension (currently less than one third (1)) it is critical that the optimal combinations of antihypertensive drugs are identified (at least in terms of BP lowering) for each of the major ethnic groups. It is a dreadful indictment on the hypertension research community that no morbidity/mortality trial data are available among the South Asian communities of the world and none are available to inform 2-drug sequencing among black or Far Eastern populations either. In 2017 a trial will start in 6 countries in Sub-Saharan Africa and a similar trial in India is in development.
- (2) In order to increase the levels of awareness among the world's hypertensive population [reportedly as low as 46% (1)] a huge awareness campaign is needed. Some years ago, the World Hypertension League (WHL) introduced World Hypertension Day (WHD) which takes place on May 17th every year. In collaboration with the WHL, ISH plans to expand WHD to a May Measurement Month in 2017 so that 25 million people previously unscreened for at least 1 year, have their BPs measured. That target, pending the 2017 results should be increased each year with commensurate increasing capacity to treat effectively those with newly diagnosed 'hypertension' (however defined).
- (3) In order to improve the level of knowledge about raised BP among those measuring and managing hypertension at the 'coal face' it is proposed that an educational programme will be rolled out to all relevant groups

worldwide. The programme which will form the model for this ISH endeavour was developed by Professor Dorairaj Prabhakaran from CCDC in Delhi, India, a member of the ISH Executive. This programme is currently being rolled out in India and will be audited and modified as required to introduce into those parts of the world which need such an educational course. The first targets after India will be Africa and Latin America.

These 3 aims form the focus of new ISH activities over the next 2 years and I am delighted to be at the helm of a ship which appears to have the wind behind it and an extraordinarily talented and committed crew!

I look forward to collaborating ever more closely with all the expanding list of ISH members and those from associated groups and societies from around the world. We must try to make a difference to the biggest single contributor to global death and burden of disease. This action is needed urgently.

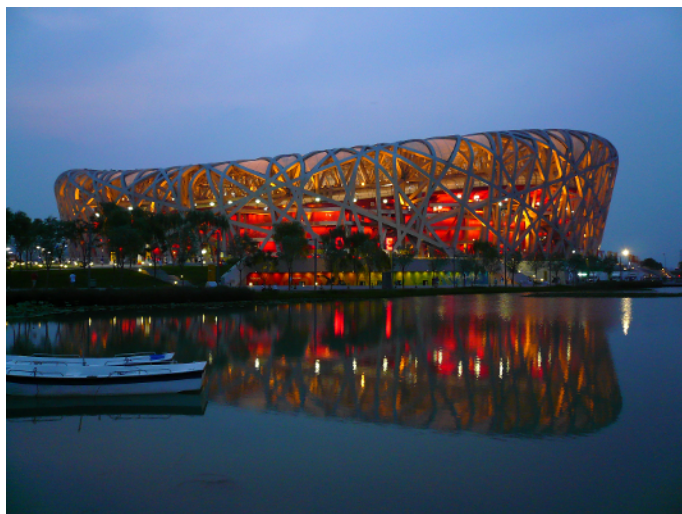
- Neil Poulter

Ref1 = PURE study (Yusuf et al)

Join us at the ISH Scientific Meeting in Beijing in 2018!

www.ish2018.org

19-23 September



AN INTRODUCTION TO THE ISH COUNCIL MEMBERS - ELECTED FROM 2016-2020 (DURING THE SEOUL MEETING)

Council members elected for a 2nd term

Agustin Ramirez
Argentina



My areas of interest in hypertension are: Renal Sodium Handling, Autonomic Nervous System and Blood Pressure Control, Metabolic Syndrome and Hypertension.

Alta Schutte
South Africa



As the Research Chair in Chronic Diseases in South Africa, my research spans clinical and epidemiological population studies focusing on the development of hypertension in African communities. By using longitudinal transdisciplinary research programmes I aim to identify novel markers and/or bio-signatures as early predictors of vascular dysfunction in an attempt to contribute to the prevention of hypertension.

Council members elected for a 1st term

Fadi Charchar
Australia



My research interests focus on genomics of cardiovascular disease in humans and animal models. I have a special interest in the contribution of the Y chromosome and microRNA to hypertension.

Dorairaj Prabhakaran
India



I am a cardiologist and epidemiologist and currently the Executive Director of Initiative for Cardiovascular Health in Developing Countries (ICHEALTH) and Director Centre of Excellence, Centre for Cardio-metabolic Risk Reduction in South Asia (strategic grant funded by the National Institutes of Health and United Health group) at the Public Health Foundation of India.

Claudio Borghi
Italy



My main areas of interest - hypertension and related cardiovascular risk factors and drug therapy of hypertensive disease, with a particular interest in the interactions between hypertensive disease and metabolic risk factors.

Sadayoshi Ito
Japan



My areas of research are the renin-angiotensin-aldosterone system and glomerular hemodynamics in basic research, and hemodynamics in hypertension, secondary hypertension and chronic kidney disease in clinical research.

Nadia Khan
Canada



I am a clinician scientist in epidemiology and health services research. My research area is focused on ethnic and sex differences in hypertension and cardiovascular disease chronic disease management.

Thomas Unger
The Netherlands



My research interest has been focused on peptidergic systems, in particular the Renin-Angiotensin system (RAS) and its CNS-related and peripheral role in the pathophysiology of cardiovascular diseases. As a basic and clinical pharmacologist, I have performed numerous pre-clinical studies and participated in clinical trials investigating the therapeutic aspects of modulating the RAS in hypertension and related diseases, and I have contributed to the development of several RAS modulating drugs.

Farewell message from the outgoing President - Rhian Touyz



It has been an honour and a privilege to serve as the President of ISH these past two years (2014-2016). I am grateful for the support, commitment and dedication from the strong leadership of ISH. Working together with the Executive and Council members, I believe we have much to be proud of, having achieved a lot over two short years. We strengthened ongoing projects, we expanded our global outreach, we developed new programmes, we strengthened our membership and we witnessed the continued growth of our dynamic and energetic new investigator team.

In my role as President, I promised to fulfil a number of objectives and feel truly gratified that all of my goals have been achieved. Highlighted below are some of these achievements:

1. Expanding global educational activities. Over the past 2 years, ISH has actively supported more than 20 educational activities in all regions of the world, including Asia and Australasia, Africa, Eastern and Western Europe, Middle East, and the Americas.
2. Consolidating interactions with global organisations. ISH has strengthened relationships with major global organisations including the World Health Organisation (WHO), World Hypertension League and World Heart Federation (WHF). By working together with these organisations to achieve the WHF 25 by 25 goals, we are in a strong position to achieve the mission of our Society.
3. The commitment of ISH to tackle hypertension globally was evidenced by the signing of two important declarations: the 2016 Kyoto Declaration and the 2016 Mexico

Declaration with the goal to 'conquer hypertension and associated cardiovascular diseases worldwide'.

4. Strengthening relationships with global leaders and societies. ISH has worked closely with AstraZeneca and the Healthy Heart Africa project, and with international societies including the European Society of Hypertension, European Society of Cardiology and American Heart Association amongst others, where we have fostered partnerships in joint sessions at scientific meetings.
5. Sharing of knowledge through peer-reviewed publications. Over the past 2 years, ISH has published 5 peer-reviewed papers, including guideline statements, regional reports and reviews.
6. ISH has been proactive in its ethos by including an equality statement '*The ISH is positively committed to opposing discrimination against people on the grounds of gender, race, colour, nationality, religion, marital status, sexual orientation, class, age, disability, having dependants, HIV status or perceived lifestyle*'.
7. Creation of a new programme, called 'Women in Hypertension Research', which provides a platform for networking to support and mentor women and other under-represented groups in all fields of hypertension research.

During my term, we were fortunate to enjoy the 26th ISH biennial meeting held in Seoul. The scientific meeting, hosted by the Korean Society of Hypertension, was an outstanding event with over 3500 participants. In Seoul, we also had the opportunity to celebrate 50 years of ISH. The Society has flourished under a very supportive Executive committee, outstanding communications through superb newsletters, a vibrant New Investigator Committee and a dedicated secretariat office. I thank you, the leadership and members of ISH, for working with me to ensure that our Society prospers. I thank you for affording me the opportunity to represent you. It has been a most enriching and truly satisfying two years as ISH President. I now hand over to the incoming President, Neil Poulter, who will certainly take the Society to even greater and stronger heights.

-Rhian M Touyz ISH President 2014-2016



Thomas Kahan

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Can converting enzyme inhibitors reduce the risk of cardiac conduction system disease?

Hypertensive heart disease is associated with an increased risk of atrial and ventricular tachyarrhythmias. Whereas atrial fibrillation may have important implications on incident stroke and heart failure, ventricular malignant arrhythmias may contribute to the increased risk of sudden cardiac death seen in patients with hypertension-induced left ventricular hypertrophy [1]. However, cardiac conduction system disorders are also common in patients with hypertensive heart disease, and may also lead to fatal outcome.

Activation of the renin-angiotensin-aldosterone system promotes inflammation, myocyte hypertrophy and myocardial fibrosis, and a link between inflammation, hypertrophy and fibrosis on the one hand, and arrhythmias and conduction abnormalities on the other has been suggested.

In this context, the recent report from the ALLHAT study by Dewland *et al* [2] demonstrating that treatment with the angiotensin converting enzyme inhibitor lisinopril reduced incident cardiac conduction system disease, is of interest.

In brief, the ALLHAT study included 42418 hypertensive patients, 55 years or older with at least one additional cardiovascular to treatment with chlorthalidone, amlodipine, lisinopril, or doxazosin [3]. For the purpose of the current analysis [2], all 21004 patients (mean age 66 years, 44% women) randomised to chlorthalidone, amlodipine, or lisinopril (the doxazosin arm was terminated early) with a valid baseline ECG and no prevalent conduction disease were evaluated for incident conduction abnormalities on standard ECG recordings 24, 48, 72, and 96 months later. Mean follow up was 5.0 years.

In all, 570 patients developed right bundle branch

block, 389 left bundle branch block, and 155 intraventricular conduction delay. Patients randomised to lisinopril had a 19% (95% confidence limits 5–31%) lower risk of developing incident conduction system disease than those randomised to diuretic therapy, while amlodipine treatment had little effect compared to chlorthalidone (-6%; -19–9%). Other independent predictors of incident conduction system disease were age, male sex, body mass index, tobacco use, diabetes and left ventricular hypertrophy, while black race was associated with reduced risk. Of note, the risk was increased three-fold in patients with left ventricular hypertrophy.

Blood pressure was reduced less by lisinopril than by chlorthalidone, indicating that the effects on incident conduction abnormalities by converting enzyme inhibition were not related to changes in blood pressure. Thus, the results of this study suggest that blocking the effects of the renin-angiotensin-aldosterone system on inflammation, left ventricular remodelling and hypertrophy, or myocardial fibrosis can prevent incident conduction system disease.

Of note, it has been put forward that some drugs may specifically reduce myocardial fibrosis [4]. Whether such treatment could affect the risk of incident conduction system disease is of interest and warrants further study. Taken together, achieved blood pressure is most important in determining future risk in hypertensive patients. However, some antihypertensive drug classes may have ancillary properties and could provide additional benefit in selected patients.

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- Thomas Kahan

Hot Off the Press

Thomas Kahan

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Automated office blood pressure and target values for treatment

The results of the SPRINT study have again started the discussions on whether it is necessary to reassess blood pressure targets for high risk patients, for whom a lower systolic blood pressure target now seems appropriate [1]. However, blood pressures in the SPRINT study were recorded as unattended automated office blood pressures, which result in lower values than blood pressures measurements as frequently practiced in general practice. Thus, as first discussed in an earlier issue of *Hypertension News* shortly after the presentation of the SPRINT study results [2], another important conclusion of that study is that we have to rethink how office blood pressure should best be measured, and how best to translate the systolic blood pressure values achieved in SPRINT to inform clinical practice around the world with widely variable standards in blood pressure measurement.

Recently Wohlfart *et al* reported from a comparison of traditional blood pressure measurements with a manual mercury sphygmomanometer (performed by trained nurses and three recordings 1 min apart; the mean of the last two values were used) and unattended measurements (five recordings performed 1 min apart; the mean of all values were used) with a BpTRU automated blood pressure device. The study was performed in a randomly selected population sample of 2145 individuals aged 25-64 years in the Czech Republic [3]. On average, manual systolic and diastolic blood pressures were 6.4 ± 9.8 and 2.5 ± 6.5 mm Hg higher than automated systolic and diastolic blood

pressure values, respectively. The difference between the methods increased with increasing manual blood pressure values. According to polynomial regression analyses, automated systolic and diastolic blood pressure values of 131.0 and 85.4 mm Hg corresponded to manual systolic and diastolic blood pressure of 140 and 90 mm Hg, respectively. These results are similar to previous smaller studies with the BpTRU, showing approximately 10/5 mm Hg lower values than those obtained in more usual clinical practice [4]. The findings by Wohlfart *et al* are in concordance with another study where unattended automated office blood recordings in 353 hypertensive patients performed with the BpTRU device were compared with blood pressures recorded by the physician with a semiautomatic oscillometric device [5]. That study showed systolic and diastolic blood pressure values recorded by the automated blood pressure values 15.0 ± 13.8 and 8.0 ± 7.3 mm Hg lower than those traditionally recorded.

Taken together, with a blood pressure value of about 140/90 mm Hg, unattended automated office blood pressure recordings show approximately 10/5 mm Hg lower values than those obtained by traditional manual blood pressure recordings, as frequently practiced in general practice. We should reconsider how to best measure blood pressure in the office. The way blood pressure measurements are performed in the office is important when defining target blood pressure values for the individual patient.

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- Thomas Kahan

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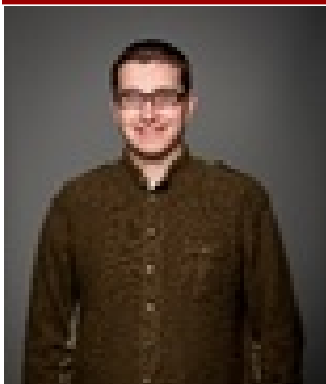
HYPERTENSION

BEIJING 2018 | CHINA

19 – 23 September 2018

27th Scientific Meeting of the International Society of Hypertension





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Cardioprotective Angiotensin-(1-7) Peptide Acts as a Natural-Biased Ligand at the Angiotensin II Type 1 Receptor

Sécolène Galandrin, Colette Denis, Cédric Boularan, Jacky Marie, Céline M'Kadmi, Claire Pilette, Caroline Dubroca, Yvan Nicaise, Marie-Hélène Seguelas, Du N'Guyen, Jean-Louis Banères, Atul Pathak, Jean-Michel Sénard and Céline Galés

Hypertension 68:1365-1374

This month I focus on an excellent study involving advanced molecular pharmacology that significantly advances our understanding of signaling through the Angiotensin II type 1 receptor (AT1R).

The AT1R is a 7 transmembrane G-protein coupled receptor (GPCR) that classically signals through activation of heterotrimeric G-proteins of the Gq/G11, Gi/o, and G12/13 families promoting numerous responses including vasoconstriction, fibrosis, and cardiac/renal remodeling [1]. More recently, AT1R has been shown to activate G-protein independent pathways through stimulation of β -arrestin and downstream activation of mitogen activated protein kinases [2]. β -arrestin mediated signaling is associated with vasorelaxation and improved cardiac performance. Thus, AT1R is capable of stimulating two, divergent signaling pathways: a "cardiodeleterious" G-protein coupled pathway, and a "cardioprotective" β -arrestin-dependent pathway. There has subsequently been considerable interest in identifying ligands for AT1R that preferentially activate β -arrestin signaling without stimulating G-protein signaling. The concept of ligand-directed preferential activation on one pathway over another has been termed "biased agonism".

While a number of synthetic Ang II derivatives capable of biased agonism have been developed (see [3]), it was previously unclear whether endogenous Ang II metabolites were capable of biased agonism.

In the present study Galandrin and colleagues assessed the ability of Angiotensin II metabolites to activate G-protein dependent and G-protein independent signaling through the AT1R. In a series of elegant studies involving receptor binding assays, bioluminescence resonance energy transfer, and functional studies in isolated aortas the authors

identify previously unrecognized biased activation of AT1R by Angiotensin II metabolites Ang (1-7), Ang III, and Ang IV. Most strikingly, the authors show that Ang (1-7) acts as an AT1R-biased agonist, selectively promoting β -arrestin activation while blocking the detrimental Gq-mediated pathways.

Once thought of as an inactive breakdown product of Ang II, Ang (1-7) is now widely recognized as an independently bioactive molecule that stimulates vasodilation and inhibits fibrosis (actions which generally oppose Ang II). The effects of Ang (1-7) were previously believed to be mediated through the Mas oncogene receptor, however the present study calls this into question and suggests that biased agonism of AT1R may also play an important role in the actions of Ang (1-7).

In summary, Galandrin and colleagues have identified highly novel interactions between Ang II metabolites and the AT1R leading to preferential activation of β -arrestin signaling pathways. Such interactions are likely to be important contributors to endogenous signaling through the renin-angiotensin system and exploiting these interactions may represent an alternative strategy to current approaches to RAS inhibition.

- Dylan Burger

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The Lancet Commission on Hypertension

A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations.

The Lancet Commission on Hypertension



Michael Hecht Olsen

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Background

Elevated blood pressure (BP) is the strongest modifiable risk factor for cardiovascular disease worldwide. Despite extensive knowledge about ways to prevent as well as to treat hypertension, the global incidence and prevalence of hypertension and, more importantly, its cardiovascular complications are not reduced – in part because of inadequacies in prevention, diagnosis and control of the disorder in an aging world.

Aim

Therefore, *The Lancet* has taken the initiative to launch a Commission on Hypertension with the aim of identifying key actions to improve the management of BP both at the population and the individual level, and generating a campaign to adopt the suggested actions at national levels to reduce the impact of elevated BP globally. The first task of *The Lancet* Commission on Hypertension was a report presented during the meeting of the International Society of Hypertension in Seoul in September 2016. The report briefly reviews the current evidence for prevention, identification and treatment of elevated BP, hypertension and its cardiovascular complications. The report focuses on unsolved issues, rethinking these in the context of approaches with population-wide impact and new methods for patient evaluation and education in its broadest sense and suggesting new ways that are not always strictly evidence-based to manage BP globally.

Structure

The report is built around the concept of lifetime risk applicable to the entire population from conception. Development of subclinical and sometimes clinical cardiovascular disease results from the lifetime exposure to cardiovascular risk factors combined with the susceptibility of individuals to the harmful consequences of these risk factors. The Commission recognizes the impact of other cardiovascular risk factors like smoking, obesity, dyslipidaemia and diabetes mellitus on cardiovascular risk, which is very important for the initiation of and goals for antihypertensive treatment. However, as a Commission on Hypertension, this report focuses primarily on issues and

actions related to elevated BP.

Essential goals and key actions

Previous action plans for improving management of elevated BP and hypertension have not yet provided adequate results. Therefore, the Commission has identified 10 essential and achievable goals and 10 accompanying mutually additive and synergistic key actions which, if implemented effectively and broadly, will make substantial contributions to the prevention and management of BP globally. The Commission deliberately has not prioritized the key actions listed below, because the actions are complementary and the balance between strength of evidence and potential benefit may be different and feasibility may vary by country context.

The lifecourse approach

An average individual follows the blue line when their lifecourse undergoes arterial ageing. This arterial ageing is – in part and simultaneously - hallmark, resultant and the driver of an increase in BP and cardiovascular risk. The black dotted lines represent the three avoidable thresholds on which preventive efforts should be focused: The development of elevated BP, subclinical cardiovascular damage, and finally overt cardiovascular disease leading to loss of quality of life. Certain individuals with "Early Vascular Ageing" (red line), will cross these thresholds earlier in life. The ideal lifecourse (green line) represents individuals who only develop elevated BP or subclinical cardiovascular damage too late in the lifecourse for them to have a substantial impact on the individual's quality of life. The main goal of preventive efforts (small grey arrows) is to shift an individual's lifecourse towards the ideal lifecourse. Depending upon genetic disposition and/or epigenetic imprinting during fetal life, individuals can start their lifecourse higher or lower on the health-disease continuum (the enlarged insert) reflecting the so-called cohort effect. The orange dashed lines show the impact of a preventive effort, with a resultant downward shift in the lifecourse curve. Early preventive efforts are likely to result in a substantial gain in time (x-axis) or disease progression (y-axis) compared to later preventive efforts.

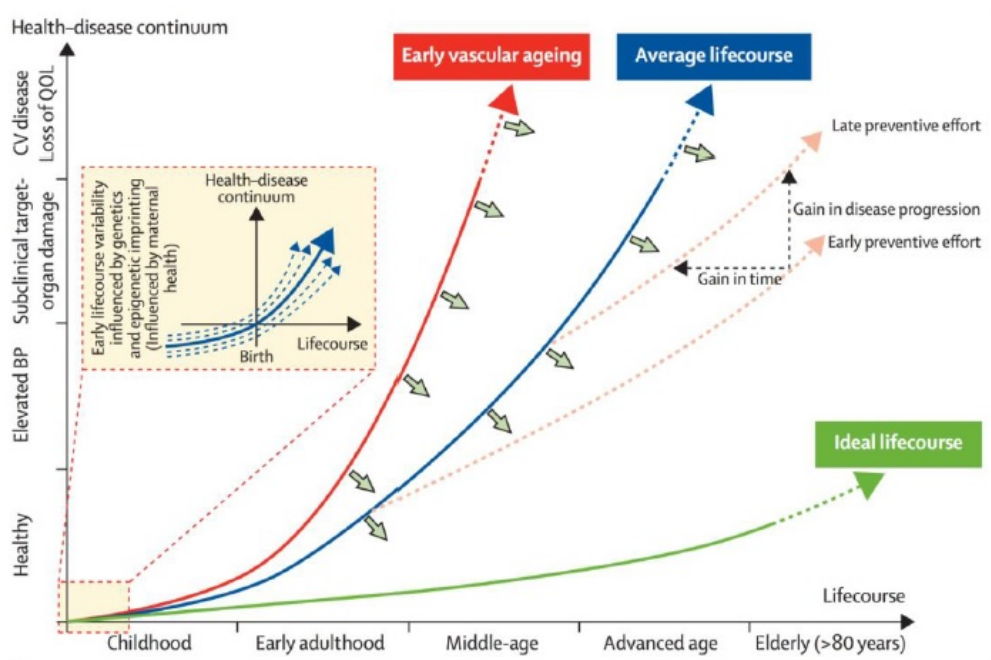


Figure 3: Early-life effects and impact of preventive efforts in the management of elevated blood pressure

The insert shows the effects of genetic susceptibility and epigenetic imprinting during fetal life. Preventive efforts result in downward shifts in the lifecourse curve, with earlier preventive efforts affecting lifecourse trajectory more than later preventive efforts. CV=cardiovascular. QOL=quality of life. BP=blood pressure.

From Olsen MH et al. A call to action and a lifecourse strategy to address the global burden of raised

blood pressure on current and future generations: the Lancet Commission on hypertension. Lancet. 2016 Sep 22. pii: S0140-6736(16)31134-5. doi:10.1016/S0140-6736(16)31134-5. [Epub ahead of print] Review. PubMed PMID:27671667.

The 10 Key Actions

-  **Health promoting environment:**
Creating a healthy environment through strategies that accelerate socio-economic improvements and implementation of accepted health promoting policies
-  **Healthy behaviours:**
Universal understanding of unhealthy and healthy lifestyles and BP through endorsed, early and sustained education using new technologies
-  **Measurement access:**
Universal access to measurement of BP through inexpensive BP monitors (linked to global BP surveil.)
-  **Measurement quality:**
Better quality of BP measurements through endorsed protocols and certified/validated BP monitors
-  **Empowerment:**
Better identification of people at high risk in order to optimize treatment approaches through endorsed education of patients and healthcare professionals (linked to stratified treatment)
-  **Secondary Hypertension:**
Better identification of people with secondary hypertension through endorsed and simple flow charts (linked to stratified treatment approaches)
-  **Workforce expansion:**
Expanded workforce engaged in the management of BP through task sharing and the use of endorsed education of community health workers (linked to health care system accountability)
-  **Medication access:**
Universal access to affordable, high quality and effective antihypertensive drugs through collaboration between all major stakeholders
-  **Standardised treatment:**
Treatment approaches stratified according to age, cardiovascular risk, social, cultural and ethnic differences through endorsed education of health care professionals and initiation of new research
-  **Health system strengthening:**
Promote and ensure capacity and accountability of the health system to conduct surveillance and monitoring, and respond appropriately to BP levels

- Michael Hecht Olsen

Pictures below taken during The Lancet Commission on Hypertension Session in Seoul on 27 September



The Lancet Commission on Hypertension



Michael Hecht Olsen

Department of Internal Medicine, Holbaek Hospital and Centre for Individualized Medicine in Arterial Diseases (CIMA), Odense University Hospital, University of Southern Denmark, Denmark

A recent paper by Mills et al. (*Circulation* 2016;134:441-450) demonstrated that the age-adjusted prevalence of hypertension increased from 2000 to 2010 in low- and middle-income countries (LMIC), surpassing that of high-income countries. Three-quarters of patients with hypertension are now living in LMIC. Furthermore, awareness and treatment improved only slightly from 2000 to 2010, whereas control rates of hypertension in men decreased in LMIC. The situation is even worse in low-income countries compared to middle-income countries. Therefore, the Lancet Commission on Hypertension will focus efforts to try to improve blood pressure control in low-income settings/countries.

To initiate this action, the Lancet Commission on Hypertension will collaborate with the International Society of Hypertension (ISH), World Hypertension League (WHL), World Heart Federation (WHF), Pan-African Society of Cardiology (PASCAR), African Heart Network (AHN), Latin American Society of Hypertension (LASH), and Centers for Disease Control and Prevention (CDC), in order to create a library of success stories (studies) on strategies to improve blood pressure control in low-income settings/countries as a foundation for more impactful initiatives.

Therefore, we invite you, as a member of the ISH, to contribute to this initiative. Are you aware of a published success story (study) on methods to improve blood pressure control in low-income settings/countries? If you recall such a success story, please go to our web-page using the link <http://bpstudyform.hypertensioncommission.org> to answer a few questions regarding the study. If some of the questions cannot be answered, please write N/A.

The Commission will present the results at the European Meeting on Hypertension and Cardiovascular Protection in Milan in June 2017. Furthermore, the Lancet Commission on Hypertension and the organizers of the ISH Meeting on Hypertension 2018 in Beijing will invite abstract submissions for a new topic "Methods to Improve Blood Pressure Control in Low-Income Settings/Countries" and host a session dedicated entirely to this very important area of clinical research.

- Michael Hecht Olsen

Pictures below: Taken during The Lancet Commission on Hypertension Session in Seoul on 27 September



THE AARDVARK TRIAL: A SUMMARY



Gaia Kiru, Clinical Trial Manager

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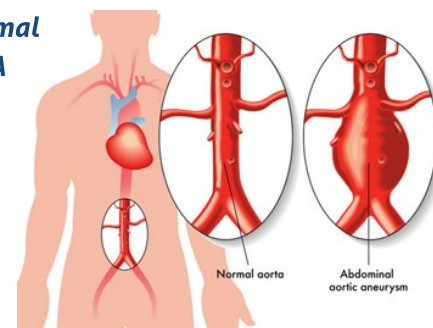
The AARDVARK (Aortic Aneurysmal Regression of Dilation: Value of ACE-Inhibition on Risk) trial took place from 2011-2015 and was designed to assess whether the Angiotensin Converting Enzyme-Inhibitor (ACE-I) perindopril reduced the growth of small Abdominal Aortic Aneurysms (AAAs) independent of blood pressure (BP) lowering.

The trial found that ACE-Is did not significantly reduce AAA growth rates compared with placebo or placebo and amlodipine combined, despite more effective BP lowering.

Background

AAAs can be defined as the ballooning of the infra-renal aorta to either 1.5 times its normal anteroposterior (AP) diameter or an absolute value of ≥ 3 cm. The single most important risk factor for AAAs has consistently been found to be smoking, although other risk factors including male sex, age, high blood pressure (BP) [particularly raised diastolic BP (DBP)] and family history of AAA.

Figure 1 - A normal aorta vs. an AAA (Adam.com)



AAAs are often described as “ticking time-bombs” due to their symptomless nature and prior to the initiation of the NHS Abdominal Aortic Aneurysm Screening Programme (for men aged 64) in 2009, AAAs were usually an incidental finding on clinical examination or imaging performed for other purposes. The most serious risk of having an AAA is that it may enlarge until it ruptures and around 80% of patients with a ruptured AAA do not survive. Currently, approximately 4000 deaths each year in England and Wales are attributed to AAA rupture. Despite the relatively strong association between hypertension and the prevalence of AAA, the association between increased BP and the rate of AAA growth or incidence of rupture is not clear and the evidence supporting increased growth as a result of hypertension is lacking. However, mean baseline BP levels reported in several large AAA surveillance studies are all above what is currently considered as controlled ($< 140/90$ mmHg) and it is possible that the AAA growth rates observed in these studies may at least in part be related to these higher BPs (see *Table 1*).

Study	Mean baseline BP (mmHg)	Mean baseline AAA diameter (cm)	Mean AAA growth rate (mm/y)
Western Australia screening study	157/91	3.4	1.6
MASS	155/83	3.5	2.6
Propranolol Aneurysm Trial	143/81	3.8	2.4
UKSAT	157/86	4.3	2.6

Table 1 - Mean baseline BPs, baseline AAA diameters and AAA growth rates as reported in the Western Australia Screening study, MASS, Propranolol Aneurysm Trial and UKSAT.

Despite the progress over the last few decades in treating other cardiovascular diseases, no medical treatments to slow the development or growth of AAAs have been identified. Various pharmacological agents have been investigated including beta-blockers, statins and doxycycline – all of which have had inconclusive results. So, although screening for AAAs has led to an increase in the number of AAA's being detected early and therefore a decrease in the number of ruptures, patients with AAAs ≤ 5.5 cm (ie. the usual threshold for surgical repair) receive only regular ultrasound scans to monitor AAA growth and smoking cessation advice with no options of medical intervention.

The AARDVARK trial was initiated after a large Canadian observational study (Hackham et al. [2006]) of 15000 patients suggested that ACE-I may reduce the rupture of AAAs by 20%. This echoed the findings of several animal studies that have suggested a key role for the renin-angiotensin system (RAS) in AAA development and progression but conflicted with other studies including the the UK Small Aneurysm Study which reported a small but significant association between ACE-I prescription and increased AAA expansion.

Methods

AARDVARK was designed as a randomised, single-blind, multicentre, placebo-controlled trial, with patients randomised to receive daily either perindopril (10mgs arginine salt), placebo (primary comparison) or amlodipine (5mgs - secondary comparison). The perindopril and amlodipine doses used were estimated to have similar effects on BP reduction and hence the secondary comparison was included to assess whether any benefits of perindopril compared with placebo, were independent of BP reduction.

Men and women aged at least 55 years with an AAA of 3.0–5.4 cm in AP diameter (internal or external) and a systolic BP (SBP) of < 150 mmHg were invited to participate. Patients who were already required to take either an ACE-I or a calcium channel blocker (CCB) (with the exception of 5 mg of amlodipine) or an Angiotensin Receptor Blocker (ARB) were excluded as were those with known renal artery stenosis ($> 50\%$) or a serum creatinine level of > 180 $\mu\text{mol/L}$.

Patients were followed up every 3–6 months over 2 years. At each visit, three BP recordings were taken in the sitting position using either an Omron 705-CPII or an Uscom BP+ device after at least 10 minutes' rest. The mean of the second and third readings was used in the analyses. Smoking was not permitted during the 30 minutes before BP measurement.

Ultrasound AAA diameter measurements were taken at each visit. A scanning protocol was provided to all participating sites in an attempt to optimise the consistency and accuracy of the ultrasound measurements made across the 11 scanning sites that serviced the 14 collaborating hospitals.

Results

Between September 2011 and April 2013, 227 patients were randomised ($n = 75$ perindopril, $n = 73$ amlodipine, $n = 79$ placebo). Because of the large number of patients who were ineligible (mainly because they were already taking an ACE-I (40%), ARB (10%), CCB (11%)), a recruitment extension of 6 months and the addition of 9 extra research sites was required (taking the total number of sites to 14). The recruitment target was met by April 2013. Trial follow-up was completed in April 2015, with 70% of patients completing all trial visits and an attrition rate of 6%. Groups were well matched at baseline for standard demographic parameters.

Throughout the trial, mean systolic and diastolic BP levels remained largely unchanged among those allocated to placebo but fell in the amlodipine group, and more so in the perindopril group (*Figure 2*). For example, mean changes from baseline in systolic BP midway through the trial (12 months) were 0.5 mmHg (standard deviation 14.3, $P = 0.78$ compared with baseline), -9.5 mmHg (13.1, $P < 0.001$), and -6.7 mmHg (12.0, $P < 0.001$) in the placebo, perindopril, and amlodipine groups, respectively. Mean changes from baseline in diastolic BP at 12 months were -0.2 mmHg (standard deviation 7.3, $P = 0.78$ compared with baseline), -5.8 mmHg (8.1, $P < 0.001$), and -4.7 mmHg (7.5, $P < 0.001$).

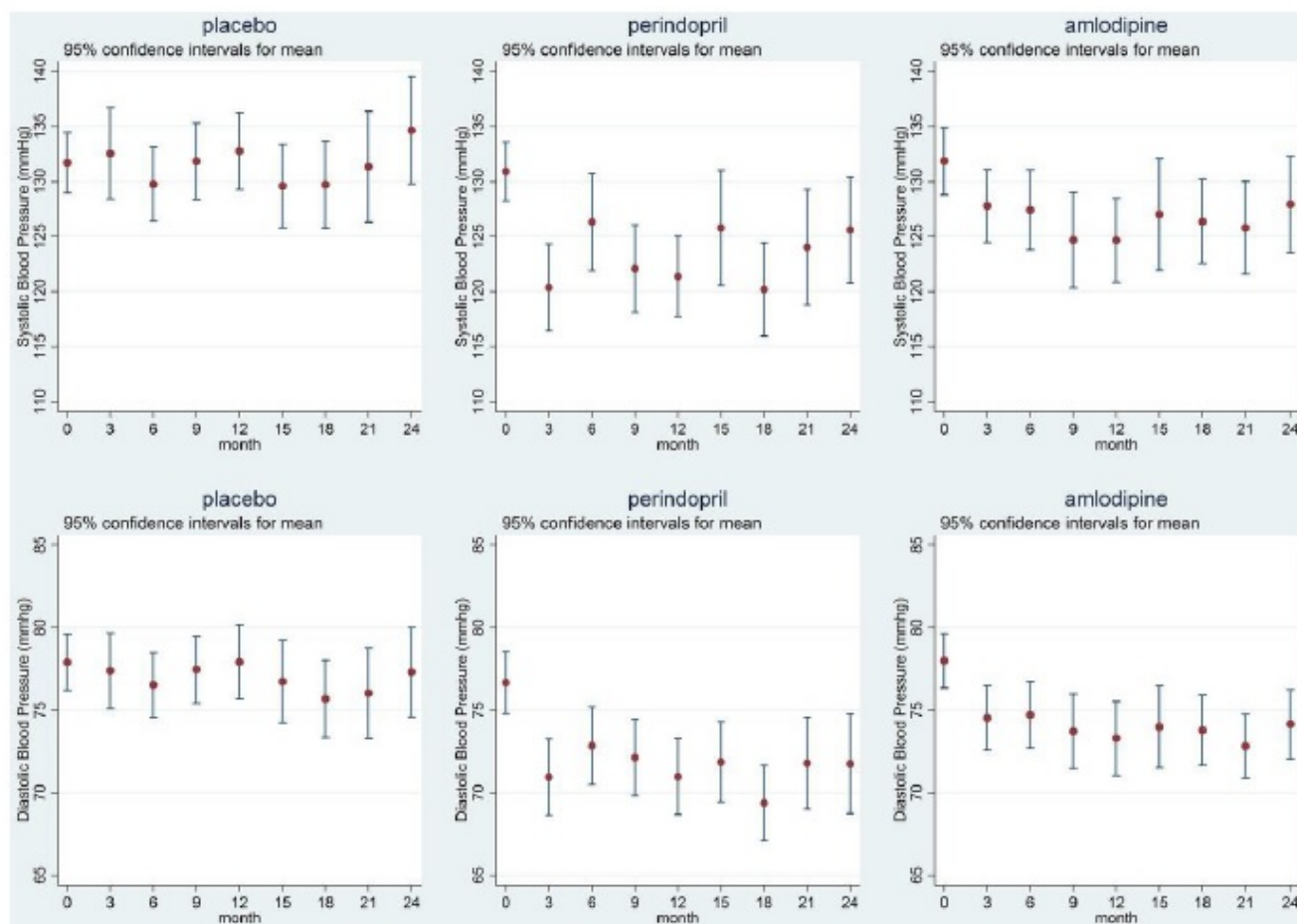


Figure 2 - Mean systolic and diastolic BP over the duration of the trial by randomised group 2

Compliance measured by pill counts was good throughout the trial (> 80% at all visit time points). There were no significant safety concerns associated with any of the three allocated trial drugs. Six patients withdrew because of AEs attributed to the study medications ($n = 2$ perindopril, $n = 4$ amlodipine). No patients ruptured their AAA but 27 patients underwent elective surgery during the trial period ($n = 9$ placebo, $n = 10$ perindopril, $n = 8$ amlodipine).

The average annual AAA growth rate observed was 1.7 (SD 3.0) mm. Multilevel modelling was used to determine the maximum likelihood estimates for AAA diameter growth. There were no significant differences in the estimated annual diameter growth rate among the three randomised groups [1.68 (standard error 0.02) mm, 1.77 (0.02) mm and 1.81 (0.02) mm in the placebo, perindopril and amlodipine groups, respectively]. Similarly, the differences in the slope of modelled growth over time were not significant between perindopril and placebo ($p = 0.78$) or between perindopril and amlodipine ($p = 0.89$). The difference in the slope of modelled growth between the perindopril group and the placebo and amlodipine groups combined was also not significant ($p = 0.92$). These results were essentially unchanged after adjustment for potential confounders including smoking, diabetes and statin use. Similarly, there were no differences between the groups in time to AAA referral for repair and/or time to reach an AAA diameter of 5.5 cm.

Conclusions

The AARDVARK trial suggests that at least among those with baseline systolic BP <150 mmHg, a systolic/diastolic BP reduction using perindopril, compared with placebo, of on average ~8/5 mmHg throughout the trial does not have a significant impact on AAA growth rate. It is important to note however, that the AAAs in the trial grew more slowly than expected and the accuracy of ultrasound scanning was less than expected, both of which may have reduced our ability to detect small differences between groups if they were present.

To our knowledge AARDVARK was unique in being the only placebo-controlled randomised controlled trial to have completed an evaluation of the impact of ACE-Is on the growth rate of small AAAs. However, two other trials of the ARBs valsartan and telmisartan are currently in progress. Interestingly, the large Canadian case-control study that reported the protective effects of ACE-Is on the rupture of AAAs did not show similar benefits for ARBs.

Surgical techniques for elective and emergency AAA repair continue to advance, leading to lower mortality rates, but the risks of surgery in this elderly population remain. Meanwhile, studies and trials continue to investigate the possible factors which lead to AAA development and progression, in hope that a pharmaceutical intervention may be found.

Central BP and BP variability (BPV) are relatively new players in the cardiovascular arena and both have been strongly linked to cardiovascular events. However research into their association with AAA development and growth is lacking. As part of the AARDVARK trial, we collected central BP data on a subset of patients, and are now able to investigate the roles of central BP and BPV in this group of patients. The results are pending but will contribute to our knowledge of hypertension and AAA.

-Gaia Kiru

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Joint ISH-ESC Session during the 2016 Congress of the European Society of Cardiology

Alta Schutte

ISH Vice President and Chair, Membership Committee

Director, Hypertension in Africa Research Team (HART), North-West University, Potchefstroom, South Africa

Report on the Joint ISH-ESC Session during the Congress of the European Society of Cardiology in Rome, Italy (27-31 August 2016)



For the first time, the International Society of Hypertension and European Society of Cardiology (ESC) jointly discussed some of the most important challenges facing hypertension, particularly in low and middle income countries. Since these countries are carrying a significant burden of hypertension globally, it is a high priority for everyone working in this field.

This session, titled "*Improving Hypertension Management in Low and Middle Income Countries: Low hanging fruit for helping reach the 25 x 25 NCD targets*" was chaired by Professor Rhian Touyz (UK) and Professor Antonio Coca (Spain). Professor Dorairaj Prabhakaran (India) shared with the audience the success stories from India regarding the training, task sharing and improved control in hypertension due to intense intervention programmes. It is hoped that many other low and middle income countries will follow suit. This linked well with the presentation that followed, given by ISH President-Elect, Professor Neil Poulter (UK), who discussed the World Heart Federation's Roadmap to improve the global situation on raised blood pressure. The presentation highlighted the potential barriers and solutions addressing the global health community to manage and control hypertension. **The interactive roadmap can also be viewed here.**

Professor Jorge Polonia (Portugal) discussed the experience of Portugal in reducing population salt intake, and how successful this undertaking has been to date. This is a high priority for Portugal, as this country has a very high population salt intake. Since the introduction of this program, similar trends have been observed in population salt reduction and reduced prevalence of stroke. The final presentation was given by Professor Alta Schutte (South Africa) who described how the present situation of poor awareness, treatment and control, especially in developing countries, should be counteracted by population-wide prevention programmes, such as regulations on tobacco and alcohol. The creation of health-promoting environments should be much higher on the agenda of these countries to make it easier for individuals to make healthy choices. After lively interactions with the audience the session was closed, and it is hoped that these joint discussions between ISH and ESC will continue during future meetings.

-Alta Schutte

The 2016 European Guidelines on Cardiovascular Prevention



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Photo by C-M Hake, Dagens Medicin

The 2016 version of the European Joint Societies Guidelines on Cardiovascular (CVD) Prevention (1) is an update of the 2012 publication (2) and uses the same structure: what is cardiovascular prevention, who needs it, how and where should it be offered?

There are no major changes in the guidance on the management of hypertension. One significant novelty is a public health chapter with recommendations on prevention at the population level aimed at providing advice to politicians and health care providers based upon updated scientific evidence.

CV prevention, for whom?

Persons with an elevated risk of cardiovascular disease should be offered risk assessment: i.e. smokers, patients with high blood pressure or with diabetes mellitus, and those with known elevated lipid values or with a history of familial hypercholesterolemia. It is even indicated in patients with rheumatoid arthritis, sleep apnea disorder or erectile dysfunction. For this group of persons risk assessment should be repeated every 5 years. General screening for women > 50 years old and men > 40 may be considered only if resources exist. There is no scientific support for screening in younger age groups.

Always lifestyle first!

The guidelines put great emphasis on a healthy lifestyle: modern treatment for patients with CVD, hypertension, hyperlipidemia or diabetes mellitus states implies that patients' habits are addressed: advice on tobacco (no exposure to tobacco in any form), food habits (a diet low in saturated fat and high intake of whole grains, vegetables, fruits and fish) and physical activity (at least 150 minutes/week of moderate aerobic physical activity or 75 minutes/week of heavy aerobic physical activity or a combination of both). Overweight should be controlled (optimal BMI 20-25 kg/m²) and for waist circumference an upper level <94 cm (men) or <80 cm (women) is recommended.

Management of hypertension, anything new?

In the 2012 guidelines the target values in hypertensive patients were defined as a BP <140/90 mm Hg for all ages but in the new document more specific guidance is provided for patients > 60 years and even for patients > 80 years, under the condition that these older people are in good general condition (**table 1**). Assessment of the total cardiovascular risk, using the SCORE algorithm, does guide the decision to commence drug treatment.

The definitions and classifications of blood pressure levels and the thresholds for defining hypertension with different types of measurement (24-hour, night-time, day time and registration at home) all remain unchanged. Given the fact that a majority of patients are above the age of 60 and that 24-hour or home measurements are becoming increasingly applied in Europe it would have been valuable with a revision of the thresholds for the elderly using the newer methodology. However, it remains uncertain which the optimal out-of-office (home and ambulatory) BP targets are and whether management based on control of out-of-office BP provide an advantage over strategies based on conventional (office) control.

The target levels for hypertensive diabetes patients follow the same recommendations as for the nondiabetic hypertensive population. The recommended target HbA_{1c} to reduce the risk for CVD and microvascular complications is for most diabetes patients, both type 1 and 2, <53 mmol/mol (7%) but at the early onset of type 2 diabetes a lower value might be desirable.

Table 1

Recommendations for management of hypertension		
Recommendations	Class	Level
Lifestyle measures (weight control, increased physical activity, alcohol moderation, sodium restriction, and increased consumption of fruits, vegetables, and low-fat dairy products) are recommended in all patients with hypertension and in individuals with high normal BP.	I	A
All major BP lowering drug classes (i.e. diuretics, ACE-I, calcium antagonists, ARBs, and beta-blockers) do not differ significantly in their BP-lowering efficacy and thus are recommended as BP lowering treatment.	I	A
In asymptomatic subjects with hypertension but free of CVD, CKD, and DM, total CV risk stratification using the SCORE model is recommended.	I	B
Drug treatment is recommended in patients with grade 3 hypertension irrespective of CV risk, as well as in patients with grade 1 or 2 hypertension who are at very high CV risk.	I	B
Drug treatment should be considered in patients with grade 1 or 2 hypertension who are at high CV risk.	IIa	B
In patients at low to moderate total CV risk and with grade 1 or 2 hypertension, lifestyle measures are recommended.	I	B
In patients at low to moderate total CV risk and with grade 1 or 2 hypertension, if lifestyle measures fail to reduce BP, drug treatment may be considered.	IIb	B
SBP <140 mmHg and DBP <90 mmHg are recommended in all treated hypertensive patients < 60 years old.	I	B
In patients >60 years old with SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg.	I	B
In fit patients <80 years old, a target SBP < 140 mmHg may be considered if treatment is well tolerated. In some of these patients a target SBP <120 mmHg may be considered if at (very) high risk and tolerate multiple BP lowering drugs.	IIb	B
In individuals >80 years and with initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions.	I	B
In frail elderly patients, a careful treatment intensity (e.g. number of BP lowering drugs) and BP targets should be considered, and clinical effects of treatment should be carefully monitored.	IIa	B
Initiation of BP lowering therapy with a two-drug combination may be considered in patients with markedly elevated baseline BP or at high CV risk. Combination of two drugs at fixed doses in a single pill may be considered because of improved adherence.	IIb	C
Beta-blockers and thiazide diuretics are not recommended in hypertensive patients with multiple metabolic risk factors, due to the increased risk of DM.	III	B
ACE-I = angiotensin-converting enzyme inhibitor; ARBs = angiotensin receptor blockers; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; SBP = systolic blood pressure; SCORE = Systematic Coronary Risk Estimation.		

The target values for lipid control are unchanged: for the very high risk patient < 1.8 mmol/l (<70 mg/dL, for high risk individuals < 2.6 mmol/l (<100 mg/dL). Statins remain the drug of choice in the treatment of hyperlipidemia. Adding a selective cholesterol absorption inhibitor is only recommended if target values are not reached on a maximal dose of statins. Further details can be found in the 2016 version of the European Society of Cardiology/European Atherosclerotic Society Guidelines on the management of dyslipidaemias (3).

Adherence to preventive treatment

Patients' adherence to preventive treatment remains a major challenge, as convincing patients to take drugs for the rest of their life is often problematic. A special chapter has therefore been dedicated to adherence and compliance with distinct stepwise guidance. Can the use of a simplified medication where several substances are combined in a single tablet (so-called polypill) prove to be an option to improve compliance?

CVD prevention at the population level

The new chapter on population health uses the conventional grading of the scientific evidence and recommendations. It calls upon doctors and other health professionals to play a greater role in striving for good public health. A few of the major recommendations are:

Tobacco: increase the price; price differences that drive cross-border trade should be removed. Smoking should not be allowed in public places or in places where children dwell, especially in private homes or cars.

Alcohol: advertising of alcoholic drinks should be reduced, the limit for alcohol while driving should be reduced further and the prevention of abuse should be given greater priority.

Food products: legislation to reduce the amount of energy, salt, saturated fat and added sugar in food products including pricing as a tool to limit the use of these products. Information on nutrient content should be uniform and sufficiently legible.

Physical activity: cities or buildings should be designed so that physical activity for the general public is an easy-accessible option.

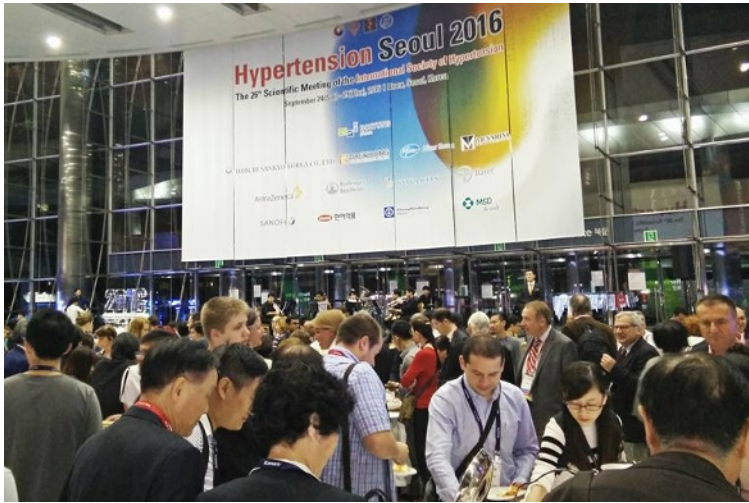
Finally, the chapter "what should or can be done and what should not be done" at the end of the document is another novelty: 24 statements "to do" ("a healthy diet is recommended as a cornerstone of prevention to all") and merely five statements "not to do" ("CVD risk screening in men <40 yr and women <50 yr without any known risk") A better balance between what "to do" and what "not to do" remains a challenge for coming prevention guidelines.

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-Joep Perk

New Investigator Reports from the ISH 2016 Seoul Biennial Meeting



A number of reports have been submitted from ISH hypertension future leaders who were in attendance at the ISH Biennial Meeting in Seoul in September. These focus on their personal meeting experiences and the standout sessions that they attended.

A contribution from Fadi Charchar (page 26) also reports on this year's hugely successful Networking and Mentorship Event that took place on the evening of 27th September. We are proud to report that this occasion was attended by over 140 new investigators and senior ISH Faculty members from 34 countries.



Sofie Brouwers

1. University Heart Center, University Hospital Zurich, Zurich, Switzerland

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Plenary session: Managing hypertension in aging societies *Perspective on elderly hypertension in Asia*

The lecture of Professor Kokubo at the plenary session on managing hypertension in aging societies provided us with a nice Miso cookbook, together with new insights into hypertension and associated complications in an aging society in Asia and especially Japan.

On one hand, age-standardized stroke mortality decreased worldwide in the past two decades, on the other the absolute number of people with first stroke, stroke survivors, stroke-related deaths and the overall global burden of stroke increased, especially with most of the



burden in low-income and middle-income countries. (*Lancet* 2014;383:245-55)

Overall in Asia, mortality rates of stroke are much higher than in Western countries and among Asian countries, stroke mortality in Japan is the lowest. Compared to Western countries coronary heart disease mortality is much lower in East Asian countries, especially in Japan and South Korea, whereas it is higher in South Asian countries. The higher stroke rates compared to coronary heart disease in Asian countries are most likely due to a higher prevalence of hypertension, attributable to a high salt intake, and a lower level of serum total cholesterol, owing to a lower fat intake. (*Circulation* 2008;118:2702-9) Moreover, the slope of the association between blood pressure and incident stroke is steeper among Asians than Westerners. (*Hypertension* 2007;50: 991-7) Excessive drinking and smoking rates are high in Asians and contribute to hypertension and cardiovascular disease. Study results in Asian populations indicated that long-term alcohol consumption is also a risk factor for stroke, although this factor had no effect on the incidence of stroke in Western populations. (*BMC Public Health*. 2014;14:776)



Pictured: Yoshihiro Kokubo

Over the last century dietary habits have changed substantially around the world, and certainly also in Japan with increased intake of calories, fat, proteins and still a moderate to high salt intake. Salt-sensitive hypertension seems to be more common in Japan, and this seems to be linked to a significantly higher frequency of salt-sensitive alleles in Japanese compared to Caucasians. (*Hypertens Res* 2003;26:521-5) In contrast to the western diet the consumption of fish and soy products, a major source of isoflavones, is very high in Asia, especially in Japan. These dietary elements have a protective effect on cardiovascular disease. The Suita Study, a Japanese prospective cohort study, showed that moderate miso soup consumption may reduce the risk of cardiovascular events, especially in women. (*Circulation* 2007;116:2553-62)

More efforts need to be done to undertake large-scale lifestyle modifications in an aging society with an increasing burden of disease. Current evidence supports a risk stratification calculated according to the different risk profiles.

-Sofie Brouwers

Antoine Caillon

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A young investigator in Seoul

Every two years it is a great pleasure to participate in the ISH meeting and discuss and share experiences with the international hypertension community. As a young investigator, I was particularly interested in the sessions and meetings that focused on the work and networking of young investigators.



ISH New Investigator Poster Presentation Award Winners

An exciting part of the meeting was the variety of sessions for new investigators, including the ISH New Investigator Award session during which young researchers brilliantly exposed the future trends of fundamental research in hypertension, presenting topics such as inflammation, vaccination, and the role of genetic and epigenetic defects in the central nervous system affecting hypertension.

Another interesting point, mentioned at the New Investigator Committee (ISHNIC) Networking and Mentorship dinner, was the importance of mentorship within our community in the development of the young investigators' careers. During the dinner, young investigators had an opportunity to discuss and share their experiences and insights about research with a principal investigator.

This mentorship is a great idea to keep up with cutting edge science and to promote future collaborations with the goal of attaining excellence in research. For these reasons, I am excited to join my international hypertension community in two years' time in Beijing.

-Antoine Caillon



Ruan Kruger

Chair, ISH New Investigator Committee

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Insights into oxidative stress-related mechanisms, from the Presidential lecture by Prof Rhian Touyz at ISH 2016

The nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) enzymes (or better known as the NOX family) are transmembrane proteins and share the capacity to transport electrons across a plasma membrane to generate superoxide and other down-stream reactive oxygen species (ROS).

Physiological oxidative stress is essential for normal cellular function, however Prof Touyz has shared her insights from her laboratory in Glasgow regarding the particular role of NOX5 in the development of hypertension. NOX5, unlike NOX1/2/3/4, has a distinct connection with calcium as it contains a calmodulin-like domain with binding sites for

calcium. The NOX5 is calcium-sensitive and undergoes conformation enhancing the expression of reactive oxygen species via NOX5.



Rhian Touyz giving her ISH Presidential Lecture

The interesting findings have implicated over-expression and activation of NOX5 in hypertension and atherosclerosis, making NOX5 a therapeutic target for isoform-specific NOX inhibitors to promote potential vasoprotective effects in cardiovascular disease. We are excited to learn more about the progress of these potential therapies at the 2018 meeting in Beijing, China.

-Ruan Kruger

involvement of the gut microbiota with high dietary fibre intake in the prevention of hypertension, cardiac hypertrophy and heart failure in a model of disease.

The role of the gut microbiota with a high fat diet in experimental metabolic syndrome was also presented by Prof Myung-Shik Lee, from Yonsei University College of Medicine, Korea. His studies pinpointed that the bacteria Akkermansia muciniphila is less prevalent with fat intake, which also impaired Paneth cells in the intestinal epithelium, resulting in loss of epithelial integrity and reduced production of antimicrobial peptides.

In an attempt to address some limitations in the field, Prof Seong-Tschool, from Chonbuk National University Medical School, Korea, proposed a new method to determine gut microbiota using circulating blood and antibodies. We are looking forward to the development of this exciting field and hoping this can be further discussed at the ISH 2018 meeting in Beijing.

-Francine Marques



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The bacteria in our gut, called the gut microbiota, have attracted increasing interest in recent literature and the media due to their role in human health. Hypertension researchers are not falling behind, and we had a small showcase at the ISH 2016 meeting in Seoul.

Professor Peter Nilsson from Lund University, Sweden, reviewed some of the recent research in this field and briefly mentioned a study by his team and collaborators showing that healthy subjects who have a family history of cardiovascular disease have a distinct gut microbiome to those without a family history. In a similar topic, I presented data from our laboratory at the Baker IDI Heart and Diabetes Institute, Australia, supporting the

The 26th Meeting of the International Society of Hypertension (Hypertension Seoul 2016) was the first ISH meeting I attended and one that I enjoyed immensely. The programme was packed with impressive presentations and speakers from around the world. The conference had a great range of both clinical and basic science, with relevant topics interrelated with my own work as a postdoctoral fellow with Professor Louise Burrell at the University of Melbourne, Australia.

One of the highlights for me personally within the programme was the launch of ISH Women in Hypertension Research, where Professor Barbara Casadei gave an inspiring presentation about her ups

and downs as a woman in hypertension research, one that I think many female researchers in the audience could relate to. I look forward to future updates from the Women in Hypertension committee and thank all of them for their efforts in raising awareness of the underrepresentation of women in research.



(From left to right): Rhian Touyz and Barbara Casadei. Image taken during the Women in Hypertension Launch



I was also fortunate enough to be shortlisted to present my work in the ISH New Investigator Award Session as a moderated poster, for which I was awarded the runner-up prize. This was a great opportunity for me and I thank the judges and ISH for considering my work.

Socially, the ISH NIC Networking & Mentorship Event was an absolute highlight. It gave me the opportunity not only to meet potential mentors, but to form networks with other young investigators and peers with similar interests, which is invaluable. The New Investigators Committee did an amazing job in putting the event together. For some, this was followed by the ECCR/HBPRCA dinner, which was also a great event for networking and socialising.

Overall I enjoyed the whole experience and I am sure other young investigators will have the same opportunity in future ISH meetings.

-Elena Velkoska



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"Where's the salt?"

The Hypertension 2016 meeting proved to be beneficial to those wishing to expand their understanding of hypertension, as well as review some foundational theories. One such session, "Sodium homeostasis and hypertension" had 3 speakers who did just that.

Dr. Richard Wainford of Boston University focused his talk on the canonical physiology of renal sodium handling, along with new insights on factors that impact this regulation. This session started with a thorough review of the Guytonian Pressure-Natriuresis Hypothesis. Following on from this, Dr. Wainford discussed the roles of genetics, inflammation and dietary modifications such as potassium and fructose on renal sodium handling and salt-sensitivity.

The speakers who followed, Dr. Liffert Vogt of the University of Amsterdam and Dr. Jens Titze of Vanderbilt University discussed the extra-renal regulation of sodium. Dr. Vogt's noteworthy talk focused on the function of glycosaminoglycans, especially regarding their possible role within the vasculature as an 'intravascular buffering' compartment. Dr. Titze's talk summarized his work showing that large amounts of sodium actually accumulate within the interstitium. These speakers discussed the interesting idea that sodium can be compartmentalized at higher concentrations.

Together, this session covered novel renal and extra-renal theories of sodium regulation and served as a reminder of the multifactorial etiology of hypertension.

-Brandi Wynne

ISH Seoul New Investigator Committee Networking and Mentorship Event



Fadi Charchar PhD FAHA

Robert HT Smith Chair in Cardiovascular Sciences.

Faculty of Science and Technology, Federation University, and Department of Physiology, University of Melbourne, Australia.

Department of Cardiovascular Sciences, University of Leicester, UK.

The mentorship event was held in the LU restaurant at the Coex, Seoul, Korea as part of the ISH 2016 Biennial Scientific Meeting. The event was very well attended (over 150 participants) by distinguished guests, ISH council members, senior faculty and junior investigators. Participants originated from 34 countries.

The night kicked off in the beautiful venue with drinks,

canapés and a sociable atmosphere. We were very lucky to have past, present and future presidents of the ISH (Chalmers 1992-1994; Beilin 2002-2004; Lindholm 2006-2008; Heagerty 2008-2010; Harrap 2010-2012; Schiffrin 2012-2014; Touyz 2014-2016; Poulter 2016-2018). We would like to thank them for their unwavering support of both the New Investigator Committee and Mentorship Scheme. After short and entertaining speeches, the crowd mingled and enjoyed the great spread on the night.

I hope that the event encouraged informal discussions amongst new investigators and faculty across fields and nationalities. We look forward to hearing about developments from the night. Most importantly I hope that some of the attendees have made new friends and collaborators. I would particularly like to thank the NIC members for their amazing work and for making the night an event to remember.

-Fadi Charchar



Reports from Oneeb Mian and Dylan Burger



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The AHA Hypertension Scientific Sessions 2016 took place in Orlando, Florida at the scenic Disney Dolphin Resort. The conference was well attended by labs based in the Americas and Europe, as well as some representatives from farther east. A key change to the format of the conference was the expansion of concurrent sessions, allowing for an increase in the number of oral presentations by one third. Approximately 430 abstracts in total were presented.

Prior to the start of the conference, The Trainee Advocacy Committee of the Council on Hypertension in conjunction with the ISH New Investigator Committee offered a special half-day workshop on how to prepare for professional careers, targeted specifically towards students and early career investigators. Dr. Randall Ribaud, co-founder and CEO of the career-development SciPhD, presented on how to translate scientific experience and accomplishments into critical skills that companies value. The workshop also provided attendees with an interactive training focused on networking, resumé and interview preparation, and self-assessment.

One of the main talking points from the opening day was the discussion of the keynote lecture on the SPRINT trial presented by Dr. William Cushman. Drs Ernesto Schiffrin, Suzanne Oparil, and Kenneth A. Jamerson discussed their views on intensive blood pressure treatment versus standard care, and later answered audience questions. The feasibility and relevance of automated blood pressure monitoring throughout the world was a key issue that was raised during the discussions. Overall, panellists and audience agreed that the trial results may prompt

changes in the guidelines for the management of hypertension.

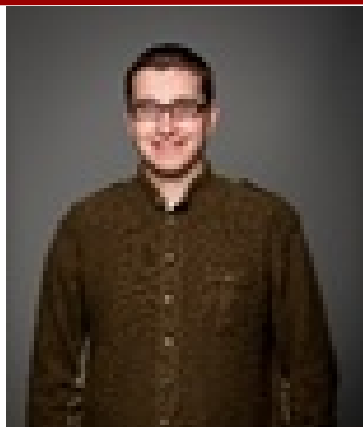
As always, investigators in all stages of their careers who have made noteworthy contributions to hypertension research were recognised through awards and special lectures. Key among them was Dr. David Robertson, who was presented with the Irvine Page-Alva Bradley Lifetime Achievement Award for his work on the neural regulation of heart rate and blood pressure. Dr. Meena Madhur was recognised with the Harry Goldblatt New Investigator award for her work on the role of cytokine interleukin 17 in hypertension. Drs. R. Ariel Gomez and Suzanne Oparil shared the Novartis Excellence Award for Hypertension Research.

There was once again a large presence of students and early career investigators at the council meeting, contributing in terms of exuberance and exciting original research. Of note, Dr. Mariane Berganolli, winner of the Hypertension Early Career Award, presented on the association between circulating endothelial colony-forming cells dysfunction and cardiovascular alterations in young adults born preterm. In a session on Immune Mechanisms in Hypertension, Dr. Antoine Caillon presented on the first experimental demonstration of the key role played by gamma delta T cells in the development of angiotensin II-induced hypertension.

The meeting closed with noteworthy changes to the council leadership committee and some important developments. Dr. Joey Granger will be the new Chairperson and Dr. Augusto Montezano will lead the Trainee Advocacy Committee.

Immediate Past Chair Dr. Christopher Wilcox talked about the proposed merger of the American Society of Hypertension with the current AHA Hypertension and Kidney councils for a unified yearly meeting. It will be interesting to see how this development impacts the programming and execution of the next meeting in San Francisco.

-Oneeb Mian



Dylan Burger

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ISH Communications
Committee member

Since 2011 the ISH New Investigator Committee has partnered with the Trainee Advocacy Committee of the American Heart Association Hypertension Council in promoting new investigator activities at the AHA Hypertension Council Scientific Sessions. The annual trainee poster session is a notable product of this working relationship. Held in the evening of the opening day, the session is always very well attended, setting the tone for the remainder of the meeting.

I have had the privilege of participating in this session for several years, first as a trainee and more recently as a judge and can personally attest to the quality of this year's session. This session was also noteworthy for a greater presence of clinical studies, including award winner Lyndsey DuBose ("Greater 24 hour blood pressure variability is associated with higher 24 hour systolic blood pressure and glucose independent of age and large elastic artery stiffness in normotensive adults").

A special thanks to members of the ISH New Investigator Committee, the AHA Trainee Advocacy, and all faculty who volunteered their time to ensure a supportive and constructive environment for the next generation of researchers in hypertension.

A total of 22 posters were awarded across 4 categories (undergraduate students, graduate students, postdoctoral fellows, and junior faculty) and are listed below.

Undergraduate

- **Eduardo Dias Jr.**

The role of the adrenoreceptors beta 3 on metabolic syndrome induced by fructose

Graduate

- **Kim Ramil C Montaniel**

Inhibition of miR-762 prevents and reverses Ang II induced aortic stiffening

- **Lyndsey E DuBose**

Greater 24 hour blood pressure variability is associated with higher 24 hour systolic blood pressure and glucose independent of age and large elastic artery stiffness in normotensive adults

- **Alissa A Frame**

Impaired central, renal, and blood pressure responses to alterations in fluid and electrolyte homeostasis in aged Sprague-Dawley rats

- **Sabrina R Gonzalez**

Renal localization of salt inducible kinase-1 and its regulation in Doca/salt hypertensive rats

- **Jin Wei**

Enhanced Nos1-beta in the macula densa contributes the diabetic hyperfiltration

- **Amanda Kennedy**

Chemokine-like receptor 1 mediates the vasoconstrictor actions of chemerin in vitro and in vivo

- **Filipe Conti**

Combined exercise training is better than isolated aerobic and resistance exercise training for an experimental model of metabolic syndrome and menopausal rats

Postdoctoral

- **Julio Gallego-Delgado**

The high blood pressure-malaria protection hypothesis

- **Robin C Shoemaker**

Mas receptor deficiency regulates obesity-hypertension and cardiac function in female and male mice

- **Seungbum Kim**

Butyrate, a microbial metabolite attenuates angiotensin II-induced hypertension and gut dysbiosis

- **Bryan K Becker**

Bilateral renal denervation attenuates hypertension in male rats deficient of functional endothelin B receptors but does not affect salt sensitivity

- **Gianluca L Perrucci**

Hypertension enhances the differentiation of cardiac fibroblasts into myofibroblasts after TGF-beta 1 treatment

- **Cesar A Romero**

Connecting tubule-glomerular feedback in renal hemodynamics and blood pressure after unilateral nephrectomy

- **Jing Wu**

Cullin3 regulated endothelial function by modulating eNOS activity

- **Chetan N Patil**

Hypertension in postmenopausal women: role of renin angiotensin system and eicosanoids

- **Theo A Meister**

Assisted reproductive technologies increase the vasoconstrictor responsiveness to Ang II by an epigenetic mechanism

- **Francisco J Rios**

Protective role of TRPM7 kinase against vascular dysfunction and fibrosis induced by aldosterone and salt

Junior Faculty

- **Jose A Gomez**

A new role of Sox6 in blood pressure through renin regulation

- **Huxing Cui**

Lateral hypothalamic leptin and melanocortin signaling in the regulation of sympathetic nerve activity and blood pressure

- **Yanfei Qi**

Spiny mice are protected from myocardial infarction induced cardiovascular pathophysiology

- **Joshua S Speed**

High salt intake desynchronizes the molecular clock in rats

-Dylan Burger

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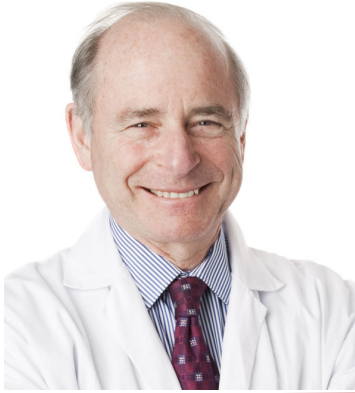


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HOT Discussion on BP lowering after SPRINT at the Recent AHA Meeting.



Ernesto L. Schiffrin MD, PhD

McGill University, Montreal, QC, Canada

Cardiovascular Seminar at the American Heart Association Scientific Sessions in New Orleans, LA, USA, entitled "Clinical Management of Hypertension: Moving Forward from SPRINT-Global Implications"

A Cardiovascular Seminar at the American Heart Association Scientific Sessions in New Orleans, LA, USA, took place on the morning of Monday, November 14, 2016. Entitled "Clinical Management of Hypertension: Moving Forward from SPRINT-Global Implications, it was a session organized by the World Hypertension League and the International Society of Hypertension.

The session was chaired the President of the WHL, Dr. Daniel Lackland from Charleston, SC, USA, and the Immediate Past President of ISH, Dr. Rhian M. Touyz from Glasgow, United Kingdom. Dr. Lackland introduced the Cardiovascular Seminar by pointing out that hypertension was an increasing source of morbidity and mortality in low and middle income countries, and that this was the reason why ISH and WHL had decided to organize a discussion on the impact of SPRINT on management of hypertension across the world.

The first speaker was Dr. Ernesto L. Schiffrin from McGill University, Montreal, QC, Canada, whose subject was: SPRINT - Is it Time to Redefine Hypertension? Dr. Schiffrin started by presenting current guideline definitions of hypertension and target BP for low and high CV risk groups, as well as the observational data from the Trialists' Collaboration suggesting that CV risk rises log linearly above 115/75 mm Hg,¹ leading to the question of whether low BP targets will provide greater CV protection than usual ones such as <140 mm Hg, particularly for high CV risk hypertensive individuals.

He then showed the main SPRINT results summarily,² as well as the recent meta-analyses by Ettehad et al.³ and Xie et al.⁴ from their 2016 Lancet publications, which support the SPRINT-based SBP target of 120 mm Hg for high CV risk patients. He indicated that Hypertension Canada had already issued a SPRINT-based guideline for SPRINT-like patients.⁵ However, this guideline recommends unattended automated office BP (AOBP) measurement, which is similar to what was done in SPRINT. In fact AOBP may give values

that are below daytime ambulatory BP and 10 or more mm Hg lower than obtained in usual clinical practice.⁶ Even unattended AOBP may give lower SBP than observed AOBP.⁷ Unattended AOBP has been shown in a recent study to demonstrate in a >6000 people community hypertensive cohort aged >66 years old, and followed for >4yrs, that the nadir of hazard occurs at 110-119 mm Hg, supporting the SPRINT conclusions regarding target BP.⁸

Therefore, if unattended AOBP is performed as in SPRINT (and in Canada, 40% of family physicians use AOBP), hypertension should be redefined as BP \geq 130/80 mm Hg, and target BP should be <130/80 for low risk patients and SBP<120 mm Hg for high CV risk SPRINT-like patients, perhaps cautiously including diabetic subjects.⁹ However, if BP is measured manually as in most of the world, the classical definition of hypertension, BP \geq 140/90 mm Hg, should remain, with a target BP preferably close to 130/80 mm Hg for most patients, and <130/80 for high CV risk SPRINT-like subjects,¹⁰ perhaps also including diabetic individuals as in the CHEP Hypertension Canada guidelines. His final thought related to AOBP becoming more widespread as a result of SPRINT, allowing 110 years after Riva-Rocci achieving reliable, accurate and stable BP measurements.

Importantly, he suggested that the main impact of SPRINT beyond the actual target SBP of <120 mm Hg for high CV risk subjects could be that intensifying antihypertensive therapy would improve outcomes in hypertensive patients.

The second speaker was Dr. Lawrence Fine of NHLBI, Bethesda, MD, USA speaking on SPRINT Results and Hypertension Management.

Dr. Fine presented an analysis of SPRINT, the 25% relative risk reduction in the primary endpoint for the 13 mm Hg difference between the standard and intensified therapy groups over 3.26 years until the trial was stopped because of dramatic benefit to the intensive therapy group, and the 37% relative risk reduction in heart failure and 43% relative risk reduction in cardiovascular death in

the intensified therapy group compared to the standard therapy group.²

Interestingly, of the components of the primary endpoint, ACS, myocardial infarction and stroke were not significantly different in both groups. He showed the consistency of results across prespecified subgroups, such as males and females, African Americans and non-African Americans, >75 years of age or <75 years old, with or without CKD, lower or higher baseline BP, etc. He showed that the elderly fit or less fit benefitted equally to the whole cohort from intensive therapy.¹¹ He underlined the similarity and paucity of serious adverse effects on standard and intensive therapy, although hyponatremia, hypokalemia and acute kidney injury were more frequent in the intensified therapy group. It would be important to reproduce the results in subsequent trials, including trials with populations excluded from SPRINT such as diabetic persons. He showed that a recent publication in JAMA demonstrated the cost-effectiveness of the SPRINT intensified treatment since it was lower than 25 thousand dollars per QALY gained,¹² and less than the 50 thousand dollars considered cost-effective for any treatment. He indicated that already some guidelines such as Canadian and Australian ones had included recommendations based on SPRINT. He concluded that SPRINT intensive treatment is achievable as demonstrated by the Kaiser Permanente data from Northern California.

The third speaker was Dr. Paul K Whelton of Tulane University, New Orleans, LA, USA, on SPRINT Results and Implications for Management of Hypertension in North America.

Dr. Whelton reported that the SPRINT results are consistent with other trials, and collectively the data indicate that "lower is better". He stated it is unlikely that the benefits of intensive treatment noted in SPRINT can be explained by overestimation of treatment effects or underestimation of adverse effects. Generalizability of all landmark blood pressure trials, including SPRINT, is challenging, but they provide the best scientific underpinning for practice of evidence-based medicine.

The fourth speaker was Dr. C. Venkata S Ram from Dallas, TX, USA, who spoke on SPRINT Results and Implications for Global Management of Hypertension. Dr. Ram described the situation in low and middle-income countries, where manual BP is the norm. In fact, this is the case worldwide with few exceptions. Thus he argued that SPRINT BP targets could not be applied worldwide. We had to accept that manual BP measurement is carried out in most countries, and that BP control is dismal around the world, and therefore we have to concentrate on getting hypertensive patients to the target BP of <140/90 mm Hg, although in high risk CV patients

130/80 mm Hg might be recommended, before concentrating on achieving the SPRINT targets.

If AOBP became accessible, then lower BP targets might be considered. He was not optimistic on this occurring in the near future, and felt that we had to content ourselves with the older targets while intensifying treatment with the idea that BPs measured with manual equipment gave results >10 mm Hg higher than with AOBP, which might be inaccessible for the foreseeable future in the low and middle income world.

A final speaker was Dr. Michael A. Weber from SUNY Downstate College of Medicine, New York, NY, USA, who also spoke about global implications of SPRINT on management of hypertension.

Dr. Weber reminded the audience of the results of the VALUE trial,¹³ and how prompt BP lowering succeeded in improving outcomes. As well, the results of ACCOMPLISH, which showed that diabetic subjects benefitted from intensive BP lowering to <130 mmHg¹⁴ despite the apparent failure of intensified BP lowering to <120 mmHg in ACCORD. He also pointed out the CLARIFY study, suggesting that in patients with hypertension and CAD, lowering of SBP below 120 mm Hg resulted in a Jcurve phenomenon with adverse cardiovascular outcomes, including mortality,¹⁵ thus raising concern about excessive office BP reduction.

He pointed out that the difference between AOBP (unobserved method) and usual office BP measurement was in his view 7mm Hg for SBP, suggesting that the SPRINT BP goal should be targeted if BP was measured as done in SPRINT. If not, and done as performed in most clinics, the SBP target should be replaced by 130 mm Hg for high-risk patients. Dr. Weber presented the ASH/ISH guideline for management of hypertension in the community,¹⁶ which suggested simple recommendations and algorithms for hypertension management, perhaps including single pill combinations to improve adherence. He pointed out that the main conclusion should be that intensifying treatment, not just intensifying lowering BP, is what will improve outcomes for hypertensive patients. Dr. Weber explained this on the basis of the fact that intensive therapy patients received more diuretics, more RAS inhibitors and more calcium channel blockers, and thus effects of the drugs, and not only BP lowering, could be responsible for the benefits found in this group.

A panel discussion ensued, with participation of Suzanne Oparil, from University of Alabama, Birmingham, AL, USA, and Dr. Paul Whelton, who reiterated the need to intensify BP lowering as the main conclusion from SPRINT, and improve the quality of BP measurement.

-Ernesto Schiffrin

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Council's Corner: Hypertension Issues - a personal view



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The will to control hypertension

('The spirit is willing, but the flesh is weak')

It remains discomfiting and almost hard to believe that, in this day and age, blood pressure (BP) control still remains woefully inadequate worldwide. We would expect that with all the advances in hypertension treatment and control, we would attain more success in lowering the blood pressure to <140/90 mm Hg in a more substantial percentage of the hypertensive population.

The stats stare us in the face like a predator eyeing its prey. Less than one of eight hypertensive individuals has controlled BP. In high-income countries, wherein it can be rightfully presumed that the big majority of the population has access to adequate healthcare and cost-effective antihypertensive medicines, control rate is less than 20%. Even in the relatively high-risk hypertensive population with two or more cardiovascular risk factors, awareness and treatment rates are <50%; and control rate is still very low at 15%. (Chow CK. *JAMA*. 2013; 310:959-968)

This brings to mind Jesus Christ's admonition to his apostles in the Garden of Gethsemane: "The spirit is willing, but the flesh is weak." Just like the 12 dedicated and loyal apostles who could not hold their heavy eyes from closing and dozing off instead of vigilantly keeping watch for the angry mob and arresting soldiers, the modern-day apostles involved in hypertension prevention and control have all the earnest intentions to stem the tide of elevated BP, yet find themselves seemingly battle-fatigued and weary to sustain all programs and interventions necessary in hypertension prevention and control.

The intention to control high BP on the part of the physicians and healthcare providers, the governments and policy makers, and certainly the people with elevated BP may not be wanting; but the *will* to do whatever it takes to attain it still leaves much to be desired. A goal of better BP control is not a far-fetched dream. Success stories in hypertension prevention and control offer excellent models which other countries can aim to duplicate. The Canadian experience has shown that hypertension control can be increased by almost 500% in a little over 25 years; from 13.2% in 1992 to 64.6% in 2009. This was clearly an offshoot of improved awareness (from 56.9% to 82.5%) and treatment (from

34.6% to 79%). (McAlister FA. *CMAJ*. 2011; 183:OL1007-1013)

Physician inertia

In surveys, physicians are quick to blame poor patient adherence and ineffective antihypertensive medicines as causes for the inadequate control of their patients' high BP, but research data suggest otherwise. Therapeutic or clinical inertia on the physicians' part is reflected by the low use of combination treatments (<5% in low income nations) when it is well known that combination treatment is required in at least two-thirds of hypertensive patients to reach BP goal of <140/90 mm Hg. The use of combination treatment in low middle income, upper middle income and high income countries is also dismally low, ranging from 12.95% to 15.65%. (Chow CK. *JAMA*. 2013; 310:959-968)

In a BP-control project study in Spain, treatment modification or revision of initial antihypertensive prescription was only done in 15.4% of hypertensive patients treated by primary care physicians. In 84.6%, there was no effort to titrate the medicine prescribed, change it, or use combination treatment. A high 85% rate of physician inertia has been shown in several other European countries. (Wang YR. *Arch Intern Med*. 2007; 167:141-147)

Although BP control rates are expectedly higher in regular clinical practice (20%-30%), and even higher in randomized clinical trials (40%-60% in VALUE and ASCOT), some degree of physician or investigator inertia is suggested by the observation that more than one third of the patients enrolled in the trials, whose BPs remained uncontrolled, were still taking their initial antihypertensive regimen with no uptitration in the doses.

Multisectoral political will

It cannot be argued that prevention and control of

hypertension is complex, and has to be approached via a multisectoral collaboration. A strong multisectoral *political will* is necessary so governments, policy-makers, as well as various health workers, professional organizations like the ISH, the private sector and individuals with hypertension can work in unison, as a team, to increase BP control.

For control of hypertension and other noncommunicable diseases the government should strengthen its primary healthcare services. A simple device is all that is needed to diagnose hypertension. Even non-physicians can be trained to help in sustained massive screening programs to increase awareness and treatment, which should translate to better control rates later on. With simple risk-assessment instruments and a modicum of training, these volunteers can also preliminarily identify those who are at risk for cardiovascular events. When resources are low, this is one way to get a bigger bang for the buck.

One best-practice that can be duplicated is the training of health volunteers in the community who go from house to house to check the BPs of everyone in the household. We recently brainstormed on this idea in our local hypertension society, in support of Prof. Neil Poulter's and ISH 'marching orders' to increase hypertension awareness. We calculated that if we have 300 of these dedicated volunteers going house-to-house and screening 100 adults/day for 22 days a month, in a year's time, close to 8,000,000 adults could be screened. Around 2 million hypertensive individuals could be identified. If this is done as a continuing program, with an expected multiplier effect, hypertension awareness can increase to 80% in 10 years' time with an achievable doubling of control rate. Duplicate this all around the world, and we should be able to achieve our global 25/25 hypertension and cardiovascular disease (CVD) vision; that is, a 25% reduction in premature deaths due to high BP and CVD by the year 2525.

Needless to say, population-directed interventions and other preventive approaches should be implemented. This may require legislative assistance; hence, a whole-of-government approach is vital to enlist the support of all government branches and agencies. Many countries, particularly in upper middle income and high income countries have already strengthened their public education campaigns and surveillance systems to increase awareness to hypertension and other cardiovascular risk factors, and improve management and control. There must be a *collective effort* to do the same in low income and low middle income countries as well.

Patient must will it, too

On the patients' side, the lack of will to detect and control high BP can be reflected in the low motivation to have their BP checked, with the misconception that asymptomatic individuals cannot have a potentially serious hypertension. All it takes is a few minutes to find out if one is hypertensive or not, but taking the initiative to spare those few minutes seems to be a tall order for many. A strengthened will to curb hypertension can make people take the initiative to have their BPs checked, and for those who are diagnosed to be hypertensive, this can translate to better treatment adherence, more health-promoting activities and more active participation in managing one's hypertension. This attitudinal shift in paradigm can certainly impact favorably on the control of high BP and prevention of complications for individual hypertensive patients, and for the entire population as a whole.

The academe and professional organizations such as ISH can pitch in their share by helping primary healthcare physicians and non-physician health workers particularly in low- and low-middle-income countries in drafting treatment guidelines which are not mere 'cut-and-paste' recommendations from foreign guidelines, but are truly suited for the country, addressing specific issues in a real-world setting. More country- or region-specific clinical practice guidelines can ensure an individualized approach to hypertensive patients and encourage more apt utilization of treatment guidelines, preventing under- or over-translation of guideline recommendations and other clinical trial findings in real-world practice.

National and local professional cardiovascular organizations, together with the rest of civil society can also help convince their respective policy-makers and governments to increase allocation of resources for hypertension and CVD control programs, particularly primary healthcare approaches. A strong-willed health leadership is imperative to effectively execute population-based integrated approaches—addressing cultural norms and practices that promote unhealthy behaviors and misconceptions about hypertension, providing a more enabling environment for healthy lifestyle practices, and correcting disparities in healthcare.

In summary, envisioning a much better awareness, treatment and control rate for hypertension worldwide is a daunting, but achievable aspiration. Wishful thinking? An attitudinal paradigm shift may be the missing component that can set on fire our collective fervor to attain this vision. If there's a will, there's a way. If we truly muster the will to do it, committing to do whatever it takes to achieve it, then there is certainly a way.

-Rafael Castillo



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The World of HyperOmics

Advances in the Omic fields are bringing personalized medicine within reach in many fields of medicine. Many researchers have investigated the genomics of blood pressure regulation, hoping to find answers to hypertension's molecular mysteries.

Some studies have struck gold with findings such as the potassium (K(+)) channel KCNJ5 gene in adrenal aldosterone-producing adenomas and rare hereditary hypertension. But for the common or garden variety of hypertension, the genetic picture is far from complete. We have come a long way in understanding the genome itself in the last few decades. In the late 80s and early 90s genetic association studies relied on a few hundred mutations (markers in the genome) and a few hundred subjects.

We can now utilize a few hundred thousand mutations and studies are conducted in thousands of subjects. In 2011 a landmark meta-analysis study described 16 novel regions in the genome associated with BP regulation¹. Recent large meta-analysis studies found 662, 303 and 314 blood pressure-associated loci respectively. Interestingly, although the sample sizes are very large the identified loci still explain a small percentage (<10%) of the blood pressure variance. There is no denying that the findings present a good basis for studying novel blood pressure pathways and molecules, but for many researchers in the field we are left wondering where to now? Holding my crystal ball, which is often as accurate as a young Harry Potter's wand, here are my predictions.

- 1) Mega genome-wide association studies. Many in the field question whether these studies would reveal more loci.
- 2) The functional validation of many of the loci, which is not a small task. With the advent of gene editing this task is much more realistic.
- 3) Over the last 10 years, next generation sequencing (NGS) technologies have revolutionized genome analysis; we can now sequence the whole genome of an individual

within a couple days for less than \$5,000. NGS could be used to create hi-fi association studies. NGS also promises to characterize hypertension and translate the power of genomic research into the clinic.

- 4) Our group and others have shown the importance of non-coding RNA5 and epigenetic regulation of blood pressure. In particular microRNA which are potent cellular regulators. These molecules remain understudied in blood pressure regulation so I expect to see a lot more on these in the future.
- 5) Proteomics will follow in the footsteps of genomics and, in combination with other omics techniques will provide deeper information into the cause of hypertension.
- 6) Surprise discoveries about our genome, open to the imagination.

-Fadi Charchar

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