



Notes from the Editor - Lars H. Lindholm

Dear ISH member,

We hope you have had a Merry Christmas and we wish you a Happy New 2017!

Here is Opus 48 of Hypertension News, the first of four in its 15th volume. Opus 49 will follow in early June, Opus 50 in October, and Opus 51 in December.



On the occasion of its 50th anniversary, the International Society of Hypertension (ISH) identified *increased awareness* as a key issue in the fight against raised blood pressure. Hence, from this year, the ISH - in collaboration with the World Hypertension League (WHL) - plans to facilitate the expansion of the World Hypertension Day (17 May) into an exciting campaign and month of global blood pressure measurement called "May Measurement Month 2017" (MMM 2017). The goal for the month is to screen 25 million people who have not had their blood pressures measured for a year. Read more about this important undertaking in the President's Address on pages 3-4.

As you know, our Society is now more active than ever and it is far from easy for the President to cover all ongoing activities in the Newsletter, four times per year. In this issue, we have therefore started a new section called "The Secretary's Voice". On pages 4-5, the hard working ISH Secretary, Maciej Tomaszewski, gives you insights into the outcomes of recent ISH activities, the status of current undertakings, and future outlooks. One example is his report on the results of the meeting in Seoul, where 3,623 people from 91 countries met at a fantastic venue and had a wonderful time. In this way, we want the ISH members to get closer to the Executive, which I think is brilliant!



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Notes from the Editor - Lars H. Lindholm - continued

The young investigators are of the utmost importance to the ISH. In this issue of Hypertension News, Ruan Kruger, the chairman of the New Investigator sub-committee (NIC) presents his three aims (increasing membership, establishing long-standing networks, and upgrading the face of NIC), as well as the profiles of his team on page 12. Moreover, Dylan Burger - a previous member of NIC - shares his views on page 9 and states that "the ISH provides an ideal environment for a PhD scientist to grow their knowledge and gain exposure for their research", which is reassuring.

With the advent of human genome sequencing in 2000, it was expected that within ten years, research would deliver clinically useful results offering new means of prevention and possibly new treatment of high blood pressure. Stephen Harrap and Fadi Charchar are still waiting for genetics to deliver, and share their critical views on pages 18-21 in a paper entitled "Genetics of blood pressure - still hoping after all these years". I hope you will enjoy reading that paper as much as I did.

The Centre of Clinical Physiology and Hypertension in Milan (founded in 1981) originally consisted almost entirely of physicians from Milan University and Ospedale Maggiore interested in cardiovascular research, who were allowed to work part-time at the Centre, with the addition of some directly employed staff. Since then, the centre has expanded to many other universities and hospitals in Northern Italy, including the University of Milano-Bicocca. On page 13, Giuseppe Mancia gives us an overview of research and education, past and present. This is an impressive paper, which I recommend you read.

In each issue of Hypertension News, we ask one or two Council members to present their views on Hypertension. Today, on pages 25 - 26, Thomas Unger shares his views, linking basic science to clinical science with a focus on renin-angiotensin-system research (RAS). In this issue, there is also a report (based on a case presentation, recently published in Hypertension) on how deep brain stimulation lowered extremely high blood pressure (in excess of 300/170 mm Hg) in a female patient on 8 drugs known to have an anti-hypertensive effect + 12 other drugs + chronic baroreflex activation (pages 22 - 24).

Finally, let me once again thank our editorial team for all the *pro bono* work they carry out: Dylan Burger (Ottawa), Thomas Kahan (Stockholm), Maciej Tomaszewski (Manchester), and last but certainly not least, Helen Horsfield and her co-workers at the ISH Secretariat in London. I would also like to thank the ISH members who (for over 14 years) seldom decline to contribute and - apart from the odd one - always deliver.

Have a good read!

Lars H Lindholm, Editor

lars.h.lindholm@umu.se



HYPERTENSION

BEIJING 2018 | CHINA

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Join us at the next ISH Scientific Meeting
www.ish2018.org

From the ISH President (2016-2018) - Neil Poulter



Four months into my presidency and the activities of ISH have been extensive and exciting, focusing mainly on the planning and delivery of May Measurement Month (MMM) 2017. This global BP awareness campaign is being developed in collaboration with the World Hypertension League (WHL) in over 100 countries worldwide. Great strides have been made, with the ISH Secretariat staff increased by one full time appointee (welcome, Shannan Tims!) to cope with the expanding workload.



We have promise of financial support from Centers for Disease Control and Prevention (CDC) and negotiations are ongoing with AstraZeneca, the Novartis Foundation, GSK, Microlife and OMRON among others. We have support from The Lancet, European Society of Cardiology (ESC), European Society of Hypertension (ESH), the World Heart Federation (WHF) and the NCD Risk Collaboration, and we are also talking with the American Heart Foundation (AHA), National Heart, Lung and Blood

Institute (NHLBI), and Global Burden of Disease (GBD), not to mention dozens of hypertension and cardiovascular societies around the world.

We are busy identifying national MMM coordinators for as many countries as possible. Their role will be to orchestrate screening activities in each of the collaborating countries.



African hypertension leaders committed to MMM17 - participating in a recent MMM meeting in Cape Town



The hearts indicate countries in Africa committed to MMM

Meanwhile, the App onto which the data will be entered, and a bespoke MMM website, are being developed and both should be ready by the end of February. In a shorter time-frame we will have a protocol in English (and Chinese) to distribute to all collaborating countries for local adaptation.

Join us to make a difference

We hope that all Society members will get involved wherever they are, and during the month of May, screen as many adults (18+ years) as possible whose BP has not been measured in the previous year.

We expect that there will be a significant research output from the MMM Campaign, given that this is expected to be the largest BP screening programme in every one of the collaborating countries. Each country will generate more BP data than hitherto available from that country, and hence there will be increasing 'power' to generate more national, regional and global data and publications.

Many thanks to all the individuals and Societies that have signed up to MMM already. To the others – please come and join us! If MMM works, the next four months could have a huge impact on the profile of 'Hypertension' around the world.

However, we are critically dependent on volunteers to set up screening sites – whether in pharmacies, shopping malls, GP clinics, hospital clinics, community health clinics, pop-up clinics or occupational sites. Nevertheless, the fruits of this labour, if marketed properly, should raise the awareness of hypertension to hitherto uncharted heights. That can only be good for people already known to have raised BP (and for those undiagnosed before MMM!)

We have engaged brilliant support and advice on our marketing strategy, pivotal to which is getting ambassadors - national, regional or global - to get involved and promote MMM. So, if you know/look after anyone famous - a star from the world of sport, music, theatre, film or TV - please ask them to help drive MMM as a huge force for good. If they agree we can get them onto YouTube, TV, radio, social media etc. and thereby spread the message!

Meanwhile other bits of important ISH news include the change of date for our 2018 Biennial Scientific Meeting in Beijing. The new dates are 19-23 September.

By way of a slight break from tradition, the annual face-to-face meeting of the ISH Council will take place in early March 2017 - earlier than the usual meeting at ESH in June. This is to facilitate the Council meeting four months earlier in the new 'Presidency'. We also propose to invite the leaders of the five RAGs and the administrators of NIC, thereby bringing together the 'top brass' of the Society, who do not normally get a chance to come together so soon (if at all) after each new President is in place.

Finally – every good wish to all ISH members, friends and families for 2017.

- Neil Poulter



**The
Secretary's
Voice:
Maciej
Tomaszewski**

Dear Readers,

Professor Lars Lindholm - the Editor-in-Chief of Hypertension News – has kindly invited me to contribute regular updates on the activities of the Executive, the Council and the Society. These short reports should provide you with some insights into the outcomes of our recent initiatives, the status of the current undertakings and the future outlooks.

ISH 2016 Scientific Meeting:

Those of you who attended our last Biennial Meeting in Seoul will be aware how successful it was. Based on the final report provided by the Organising Committee, I can confirm that a total of 3,623 participants from 91 countries attended the conference. The Organising Committee invited 94 faculty members from 41 countries to deliver their keynote lectures. Of 1,607 submitted abstracts, 1,555 were accepted for presentation and of those, 335 were selected as oral presentations. Congratulations to presenters from Korea, Japan and China who submitted the greatest numbers of abstracts. I am happy to report that 96% of participants who submitted their feedback after the meeting agreed or strongly agreed that the scientific programme of the meeting was well balanced.

WHO Partnership:

The Society partnered with the World Health Organisation (WHO) and other key stakeholders in the battle against cardiovascular disease. In December 2016 I represented the President and the Society at HEARTS Technical Package Implementation Planning Meeting at WHO Headquarters (Geneva, Switzerland). The main goal of this new initiative under the leadership of WHO, the Pan American Health

Organization (PAHO) and the US Centers for Disease Control and Prevention (CDC) is to strengthen the management of cardiovascular disease in primary health care.

May Measurement Month:

Many of you will be familiar with the new flagship initiative of the Society - May Measurement Month (MMM2017). Through partnership with the World Hypertension League we aim to raise awareness of hypertension by measuring blood pressure in 25 million people around the globe! The President himself will provide separate coverage of this exciting undertaking in his report. I also encourage all of you to follow information on MMM2017 through our website.

2017 Membership Renewals:

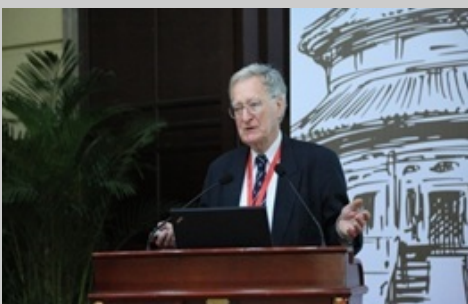
Professor Alta Schutte (the Vice-President and Chair of the Membership Committee) and her team are undertaking the review of non-paying members of the Society. Those of you who have forgotten to submit your annual dues, please do so by the end of February at the very latest.

New Committee - RSE:

We have a new Research, Scientific and Education Committee (RSE) in the Society. The Committee will be chaired by the President. Further information on the membership of this Committee is available on our website.

Our thanks to Trefor Morgan:

Many thanks to Professor Trefor Morgan who has stepped down as a chair of our Regional Advisory Group (RAG) for Asia and Australasia. We are indebted to Trefor for many years of outstanding service as a chair of the RAG and representing the Society in this part of the world. Trefor has kindly agreed to support the RAG as a regular member.



New RAG Chair: Markus Schlaich:

Congratulations to Professor Markus Schlaich, a member of the Council, who is the newly appointed chair of our RAG for Asia and Australasia. We wish Marcus all the best in his new leadership role.



Research Scholar Programme:

Our new Research Scholar Programme has generated a lot of interest. The shortlisting has now been completed and the winning scholar will be identified in the next few weeks.

IASH-SAHA Meeting:

The Society is supporting the joint Intra-American Society of Hypertension and Argentinian Society of Hypertension in Mendoza in April 2017. We are providing support for travel awards for young investigators from Latin America to attend this meeting. Please check out the conference website for further information. <http://www.saha.org.ar>

A poster titled "CALL FOR ABSTRACTS" for the "JOINT SCIENTIFIC SESSIONS" of the "THE ARGENTINIAN SOCIETY OF HYPERTENSION" and "THE INTER AMERICAN SOCIETY OF HYPERTENSION". The sessions are held on "April 20, 21, and 22, 2017" at the "Intercontinental Hotel, Mendoza, Argentina". The poster lists prizes: "All accepted abstracts from Latin American contributors qualify to compete for one of three IASH-ISH awards (First prize \$1,000.00 dollars; Second prize: \$750.00; Third prize \$500.00 US dollars)." It provides the submission website: <http://www.sbcongresos.com/resumenes.php> and the deadline: "IASH abstract submission deadline: January 23, 2017". Logos for the International Society of Hypertension and Sociedad Argentina de Hipertension Arterial are visible. Contact information for the secretariat and hotel is also provided.

Beijing 2018

For those of you who plan to attend the ISH 2018 Meeting in Beijing, there is a slight update in the schedule - as mentioned in the President's report. The new dates for the meeting are 19-23 September 2018. Let me take this opportunity to wish you all a happy and prosperous 2017!

- Maciej Tomaszewski

Thomas Kahan

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

Antihypertensive treatment with thiazide type diuretics may prevent osteoporotic fractures

Hypertension and osteoporotic fractures are common in older persons and share several risk factors such as smoking, physical inactivity, postmenopausal status and older age. Indeed, there is an increased risk of osteoporotic fractures in hypertensive patients, as compared to persons with normal blood pressure. The effects of thiazide type diuretics on calcium balance have been taken to suggest that diuretic treatment may reduce the risk of osteoporotic fractures.

In a recent *post hoc* analysis of the ALLHAT study [1], Puttnam *et al* show that chlorthalidone, a thiazide type diuretic, reduces the risk of osteoporotic fractures [2]. Patients eligible for participation in ALLHAT were women and men 55 years or older with mild-to-moderate hypertension (a systolic blood pressure of 140 mm Hg or above and/or a diastolic blood pressure of 90 mm Hg or above, or on drug treatment for hypertension) and with at least one additional risk factor for coronary artery disease. Mean age was 70 years, 43% were female, 50% were white non-Hispanic and 31% African American. The participants were randomized double blind to chlorthalidone, the dihydropyridine calcium channel blocker amlodipine, the angiotensin converting enzyme inhibitor lisinopril, or the alpha adrenergic receptor blocker doxazosin (this arm was stopped early and was not considered for the current analysis). The beta adrenergic receptor blocker atenolol was added if needed to achieve a blood pressure below 140/90 mm Hg, with additional medications to be added if required. For the purpose of the current study 10,174 patients on chlorthalidone and 12,006 on amlodipine or lisinopril were evaluated after a mean follow up time of 4.9 years. Hospitalized hip and pelvic fractures were chosen as outcome. An additional post trial follow up was performed on 7,631 and

8,991 patients, respectively, and a total mean follow up of 7.8 years. There were 34 pelvic fractures and 307 hip fractures during the trial, and the authors show a 21% (95% confidence interval 2–37%; $P=0.04$) in trial risk reduction of fractures on diuretic therapy, as compared to other antihypertensive therapy, after adjustment for demographic and clinical potentially confounding factors [3]. The effects on fracture risk by amlodipine and lisinopril were similar, and atenolol did not seem to influence the risk of incident fractures. A similar, although not significant, benefit of diuretic treatment was seen with the prolonged post trial follow up.

That antihypertensive treatment with a diuretic can reduce the risk for osteoporotic fractures is supported by a recent large retrospective cohort study of hypertensive patients attending primary health care in Sweden by Bokrantz *et al* [3]. These authors used the Swedish Primary Care Cardiovascular database [4] to assess 57,822 hypertensive patients 45 years or older attending primary health care in 2006. Data on antihypertensive (and other potentially confounding) drug treatment was achieved from all pharmaceutical dispensations, obtained by data linkage to the Swedish Prescribes Drug Registry. Thiazide diuretics were taken by 54%. Other thiazide like diuretics (chlorthalidone, metazolone and amiloride) were used in 2% only. Mean age was 66 years, 55% were female, and 95% were of European ethnicity. The primary outcome was an osteoporotic fracture, which included hip, spine, distal forearm, and proximal humerus.

There were 2,345 incident osteoporotic fractures (1,210 hip fractures) during a follow up of 7 years. Patients with fractures were older, more often female and had lower socioeconomic status, had slightly higher blood pressure values, more comorbidity, and were on more medications. Current thiazide use was associated with an 11% (95% confidence interval 2–19%; $P<0.05$) lower fracture risk, as compared to other antihypertensive therapy, after adjustment for demographic and clinical potentially

confounding factors [3]. Of note, the protective effect of diuretics appeared to increase with prolonged duration of use, and former use was associated with an increased risk up to 4 months after the last dispensed prescription.

These two studies in consort suggest that treatment with a thiazide type diuretic reduces the risk for osteoporotic fractures in hypertensive patients. This makes the results clinically relevant and potentially important. The *post hoc* analysis of ALLHAT [2] is the first large randomised controlled study in hypertension to demonstrate a benefit of diuretic treatment on incident fractures. However, that study excluded several patients with high risk for osteoporotic fractures such as coronary artery disease, chronic heart failure, and chronic kidney disease. Second, ALLHAT studied chlorthalidone, an often preferred thiazide type diuretic in the United States, whereas hydrochlorothiazide or other diuretics are preferred in many countries. Third, at least one out of five patients assigned to chlorthalidone, amlodipine, or lisinopril did not take their assigned drug class medication, and a similar proportion in the amlodipine and lisinopril group patients took a diuretic at their five year follow up. Thus, the magnitude of the potential benefit of diuretic treatment on fracture risk may be difficult to assess from these results.

The large Swedish registry study [3] represents an unselected hypertensive population with more comorbidity than ALLHAT. Data were obtained from electronic health records and registries with minimal risk of selection bias; however, there was no formal protocol for data collection and follow up. Drug adherence was accounted for by use of data on dispensed drugs but, inherent to a retrospective cohort study there was no randomisation to treatment. Taken together, the results of these two studies extend previous findings of an

association between antihypertensive treatment with thiazide type diuretics and an approximately 10-25% reduction in osteoporotic fractures [5,6]. Furthermore, the association between duration and timing of thiazide exposure and fracture incidence [3] may be taken to suggest a causal relation.

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- Thomas Kahan

Hot Off the Press



Noriko Daneshtalab

Professor (Assistant) and Researcher, School of Pharmacy and Cross-Appointment to the Division of BioMedical Sciences, Cardiovascular and Renal Group, Faculty of Medicine, Memorial University of Newfoundland, Newfoundland and Labrador, Canada

Immune system regulation of hypertension evident in the homeostatic role of cyclooxygenase-2-derived PGE2 in response to increased dietary salt

Hypertension on its own is a complex trait traditionally determined by both genetic and environmental factors with a high prevalence (~30% worldwide) and a major risk factor for other cardiovascular diseases.

Interestingly, it is also a disease which patients with autoimmune diseases such as psoriasis and arthritis are more prone to having at a higher prevalence than the normal population (1). These patients also have a significantly

higher cardiovascular morbidity and mortality (e.g. arrhythmia and stroke) compared to non-arthritic populations.

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) by the autoimmune patients have been traditionally implicated in the increase in hypertension; the inhibition of cyclooxygenase (COX) 1 and 2 isozymes reduce renal blood flow, glomerular filtration rate, and cause sodium retention by reducing urinary sodium excretion particularly when sodium-loaded. In salt-sensitive subjects, this retention of sodium will cause blood pressure to rise (2) and may affect the BP-lowering effect of some antihypertensive medications (3, 4).

Considering the current surge in dietary salt intake in the developed countries, the actual role of COX inhibition and the role of the immune system in the mechanism of salt-sensitive hypertension development is an important avenue for investigation.

In that light, Zhang et al (5) from Raymond Harris' research group have been looking at the mechanism by which COX-2 inhibition is associated with salt-sensitive hypertension and the important role of immune cells in its mediation. As macrophages express COX-2 and are a rich source of prostaglandins (PGs), they studied the multi-variate role of COX-2-derived PG expression and activity in Bone Marrow (BM)-derived cells in mediation of salt-sensitive hypertension.

Using various techniques and strains of mice such as C57BL/6 *Cox2*^{-/-} and BM transplantation (BMT) from either WT or *Cox2*^{-/-} males into syngeneic animals, their study indicated that with chronic salt loading, COX-2-generated PGs from BM-derived cells mediate BP homeostasis such that selective deletion of either COX-2 expression (*Cox2*^{-/-}WT BMT) or PGE2 production (*mPGES-1*^{-/-}WT BMT) in these cells increased predisposition to salt-sensitive hypertension.

Furthermore, selective deletion of the PGE2 receptor subtype EP4 in monocytes/macrophages also led to development of salt-sensitive hypertension, likely due to the net effect of an increase in macrophages as well as T cells and neutrophils in the kidney.

The lack of COX-2 or inhibition of EP4 signaling also altered macrophage/dendritic cell polarization, leading to a pro-inflammatory, or M1-like, phenotype rather than an anti-inflammatory, M2-like phenotype. Interestingly, both renal sodium chloride cotransporter (NCC) expression and phosphorylation were increased in mice with alterations in macrophage/dendritic cell COX-2 expression or activity, suggesting a role for PGs in direct regulation of NCC.

All in all, these studies suggest an important role of hematopoietic COX-2-derived PGE2 in both kidney and skin in maintaining the balance between pro- and anti-inflammatory responses to chronically increased dietary salt. Treatments that target COX-2 inhibition may predispose them to salt-sensitive hypertension.

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New Investigator Spotlight features for January and February 2017



January spotlight of the month **Yusuke Kobayashi**

Yokosuka City Hospital; Visiting Researcher, Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine; Director, The Kobayashi Medical Clinic, Japan.

[Read an interview](#)



February spotlight of the month **Brandi Wynne**

Instructor of Medicine at Emory University, Atlanta, GA, USA (Department of Medicine, Renal Division)

[Read an interview](#)



Dylan Burger

ISH Communications Committee member

Scientist, Ottawa Hospital Research Institute

Assistant Professor, Department of Cellular and Molecular Medicine, University of Ottawa, Canada

CD47-blocking antibodies restore phagocytosis and prevent atherosclerosis

Kojima et al. (2016) *Nature* 4; 536(7614):86-90

In atherosclerosis, the transition from stable plaque to an unstable plaque is associated with significant cell death and the accumulation of dead cells and debris in the necrotic core (1). Considerable research has focused on approaches to inhibiting the cell death seen in atherosclerosis for therapy, however increasingly there is an appreciation for the role of failed clearance of the dead cells in the necrotic core.

The clearance of dead/dying cells in the body is accomplished through a process termed efferocytosis (from the Latin efferre, meaning "to take to the grave") (2) This is largely performed by phagocytic cells such as macrophages, although non-phagocytic cells such as endothelial cells also contribute. Critically, efferocytosis requires the presence of "eat me" signals (i.e. the presence of phosphatidylserine) to distinguish dead from living cells (2).

In a manuscript published late last year, Kojima and colleagues provide new insights into the process of efferocytosis in atherosclerosis and identify a novel dysregulated pathway which causes deficient efferocytosis, ultimately contributing to increased necrotic core development (3).

The authors report a TNF-alpha dependent upregulation of the transmembrane protein CD47 in atherosclerotic plaques and provide evidence that CD47 serves as a "don't eat me" signal preventing efficient efferocytosis. Using several well-established mouse models of atherosclerosis they subsequently showed that administration of a CD47 antibody could restore efficient efferocytosis and that this was associated with smaller atherosclerotic plaques. The authors conclude that pro-efferocytic approaches may be a new avenue for the treatment of atherosclerosis.

The work presented by Kojima and colleagues is exciting and many questions arise from this work. Do other "don't eat me" signals contribute to atherosclerosis? At what stages in plaque development are these "don't eat me" signals activated? Is this activation unique to unstable plaques, or do all plaques activate CD47? Finally, if the process ultimately results in accelerated plaque rupture, why produce a "don't eat me" signal in the first place? Is there some long term benefit to impaired efferocytosis that is not fully appreciated in the present study?

Another consideration with respect to translation of this work is the use of anti-CD47 antibodies as therapy. The majority of dead/dying cells in an atherosclerotic plaque are underneath the fibrous core. To access these cells (and their "don't eat me" signals) an antibody would have to penetrate this fibrous core. While the endothelium does not represent an absolute barrier to antibodies, it does serve to limit tissue access (4). It is noted that the authors provide evidence that the CD47 antibodies accumulate in the vasculature of atherosclerotic mice, however it is possible that the full benefit of this approach is not realized due to the limited access of the antibody. I wonder if alternative approaches (i.e. drug/small molecule inhibitors or genetic approaches) may prove more successful in acting on this newly identified pathway.

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- Dylan Burger

Aims of the ISH New Investigator Committee: 2016-2018



Ruan Kruger, PhD

Chair, New Investigator Committee

Associate Professor of Cardiovascular Physiology Hypertension in Africa Research Team (HART), North-West University, Potchefstroom, South Africa

Ruan Kruger: I am a basic scientist with special interest in clinical and epidemiological population studies focusing on ethnic phenotyping of cardiovascular pathophysiology related to hypertension, arterial stiffness and cardiac impairment (echocardiography). My research particularly includes novel biomarkers and early predictors of cardiovascular disease aiming to contribute to the prevention of early incidence in sub-Saharan Africa.

As a young sub-committee of the ISH, the New Investigator Committee (NIC) grew rapidly as one of the strongest pulses in the ISH community as well as globally among hypertension societies. In 2011, the first meeting for young researchers was held in conjunction with the High Blood Pressure Research Council meeting in Orlando, and ever since, this committee has thrived. In a short period of about 5 years the NIC established itself as a familiar platform for all upcoming enthusiasts aiming to fight the worldwide burden of hypertension. A free membership category (Research Fellow) was further introduced to promote involvement of young and upcoming researchers in the field of hypertension.

It is not just a tremendous honor, but also rather daunting as the new Chair of the NIC to follow in the footsteps of a great leader and the immediate past Chair of the NIC, Professor Maciej Tomaszewski (current Secretary of the ISH), who inspired many young researchers through his leadership and guidance. With a new committee of skilled and excited young members (see page 12), the NIC shows great promise to excel in the next two years.

Under the Presidency of Neil Poulter, and for my first goal as Chair of the NIC, we decided to restructure the committee to have numerous core members, functioning within two working groups. Previously the NIC consisted of three working groups, with Mentorship as the third, however a new committee within the ISH was recently established under the leadership of Professor Fadi Charchar, namely the Mentorship and Training Committee. Within the new NIC structure, each working group consists of four core members



of which one senior member is the lead. These working groups are Networking and Recruitment, and Media and Communications. We have good representation from eight countries and six continents on the committee and aim to increase this even more in the future.

The main aims of the NIC for the next two years include:

(1) Increasing membership

Although ISH membership is sustained, we aim to increase the number of New Investigators, especially from regions currently not well-represented in the Society. These include countries from Africa, Asia, and South America. The NIC is driven to participate at various scientific meetings across the globe over the next two years in order to enlarge the NIC footprint. By doing so we could reach more young researchers and have them engage in all ISH activities and become members.

(2) Establishing longstanding networks

We furthermore aim to establish a large network among all societies with a young investigator community for a united representation of young and upcoming researchers in the field of hypertension and related disciplines. The NIC wishes to become the link among all hypertension new investigators – similar to ISH being the international community for hypertension researchers. The NIC wishes to extend invitations to all young investigator communities, councils, committees and individuals to join us in establishing a global network by which new relationships, partnerships and communications can develop or propagate.

(3) Upgrading the face of the NIC

The NIC is involved in most social media and aims to incorporate a unified design among all social media and

web-related platforms. This will create a professional impression and also be more recognizable in the broader community once all platforms are identified by the same design. As the name implies, the NIC strives to keep up with current trends and also develop new insights and ideas as we grow. The Media and Communications working group is a creative team with many fresh ideas and potential, which enables the NIC to stay updated.

(4) Streamlining processes

The ISH greatly supports sessions for the NIC which provide the opportunity to New Investigators to present their work at various scientific meetings, summer schools and symposia. During these sessions the ISH wishes to acknowledge exceptional candidates by providing awards and also promote the development of independent and professional chairmanship among committee members. The NIC therefore aims to develop guidelines and criteria for identifying the most deserving candidate as award winner, Spotlight feature, or mentee in the most unbiased manner possible. Therefore the NIC members are working hard to establish traditions in which we can be recognized as diligent and

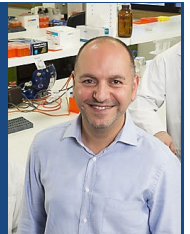
professional when awarding young researchers independently.

(5) Contributing to the new "May Measurement Month" initiative

One of our very important aims is to support the current President's most important goal of his term. The NIC wishes to extend our networks and ideas to making this endeavor, of reaching the target of measuring the blood pressures of 25 million un-screened people during the month of May, a reality. This highly ambitious goal is a great challenge among hypertension researchers and hard work will determine the success of this endeavor.

I am excited and intrigued by the many challenges we are facing and also look forward to the great pleasure I will experience by working with a wonderful group of skilled professionals.

Fadi Charchar (ISH Executive Committee member) holds the role of NIC Liaison Officer.



Follow ISH New Investigator Network activities on social media



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



Introducing the ISH New Investigator Committee 2016-2018

NIC Chair: **Ruan Kruger** (South Africa) and NIC Liaison Officer: **Fadi Charchar** (Australia)

Lead, Media and Communications

Cesar Romero
USA



My research focuses on the mechanisms of hypertension. As a basic researcher I am interested in the renal mechanism of hypertension and as a clinician I have been working in hypertension in special populations like young patients, HIV-infected patients and resistant hypertensive patients.

Media and Communications Working Group Members

Fady Hannah- Shmouni
USA



I am a clinical fellow in endocrinology and biochemical genetics at the National Institutes of Health, USA. My research interests are in adrenal disorders, secondary forms of hypertension and late-onset inborn errors of metabolism. I joined the ISH New Investigator Committee in 2012 and led the ISH Spotlight initiative from 2014-2016.

Ooneb Mian
Canada



As a postdoctoral researcher, I conduct translational research to explore the developmental origins of adulthood cardiovascular abnormalities. My research focuses on understanding the adverse cardiovascular consequences of prematurity-related conditions, with special interest in the pathophysiological role of immune-inflammatory mechanisms thereof.

Elena Velkoska
Australia



I am a senior research scientist at The University of Melbourne, investigating the role of the renin angiotensin system in cardio-renal disease and hypertension, with the aim of identifying novel treatment targets and biomarkers of disease. My research encompasses both experimental and clinical studies, providing translational opportunities for basic research findings.

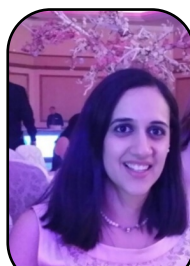
Lead, Networking and Recruitment

Sofie Brouwers
Switzerland



As a clinician-scientist, I am mainly interested in cardiovascular risk factors and anti-hypertensive pharmacotherapy. My basic research activities have been focussed on the pathophysiology of hypertension, with special interest in the role of the renin angiotensin system and the central nervous system in the long-term regulation of blood pressure.

Evi Christofidou
UK



My research passion focuses on the genomics of cardiovascular disease with a particular emphasis on coronary artery disease and hypertension. I have an interest in the use of computational methods in exploiting patterns of genetic variation to discover novel mediators of cardiovascular disease.

Akira Nishiyama
Japan



My research interests in both basic and clinical studies have been focused on the pathophysiology of life-style disease including hypertension, renal disease, diabetes, senescence and cancer with particular regard to the renin-angiotensin-aldosterone system, renal salt and glucose handling, sympathetic nervous system, genome instability, etc.

Brandi Wynne
USA



I am a cardio-renal physiologist, with a focus on inflammation and hypertension. In particular, I investigate the role of innate immune cells and cytokines in the etiology of salt-sensitive hypertension via excessive sodium retention.

Institute Focus

Giuseppe Mancia

The Centro Interuniversitario di Fisiologia Clinica e Ipertensione, Università di Milano, Milano-Bicocca e Pavia, Italy

Figure 1c - Giuseppe Mancia

The Centre of Clinical Physiology and Hypertension was founded in 1981 as a unit of the University of Milan, devoted to experimental and human research on hypertension and cardiovascular disease, in the adjacent "Ospedale Maggiore" (Figure 1a) where several other research and clinical institutions of the Milan Medical Faculty were also located.



Figure 1a

Over the following 10 years, a number of investigators moved to other universities either within Milan or in the region (Lombardy), so the Centre modified its statute in 1993 and has since become the Interuniversity Centre of Clinical Physiology and Hypertension of the Milan, Milano-Bicocca and Pavia Universities.

The first Executive Director (and founder) of the Centre was Alberto Zanchetti (Figure 1b) who was followed by Giuseppe Mancia (Figure 1c). The current Executive Director is Guido Grassi (Figure 1d).

Personnel and structure

Originally, the personnel of the Centre of Clinical Physiology and Hypertension consisted almost entirely of physicians from Milan University and Ospedale



Figure 1b
Alberto Zanchetti



Figure 1d
Guido Grassi

Maggiore who were interested in cardiovascular research and who were allowed to work part-time in the Centre, with the addition of a small, directly-employed technical and administrative staff. The overall staff dimension has grown in parallel with the expansion of the Centre to other universities and hospitals, albeit always with a restriction to personnel with a university or hospital tenure.

Today, research activities are performed by a large number of investigators operating in 5 large university hospitals (4 public and 1 private) - the Ospedale Maggiore, Niguarda Hospital and Istituto Auxologico in Milan; the San Gerardo Hospital in Monza; and the Policlinico Universitario in Pavia.

Local research coordinators are: Alberto Morganti, Cristina Giannattasio, Gianfranco Parati, Guido Grassi and Stefano Perlini respectively. Three hospitals (Ospedale Maggiore, Istituto Auxologico and Policlinico Universitario in Pavia) are recognized as National Research Institutions by the Ministry of Health.

The HIGHCARE team



www.highcareprojects.eu

HIGHCARE ALPS – HIGHCARE HIMALAYA – HIGHCARE ANDES

Research is predominantly supported by public Italian sources (grants from the Ministry of Health, the Ministry of Research and University and the Lombardy Region) as well as by the European Community when research projects manage to be funded. A private association (now structured as a non-profit Research Foundation) has always helped to raise financial contributions from private sources for the research performed in the Centre.

Research areas

From the beginning, the Centre of Clinical Physiology and Hypertension aimed to create an environment that might favour interaction between animal and human research, the goal being to perform, when possible, human studies based on or inspired by evidence previously obtained in the experimental setting.

It thus fostered “translational” research before the word began to be used for this purpose. This was achieved, among other means, by requiring all investigators to 1) maintain their full clinical activity in the nearby departments and 2) be involved as often as possible in either animal or human research.

This format has been kept unchanged over the years, although with a progressive loss of ground of animal research, due in part to the difficulty this research faces in Italy.

Currently, human research has expanded well beyond the original areas (neural and humoral cardiovascular control as well as clinical pharmacology and hemodynamics of hypertension) and now ranges from cardiovascular genetics to clinical trials. In each research area, widely recognized contributions to current knowledge have been made.

The investigators of the Centre have also conducted or participated in leading positions in major clinical trials (HOT, VALUE, ELSA, CONVINCe, INSIGHT, INVEST, PROGRESS, ADVANCE, ON-TARGET, etc.) and one of them (Alberto Zanchetti) is the principal investigator of the ongoing ESH-CHINA SHOT trial which addresses the debated issue of the optimal blood pressure target for treatment in patients with cerebrovascular disease.

Although research activity has always been centered on hypertension, significant contributions have extended the basic and human knowledge of other cardiovascular

diseases, such as sudden death, coronary insufficiency and heart failure.

An entirely new area of research (cardiovascular physiology and pathophysiology at high altitude) was started about 15 years ago by Gianfranco Parati whose group has since significantly contributed to the knowledge of circadian blood changes and blood pressure control mechanisms in normotension and hypertension under hypoxic hypobaric conditions via numerous stages in a hut in the Alps (4550 m above sea level) as well as via Himalaya and Andes scientific expeditions.

Educational activity

Virtually all research members of the Centre are engaged in under-graduate and post-graduate educational activity in their respective universities and teaching hospitals. Teaching activities extend to supervision of doctoral and post-doctoral Pd. D theses and coordination of Master Courses both within the structures of the Center and elsewhere. Staff members have been responsible for the biannual organization of the meeting of the European Society of Hypertension (and of several meeting satellites) since 1983. They have played a leading role (President, Secretary, Treasurer or Scientific Board member) in the conduct of national and international Hypertension Societies (including ISH), as well as in the finalization of hypertension guidelines, including all those issued by the European Society of Hypertension since 2003.

Giuseppe Mancia's Research Group

My research activity in the Centre started with its birth, following several years in which I was almost exclusively involved in animal research (hemodynamic effects of sleep, cardiovascular changes during emotional behaviour, cardiopulmonary reflexes) at the Siena and Milan Universities and at the Mayo Clinic and Foundation in the USA. I was fortunate to count from the beginning on the valuable contribution of several brilliant collaborators who worked with me on all projects completed in the first 15 years, and later developed independent research lines, expanding old areas of investigation and initiating new ones (Table 1). Overall the research of the Group has led to a considerable number of interesting observations, often entirely new for the existing state of knowledge, a sample of which is reported in Table 2. To be mentioned, in particular, are:

- Pioneer studies on ambulatory blood pressure monitoring by means of an intra-arterial approach

TABLE 1

Main research areas and coordinators within the Group

Experimental Hypertension	Alberto Ferrari
Arterial Mechanical Properties	Cristina Giannattasio
Cardiovascular signal analysis Out-of-office blood pressure monitoring New blood pressure measuring devices/ Telemetry High altitude pathophysiology	Gianfranco Parati
Sympathetic activity in hypertension Cardiovascular and metabolic diseases Cardiovascular epidemiology	Guido Grassi
Cardiac and vascular bioimaging	Cesare Cuspidi

TABLE 2

Baroreflex control of blood pressure in normotensives and untreated and treated hypertensives

Baroreflex control of A-V conduction in man

Normal and deranged cardiopulmonary reflex control of circulation and renin release

Sympathetic activation in early and late complicated or resistant hypertension, including the effects of non-pharmacological and drug treatment

Sympathetic activation in metabolic disorders

Prognostic value of out-of-office blood pressure

Clinical phenotypes and significance of white coat and masked hypertension

Short and long-term blood pressure variability in normotensives and hypertensives: phenotypes and prognostic significance Sympathetic activation in untreated/treated heart failure

Circulatory physiology and pathophysiology at high altitude

Long-term prognostic value of left ventricle and atrial structural phenotypes



concomitant measurements of office, home and ambulatory blood pressure (along with echo-devised cardiac damage) has provided key information on the relative prognostic importance of office and out-of-office blood pressure, with a significant impact on the growth of studies in this area.

The contributions of the Group have been widely acknowledged, and to date can count more than 100,000 citations in peer-reviewed literature.

-Giuseppe Mancia

- Thorough description of normal and deranged reflex control of the circulation in humans
- Alterations of sympathetic activity in a variety of human cardiovascular and metabolic disorders
- Contribution to early seminal studies that have allowed the importance of alteration of arterial distensibility in hypertension to be established on solid grounds
- Design and conduction of the PAMELA longitudinal study, a survey of a population located in the outskirts of Milan in which

Beyond "Basic Training": The role of an international society in discovery science



Dylan Burger

ISH Communications Committee member

Scientist, Ottawa Hospital Research Institute

Assistant Professor, Department of Cellular and Molecular Medicine, University of Ottawa, Canada

I am just a PhD Scientist.

Early in my career I would often utter this phrase when asked if I was a clinician. I said this, not because I felt that my chosen career path was any less important than a clinical one, but as a disclaimer that I was not versed in clinical practice and terminologies. Years ago a colleague suggested that statements like the above devalued discovery research and I stopped using it, but it has been my involvement in the ISH that has largely eliminated the need for a disclaimer at all.

As a world organization, the ISH distinguishes itself from other national or regional hypertension societies in its commitment to the application of scientific knowledge globally. Inevitably, this commitment means that clinical and population-based work will be major research and teaching foci as they can most effectively ensure that best practice is distilled and disseminated globally.

On the surface then, the ISH might seem an odd choice for a basic scientist to call home. Indeed, many of my colleagues in fundamental research prioritize regional or national meetings in hypertension/cardiovascular disease. Nevertheless, the ISH has provided the ideal platform for my career development.

Fundamentally this is because basic research in the ISH is strong. Four of the past five ISH presidents have been world leaders in discovery and translational research and the biennial meetings always include active, well-attended, basic science tracks. My MSc student presented her work in Seoul in an incredibly active session with high quality presentations and a very constructive Q&A period that launched new research questions for us. It was an incredibly positive experience for her that has served as strong motivation to push forward with her project. The New Investigator Sessions in Seoul were also littered with excellent preclinical work across a variety of research areas including immunology, genetics, and molecular biology. The research was diverse, but always well conducted, and innovative.

A critical compliment to the strong basic content is the fact that many of the more clinically focused ISH members show a genuine respect for basic research and are very interested in discussing pathways to translation of this work. This has been significant in my personal career development as interactions with several senior clinician scientists in ISH have educated me in clinical practice and current challenges. This knowledge has allowed me to better focus my research in terms of unmet clinical needs. The ability to interact with these individuals (too numerous to mention) is a direct result of the intimate, supportive environment that the ISH cultivates. Events such as the always well-attended New Investigator Sessions and Networking events opened many doors within the Society and I am pleased to see the continuation of this investment with the next generation of new investigators.



ISH NIC Networking and Mentorship Event, Seoul, September 2016



ISH NIC Symposium, New Orleans, 2013

An underappreciated aspect of ISH is the fact that the biennial meeting regularly moves between regions. This inevitably leads to greater variety in the research that one is exposed to. While there exists a strong core of regular, highly active attendees who continue to produce excellent basic research, a significant number of abstracts come from individuals from the host country/region. Accordingly, there can be great variety from meeting to meeting in terms of the research being presented and the opinions being shared. This can only serve to foster new collaborations and ultimately, promote the most innovative research.

At last count I was a member of 7 research societies. Despite this, I consider the ISH to be my "home". A major reason is the continuing support and education that I receive through interactions with my clinical colleagues. When coupled with the always strong basic research, the ISH provides an ideal environment for a PhD scientist to grow their knowledge and gain exposure for their research. Particularly for those individuals who may still consider themselves "just" a basic scientist.

-Dylan Burger

Genetics of Blood Pressure – Still Hoping After All These Years



Stephen Harrap^A (Pictured left)

and

Fadi Charchar^B (Pictured right)

A. Professor of Physiology

Department of Physiology

University of Melbourne, Parkville, VIC 3010, Australia

e-mail: s.harrap@unimelb.edu.au

B. Robert HT Smith Chair in Cardiovascular Science

School of Science and Technology

Federation University Australia, Ballarat, VIC 3350, Australia

e-mail: f.charchar@federation.edu.au

Coming to terms with unfulfilled promises feels like the fate of those of us involved in the genetics of blood pressure. With the advent of human genome sequencing in 2000 it was expected that within 10 years, research would deliver clinically useful outcomes. Genetic discovery would not only accurately identify those at risk for high blood pressure, but also offer new means of prevention and treatment. How many successful grant funding applications were written with those very words? Yet, save for some terrific work in rare major Mendelian genetic causes of hypertension, common essential hypertension is still waiting for genetics to deliver something really useful.

Why so? The problems facing genetics (and not just for blood pressure) are essentially those of discovery and understanding.

Throughout, discovery has depended on the existence of differences in DNA sequence that can be used as map markers that might point to (and occasionally might be) DNA sequences that cause changes in physiology to affect blood pressure. The ability to detect these sequence variants is where technology has ruled. The advances here have been truly remarkable. Each step in the technological ladder has brought renewed hope that the problem will be

cracked. Sadly, not yet.

Early genetic discovery was in rats using technically cumbersome restriction fragment length polymorphisms (RFLP) to demonstrate association between a polymorphism in the renin gene and blood pressure in the Dahl rat(1). Soon followed human studies of association built around candidate genes. By today's standards these were very narrow analyses, often using few and often single markers. The association between the M235T polymorphism of the human angiotensinogen gene and blood pressure is a famous example(2). Unfortunately, if anything were to characterize the candidate gene era, it was inconsistency of results. Contradictory findings for the same markers frustrated readers and editors alike and the days of small (less than 1000 subjects) studies using limited markers were numbered.

Thankfully the era of whole genome analyses emerged at about this time with the availability of the genome sequence and the increased throughput technology that went with it.

Instead of focusing on a single gene, genomic studies scan all the chromosomes. Maps with 500,000 and 1 million markers soon became readily accessible. With about 13 million available in the human genome, the markers chosen were Single Nucleotide Polymorphisms

(SNPs). Suddenly the discovery of entirely novel genetic explanations outside the known candidate genes became a real possibility. The era of genome-wide association studies (GWAS) was upon us.

In a test of the new technology (as much as anything), the Wellcome Trust Case Control Consortium (WTCCC) applied GWAS technology to 7 common conditions: bipolar disorder, coronary artery disease, Crohn's disease, hypertension, rheumatoid arthritis, type 1 diabetes, and type 2 diabetes(3). Using a common set of 3000 controls and about 2000 individuals with each of the 7 conditions, GWAS revealed associated loci with 6 of the conditions, but nothing of significance for blood pressure.

Questions were being asked. Why was blood pressure resisting GWAS discovery? Was the blood pressure genetic architecture fundamentally different? Was the inherent variability in the blood pressure phenotype blurring the genetic focus?

The response was to build bigger studies of 100,000 and more individuals. Inevitably these depended on compiling DNA and phenotypic data from large numbers of independent studies. This came with the price of heterogeneity, particularly in relation to blood pressure measurement protocols and methods, that did not improve phenotypic variability.

Notwithstanding, these mega-GWAS were able to identify around 80 chromosomal loci with effects on blood pressure(4). This was a major advance on WTCCC, but tinged with disappointment. Two problems stood out. First, the size of the effect of the individual loci was typically less than 1 mmHg and commonly less than 0.5 mmHg. Individually, these are clinically unmeasurable effects and of little use as predictive markers of blood pressure, let alone cardiovascular risk.

It was argued that it might be worth constructing a predictive test based on combining all the available markers – a so-called genetic risk score (GRS). However, the sum of the estimated effect of all the available markers could only account for less than 5% of blood pressure variance, while it had been expected that genetics should account for 40-50% of blood pressure variance. So, something was missing. Additionally, the number of individuals who carried sets of the existing markers became fewer and fewer as more markers were considered.

In any case, GRS with the best available markers in independent populations has not really improved risk prediction in any meaningful way beyond standard clinical risk evaluation(5).

One explanation for the unexpectedly poor yield of

genetic discovery from GWAS might be analytical. A GWAS examines the probability of association with blood pressure 1 marker at a time. What if blood pressure effects weren't obvious for individual loci, but were present when 2 or more markers (actually their adjacent causative loci) interacted to produce an effect greater than the sum of their parts? Such interaction is known as epistasis. Although there didn't seem to be much evidence for epistasis in the GRS, these were limited tests for such effects. However, a more comprehensive genome-wide survey for epistasis is a statistical nightmare. Think of the daunting prospect of testing all the possible combinations of a million individual markers for association with blood pressure and the potential for false positives that would result.

There are other factors that might need be taken into account. One obvious one is sex. There are many reasons, from sex chromosomal loci to sex hormones themselves, why individual GWAS markers might only reveal their association with blood pressure in one sex. Lumping men and women together only dilutes such effects. Unfortunately, sex-specific analyses don't figure prominently in contemporary GWAS.

Another phenomenon relevant to discovery is epigenetics. Here exogenous influences (broadly termed environmental) can influence the genetic expression. Chemical changes such as DNA methylation and histone modification(6) can be modulated by environmental exposure and affect gene expression, yet won't be obvious when only the DNA sequence is measured. For example, the same GWAS marker might have different blood pressure implications depending on whether it is methylated or not. So, in 100,000 individuals in a large GWAS based on SNPs alone the association of a marker that depends on epigenetic modification could be missed.

Beyond factors (epistasis, sex and epigenetics) influencing the association of GWAS markers and blood pressure, it is important to recognise that the genome-wide net of 1 million SNP markers has many potential holes. Because individual SNPs are common and most often between genes (protein-coding genes make up about 2% of the genome) they are not suited to detecting infrequent or rare variants that might influence the protein products of gene expression.

Early studies suggested that although infrequent, DNA variants in the coding sequences of genes (the exomes) might be present in around 1 in 1000 or so individuals and impart an effect on blood pressure of potentially measurable significance – around 5 mmHg(7).

Hence the next logical step in discovery was the genome-wide study of exomes – so-called exomics. Ideally this would involve screening the actual DNA

sequences of exomes in large numbers of individuals. However, with studies of several 100,000 people, the most recent studies have used chip technology based on known markers that are of low frequency (1-5%) or rare (<1%). Two large recent studies used the same Exome Chip and both resulted in the discovery of coding sequence markers associated with blood pressure(8,9). There was some overlap in the findings, but differences also. Interestingly the most consistent marker associations were those for diastolic blood pressure. Moreover, rare variants were hard to find and most of the markers were associated with an estimated blood pressure effects of less than 0.5 mmHg. So, still there remains a gaping hole in the molecular genetic answers to the heritability of blood pressure, with less than 10% of variance explained.

This is all very frustrating. Despite the enormous resources spent to date, the returns have been small. Indeed, the inverse relation between the size of the study and the magnitude of the blood pressure effects discovered must leave funding bodies wondering whether or not present strategies for genetic discovery are becoming cases of diminishing returns.

For those of us from a more physiological, less molecular era, the more important questions relate to understanding exactly what the markers associated with blood pressure actually mean and the mechanisms by which causal variants might operate.

There are 2 basic approaches to understanding here. One is to try and deduce what the DNA sequence variants might imply downstream. The other is to place the variants in model systems and organisms and study their real-life effects. In reality, both are required and its sensible to begin by identifying the presumed molecular culprits before investing in functional experiments.

It's important to appreciate that the markers used for discovery are not necessarily (or even often) the DNA variants that influence blood pressure. However, we can be assured that they are in close proximity on the chromosome.

Around a particular marker there might be many (sometimes thousands) of potentially important variants. Finding the right one is predicated on understanding the operation of human genome, particularly those parts outside the protein-coding regions. These intergenic regions comprise sequences that code for things such as non-coding RNA that manage the sophisticated coordination of gene expression in particular cells at certain times of life(10). They also influence the epigenetic interactions between environment and the genome and likely a host of other factors, yet to be defined. Our relative

ignorance of these factors limits our ability to decide which of a list of variants around a marker might be the target for further study. Yet these intergenic regions are precisely where the majority of the GWAS markers associated with blood pressure reside.

We are at something of a crossroad at the moment. We have accumulated masses of data and potential markers from the GWAS and exomic studies so far. And we are likely to accumulate much more with Next Generation Sequencing technologies. Do we continue down these paths with larger and larger studies with more subjects and more markers? How likely is it really that by continuing down this path that a genetic variant of major effect on blood pressure will suddenly reveal itself?

More effort should be devoted to working with the information we have to date. It's time to curate rather than just catalogue the collection. Investigate the markers that associate consistently across the various studies, identify the causative variants and determine by what mechanisms they influence blood pressure. In the end, how will all this effort for the genetics of blood pressure be judged? Here the family doctor might have the appropriate threshold question. Will genetic discovery and understanding add anything significant to my ability to predict cardiovascular risk beyond simple blood pressure measurement and clinical assessment, and will there be changes to my ability to reduce blood pressure beyond current effective treatments?

Only time will tell, but we are still hoping.

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- Stephen Harrap and Fadi Charchar



HYPERTENSION
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Secretariat: K.I.T. Group
info@ish2018.org

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Deep Brain Stimulation Lowers Blood Pressure in Extreme Case of Drug And Device Resistant Hypertension



Erin O'Callaghan, BBiomedSci (Hons), Ph.D
Senior Research Associate, School of Physiology,
Pharmacology and Neuroscience, University of Bristol,
UK (pictured left)

Nikunj Patel, BSC, MBBS, MD, FRCS (SN)
Consultant Neurosurgeon, Southmead Hospital North
Bristol NHS Trust Honorary Senior Clinical Lecturer,
School of Clinical Sciences, University of Bristol, UK
(pictured right)

What is the highest blood pressure (BP) you've ever seen in a patient? Was this patient alert and coherent? You may be as shocked as we were to observe blood pressure readings in excess of 300/170 mmHg (clinic aneroid manometer and finger plethysmography), despite taking 8 antihypertensive medications, receiving chronic baroreflex activation therapy (BAT)(RheosTM, CVRx, MN, USA) and having undergone bilateral renal nerve ablation.

This slim, 54 year old female patient was attending our clinic in Bristol from her home in Germany, in May 2012, for medical and physiological screening in preparation for undergoing the first ever elective Deep Brain Stimulation (DBS) procedure for the indication of hypertension.

She had, for the past 10 years, been treated by internationally renowned hypertension specialists at both the Hannover Medical School and Experimental and Clinical Research Center, Charité Berlin-Buch, and who had provided details of her extensive treatment, meticulous exclusion of secondary causes and last recorded her BP as 280/130 mmHg measured by an intra-arterial line (Schroeder C et al., 2013).

This patient had run out of options. Her lucid behaviour at our first meeting belied the severity of her symptoms. A slim, previously active, mother of 4, was now regularly suffering from debilitating malaise and severe migraines 1-3 times each month. She was also cognisant of the increased risk of stroke, cardiac and renal failure that she faced. Desperate for treatment, she first contacted Mr Patel directly after finding his contact details online.

Remarkably, whilst conducting her own internet searches for new treatments of hypertension, she found reference to Mr Patel's 2011 publication of a case where he prescribed DBS for intractable neuropathic pain in a resistant hypertensive patient, which subsequently resolved that patient's hypertension (such that medication was withdrawn) independent of analgesic effects (Patel NK et al., 2011). Excited by the potential of DBS, she emailed Mr Patel directly, asking him to consider treating her with this technique.

DBS is an established neurosurgical treatment for psychiatric disorders including Parkinson's disease and intractable neuropathic pain. It has been used in >100,000 patients to date and occurrence of SAEs at North Bristol NHS Trust Hospital is less than 0.3 %, most of which are asymptomatic hemorrhagic stroke. In Bristol, Mr Patel and his team use a state-of-the-art, robot-assisted (Renishaw plc, UK) MRI-guided stereotactic technique to implant a thin stimulating electrode precisely into a pre-selected, pre-surgically mapped brain region.

We targeted a brain region called the ventrolateral periaqueductal grey (vlPAG). In humans, acute decreases in BP have been observed in patients receiving DBS of the vlPAG for treatment of intractable, neuropathic pain.

We know from animal studies that this region is involved in the coordination of motor outputs to mediate a survival instinct consistent with 'playing dead' to a perceived threat. As such, activation of the vlPAG in animals (feline and rodent species) causes potent analgesia, bradycardia and peripheral vasodilation lowering BP. Whilst the direct mechanism is yet to be discovered, significant evidence suggests that the vlPAG could be directly inhibiting sympathetic neurons that innervate the heart and peripheral vasculature.

There is also new evidence suggesting the vLPAG can increase the sensitivity of the baroreceptor reflex, which may also have an anti-hypertensive effect by a long term lowering of the arterial pressure set point (for a review see O'Callaghan EL et al., 2014).

When we first brought our patient into clinic, we measured her muscle sympathetic nerve activity (a measure of sympathetic drive to the vasculature in the skeletal muscle bed) and found it to be abnormally high for her post-menopausal status and age and weight, notwithstanding the fact that sympathetic activity should be completely shut down with a BP of that magnitude.

Whilst we are not convinced that this was the sole source of her extraordinarily high BP, we thought it was at least contributing to maintaining a high BP and, consistent with our understanding of vLPAG in lowering blood pressure, she would benefit from undergoing this procedure.

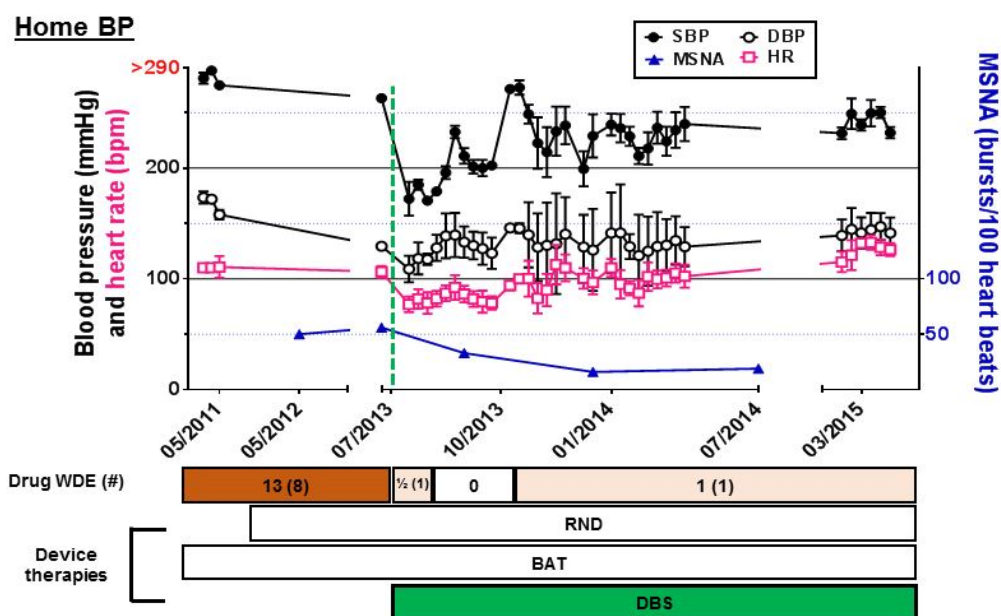
In July 2013, our patient underwent surgical implantation of a DBS electrode into the vLPAG. She recovered from surgery without complications. DBS was switched on 4 days after surgery and her BP (intra-arterial line) dropped from 205/130 mmHg to 170/109 mmHg during the day and dipped to 119-77 mmHg overnight. Whilst her daytime BP was still above recommended guidelines (140/90 mmHg) she said she felt lethargic, so her antihypertensive medications were removed with the exception of clonidine and her BP remained low.

During our regular follow up appointments with the patient, we measured her MSNA and found it reduced considerably over the first year of DBS and stabilised 40% lower than pre-DBS levels (Figure 1). After 2 years of DBS, it is maintained at 225/142 mmHg (ABPM), a level substantially lower than that we recorded pre-DBS.

Figure 1 (below):

Blood pressure and MSNA remain decreased with long term DBS therapy. Weekly averages of evening systolic and diastolic BP and heart rate recordings from the patient's home BP diary over a 4 year period pre- and post- DBS therapy. The timeline of the patient's regime of anti-hypertensive medication is indicated below the graph along with the whole drug equivalent (WDE) and number of medications in brackets. The timeline of device therapies is also indicated. Patient underwent surgery for prolapsed uterus in October 2013. Data are mean \pm SD.

BAT, bilateral baroreflex activation therapy; DBP, diastolic blood pressure; DBS, deep brain stimulation; HR, heart rate; MSNA, muscle sympathetic nerve activity; RDN, renal nerve ablation; SBP, systolic blood pressure; WDE, whole drug equivalents.



Whilst we cannot be precise in the magnitude of the reduction in our patient's blood pressure, since the year before undergoing DBS her systolic blood pressures exceeded that which could be measured by a standard oscillometric device and ABPM, we are confident that before DBS it regularly exceeded 270 mmHg and likely fluctuated up to 330 mmHg. Thus, the patient, now taking only 1 antihypertensive medication per day with continual and combined BAT and DBS has decreased her BP from between 45-125 mmHg.

She has told us that she feels in much better health (probably also because of the reduction in daily medications), so much so that she even took up horse riding again, a hobby that she had missed during her years suffering from the debilitating side effects of extremely high BP.

We conclude that this case report is the first to suggest that DBS is safe and helpful in reducing BP in a patient with severe refractory hypertension in whom aggressive drug therapy, RDN and chronic baroreceptor stimulation were unsuccessful. She was described as both drug- and device-resistant. However, whilst her blood pressure remains pathologically high, DBS has made a quantitative and qualitative improvement to the patient's health. Given that the patient's BP remains high despite normal range MSNA, it is clear that other factors are contributing to her hypertension, at which we can only speculate.

Therefore, we propose that DBS therapy should be systematically tested in patients with Grade III, refractory hypertension not responding to existing drug and device therapies.

This case, 'Chronic Deep Brain Stimulation Decreases Blood Pressure and Sympathetic Nerve Activity in a Drug and Device Resistant Hypertensive Patient' is published in the CPC sessions of the January edition of Hypertension. It was led by Mr Nik Patel of North Bristol NHS Trust Hospital with assistance from Erin L. O'Callaghan, Emma C. Hart and Julian F.R. Paton (University of Bristol, UK), Amy E. Burchell, Angus K. Nightingale (University Hospital Bristol, UK), Hugh Sims-Williams, Shazia Javed and Mark Papouchado (North Bristol NHS Trust Hospital, UK) and with the support of her physicians in Germany, Jens Tank, Karsten Heusser, Jens Jordan, Jan Menne and Hermann Haller (Hannover Medical School, Germany). The case was funded by the Severnside Alliance for Translational Research (SARTRE) and British Heart Foundation.

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-Erin O'Callaghan and Nik Patel

India Certificate Course in Management of Hypertension

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CCMH is a ten month course with once- a- month contact sessions, being conducted on a designated weekend at 25 regional training centers across India. The education grant for the program has been provided by Sun Pharma Laboratories Limited.

The program includes a core team of 11 National Experts, 25 Regional Faculty and 28 Observers. The course has received an overwhelming response and over 600 primary care physicians have been enrolled for its first cycle against the initial target of 375. The program was launched on 24th July 2016 across all its centres in India.



[View a full report on this initiative.](#)

Council's Corner: Hypertension Issues - a personal view

Thomas Unger MD, PhD, FESC, FAHA

**Professor of Pharmacology and Experimental Medicine, Scientific Director,
CARIM, School for Cardiovascular Diseases, Maastricht University**

My way to hypertension research



We thought that the secret of hypertension could be explained by CEPS. What is CEPS? Well, quite easy: CEntral Peptidergic Stimulation. This was in the early eighties of the last century.

I had joined Detlev Ganten's group at the Institute of Pharmacology of Heidelberg University, Germany, in 1978 after a post-doc period at the Clinical Research Institute of Montréal (IRCM), Canada. My "patron" in Montréal was Otto Küchel, a nephrologist who emigrated from Czechoslovakia in 1968, and my teacher was a Vietnamese chemist, Nguyen Tanh Buu, who ran the lab.

Otto Küchel was a fan of dopamine, and "Le Docteur Buu" had thoughts of a new pathway to generate endogenous adrenaline from conjugated precursors in tissues. So it was all sympathetic nervous system and catecholamines, and I had to survive between the nephrology department at the Hotel Dieu Hospital, renal hypertension in dogs and biochemical pathways that I tried to understand.

In the Montréal Institute, there was some knowledge about how to measure vasopressin, a treasure at the time, and I was supposed to learn this assay and bring it back to the nephrology department of Eberhard Ritz at Heidelberg

university. But then Detlev Ganten, who had also spent some years at the IRCM before me, came along and offered me a position in his newly established group.

After painful deliberations, I decided to accept; I wrote a long letter of apology to Eberhard Ritz, which he has probably never read to the end, and I started a career in theoretical medicine.

Detlev Ganten had already gained some merit in renin-angiotensin system (RAS) research, e.g. by demonstrating that tissues, notably the brain, possess a renin-like capacity to generate angiotensin peptides. In a paper published in 1983 in *Science*, we demonstrated for the first time a local generation of angiotensin peptides in brain tissue. We showed further that the angiotensin generation was exaggerated in spontaneously hypertensive rats (SHR), supporting the idea of CEPS.

In those days, the angiotensin converting-enzyme (ACE) inhibitors were being developed and brought to the market by the pharmaceutical industry with immense success. This was a great time for RAS research and one could just swim in the middle of the stream. I was lucky to get hold of several ACE-inhibiting compounds from different companies before they were marketed, and we could establish their beneficial effects in various animal models of cardiovascular disease.

Among others, we could demonstrate in SHR an impressive, dose-dependent blood pressure decrease over weeks by SQ14225, later marketed as captopril, the first ACE-inhibitor. Our findings caused some irritation with those colleagues who believed that high blood pressure in SHR was dependent on sympathetic drive and not on the renin-angiotensin system (RAS) since these animals had a suppressed RAS in the blood.

We rather saw our results as a stimulus to search for antihypertensive and tissue-protective effects of these new drugs by mechanisms apart from inhibiting the plasma RAS. Together with colleagues in the industry, particularly with Bernward Schölkens and his group at Hoechst, Germany, who generously let us have some of their compounds under development, we explored several of these non-plasma RAS-related mechanisms

such as kinin potentiation or ACE inhibition in different tissues including the brain. The development and successful introduction of the ACE-inhibitor, ramipril, is closely linked to this work.

Back to CEPS. This idea was certainly a bit special in the field of RAS research but it allowed us to explore the physiology and hypertension-related pathophysiology of centrally acting peptides and their pathways. I specialized in trying to decipher the central cardiovascular and behavioral actions of angiotensin peptides and substance P, a tachykinin involved in pain perception and related responses. We developed new methods to measure all kinds of cardiovascular parameters together with behavior, as well as regional blood flow and Sympathetic nerve activity in chronically instrumented conscious rats. By these means we could differentiate various central peptidergic pathways and responses and characterize their role in blood pressure regulating processes.

Substance P, for instance, could be demonstrated to generate a classical defense reaction with blood pressure increase and generalized sympathetic stimulation. One of our most original later findings in male rats was that oxytocin was a major player in the pain-induced, substance P-mediated, stress reaction. This role of oxytocin is certainly different from currently wide-spread views of this peptide as a "love hormone".

Angiotensin, on the other hand, also markedly increases blood pressure but does not initiate a generalized arousal reaction like substance P when binding to its brain receptors. Angiotensin rather induces a finely tuned cardiovascular and behavioral response including copious drinking, release of vasopressin, oxytocin and other hormones.

These two peptides exemplify different ways of raising blood pressure via the central nervous system and demonstrate how brain peptides can be involved in the pathophysiology of hypertension. Thus, while the initial concept of CEPS might have exaggerated things and has certainly over-simplified the real situation, it was nevertheless instrumental in approaching the complex issue of central blood pressure regulation.

Towards the end of the eighties, RAS researchers were confronted with a little revolution: Angiotensin peptides obviously did not bind to one single receptor as was thought for many years, but to at least two receptors, the AT1R and AT2R. While the AT1R seemed to convey all known physiological and pathophysiological actions of the RAS, the AT2R was obviously not doing the same. Indeed, stimulating this receptor would in many cases antagonize the actions of

the AT1R or even engender some effects of its own which were opposed to those of the "classical" RAS.

Together with the lab of Victor Dzau in Boston, Tad Inagami in Nashville, Marc de Gasparo and Serge Bottari at Novartis in Basel and a few other groups, we set out to unveil the secrets of the "enigmatic" AT2 receptor, and this became my main scientific interest for more than a quarter of a century. Today, the AT2 receptor is no longer enigmatic, on the contrary, a highly selective AT2R agonist, compound 21, developed by Swedish chemists at Uppsala University is currently in a phase I clinical study, harboring, among others, the unique combination of strong anti-inflammatory, anti-fibrotic and neuro-regenerative properties.

Together with ACE2 and the angiotensin 1-7/Mas system, the AT2R forms part of the "protective arm of the RAS" as we have coined it(1). Stimulating the AT2R does not directly lower blood pressure, but can reduce pulse wave velocity in hypertensive animals together with antifibrotic actions. One might speculate that a combination of an AT1R antagonist and an AT2R agonist may exert even more sustained antihypertensive and tissue protective actions than the currently used AT1 antagonists alone.

Apart from blood pressure, AT2R research in numerous labs around the world has revealed a wealth of potential clinical indications for compounds stimulating the AT2R1. The future will tell which of those will stand the clinical test.

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-Thomas Unger

Chronic kidney disease as independent risk factor for cardiovascular disease



Omar Al Dhaybi, MD (pictured left) and George Bakris, MD (pictured right)

ASH Comprehensive Hypertension Center University of Chicago Medicine Chicago, IL, USA

Chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m², is a broad public health problem. The mean global prevalence of CKD is estimated to be 13.4% [1]. This percentage encompasses the estimated prevalence of diabetes, which is close to 8.2% [1]. Diabetes was considered a coronary artery disease risk equivalent, but subsequent data have not supported this contention. Conversely, CKD is associated with higher all-cause mortality rates compared to previous myocardial infarction [2]. Thus, patients with a coronary heart disease equivalent should have a risk for a coronary event comparable to those with a history of myocardial infarction. Most of the coronary risk in patients with CKD is driven by longstanding exposure to traditional cardiovascular risk factors [3].

Nonetheless, CKD is associated with increased all cause mortality, and remains a well-established, independent risk factor for cardiovascular death, and this is supported by extensive clinical data [2] [4]. Older studies that failed to demonstrate an association between CKD and cardiovascular events were limited by non-uniform definitions of kidney disease, and the inclusion of small number of patients with actual CKD, limiting the statistical power to identify factual associations.

Chronic kidney disease is a highly inflammatory state. Left ventricular hypertrophy, arterial calcifications, and endothelial dysfunction are only part of the main underlying factors that contribute to CKD-mediated cardiovascular disease. Go et al. showed that the risk of death from any cause increased steeply as eGFR

diminished, increasing from 17% when eGFR is between 45 - 59, to 343% when eGFR is below 15 [5]. These analyses were adjusted for established risk factors, and derived from a large cohort of 1,120,295 patients. Patients were followed for a median of 2.84 years [5]. Age-standardized rates of death and cardiovascular events also increased considerably when eGFR declined. The adjusted hazard ratio for cardiovascular events was inversely proportional to eGFR: HR=1.4 with eGFR of 45 – 59, HR=2 with eGFR of 30 – 44, HR=2.8 with eGFR of 15 – 29, and HR=3.4 with eGFR below 15. The risk of death was greatest when eGFR fell below 45, and eGFR of 15 – 29 and below 15 were associated with remarkable age-adjusted mortality rates (11.4 and 14.1 per 100 person-years) [5]. A graded inverse association between eGFR and all-cause mortality and cardiovascular mortality in patients with or without hypertension was shown in a meta-analysis of 13 chronic kidney disease cohorts that included more than 38,000 patients [6]. This graded relationship was also demonstrated in a systematic review and meta-analysis of 100 studies, and was independent of age, sex, and other traditional risk factors [1].

With the advent of statins and newer antiplatelet agents as well as extensive investment in research over the last twenty years in management of coronary artery disease, there has been a tremendous decline in incidence rates of acute coronary events among those with diabetes. Gregg et al. showed that there were 95.6 fewer cases of acute myocardial infarction

per 100,000 persons per year in 2010 compared to 1990[7]. The decline in the incidence rate of end stage renal disease (ESRD) was much less pronounced (7.9 fewer cases per 10,000). The annual number of cases of ESRD increased by 32,434 cases from 1990 to 2010, whereas the number of acute myocardial infarctions decreased by 4,379 cases. Conversely, the incidence rate of ESRD increased by 65% between 1990 and 2010 in adults without diabetes. This reflects the success that blood pressure control utilizing angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) has had on progression of diabetic kidney disease [7].

The prevalence of CKD increases steadily with age. Note that the average annual loss of GFR among those with no kidney disease or diabetes is about 0.8 mL/min/year; thus, a normal eGFR in an 80-year-old would range between 55 – 65 mL/min/1.73 m². It has been estimated that 27.9% of CKD patients are older than 70 years of age. The rising prevalence of CKD seem to be mainly due to the aging of the population, as well as to the increased rates of hypertension and diabetes [1].

The dialysis population has grown notably older over the past decade. Forty-eight percent of 5,989 patients started on renal replacement therapy between 2007 and 2011 were 65 years of age or older in a large Southern California health system, per 2015 United States Renal Data System (USRDS) data. The mean age for dialysis initiation was 69 years in 2013 and among US veterans. Incidence rates for new renal replacement therapy starts were 583 per million for veterans aged 55 to 64 years, compared to 1,186 per million for veterans aged 75 years of older, again per a 2015 USRDS report.

Sixty percent of US adults aged 60 or older have hypertension, according to the 1999-2004 NHANES, a 10% increase from the previous NHANES III (1988-1994) [8]. Reduced arterial elasticity is a cardinal feature of aging, affecting the aorta and other large compliance vessels. Subsequent fibrosis ensues, amplifying arterial stiffness, and resulting in the widened pulse pressure typically seen in older hypertensive individuals. Patients over the age of 70 are less able to excrete a salt load and therefore are more likely to be salt sensitive with regard to blood pressure elevations [8].

The prevalence of hypertension increases markedly from stage I CKD (22%) to stage IV CKD (80%). It is inversely correlated to eGFR, and uncontrolled hypertension remains one of the greatest risk factor for progression of CKD into ESRD [6]. Controlling blood pressure in men aged over 70 was consistently harder in clinical trials [7].

Mahmoodi et al. conducted a meta-analysis that included 13 chronic kidney disease cohorts (a total of 17,088 hypertensive patients and 21,072 non-hypertensive

individuals). The hazard ratio for ESRD was 4.90 in hypertensive patients with eGFR between 45 – 74 and proteinuria less than 1.5 grams (compared to 1.99 in non-hypertensive patients). The hazard ratio for progression into ESRD accrued to 8.57 in hypertensive patients with eGFR below 45 and with less than a gram of proteinuria, compared to 5.08 in non-hypertensive patients. The authors also demonstrated that the risk of ESRD significantly increased in patients with CKD regardless of the cause of their kidney dysfunction, whether they had diabetes or not [6]. Major clinical trials in the elderly have shown a substantial reduction in cardiovascular events with the widespread use of antihypertensive medications.

Blood pressure lowering to a routine office measurement between 125 – 130 mm Hg decreased incident cardiovascular disease by 33% per year and total mortality by 32% per year in patients aged 75 or older in the Systolic Blood Pressure Intervention Trial (SPRINT), as well as in people with CKD [9]. Note, the way blood pressure was measured in SPRINT is not typical of office practices and yields much lower values than achieved in routine medical practice, therefore slightly higher BP ranges should be the desired goals [10]. Additionally, elderly patients living in nursing homes, or who have diabetes, stroke, or symptomatic heart failure were excluded from SPRINT, thus, affecting its generalizability.

The consensus of almost all international guidelines is that the systolic blood pressure target be <140 mm Hg up to age 80. Note also that in almost all these trials, including SPRINT, very few individuals had a high pulse pressure (i.e., more than 70 mmHg at baseline). This subgroup of patients tends not to handle lower pressures less well and are quite symptomatic. Moreover, the use of ACEi/ARBs in the older people with advanced kidney disease is often not achievable secondary to hyperkalemia, thus limiting the ability to achieve blood pressure goals. The most important time to intervene in this subgroup is early in the CKD staging, by keeping blood pressure values well below 140 mmHg, to slow down CKD progression.

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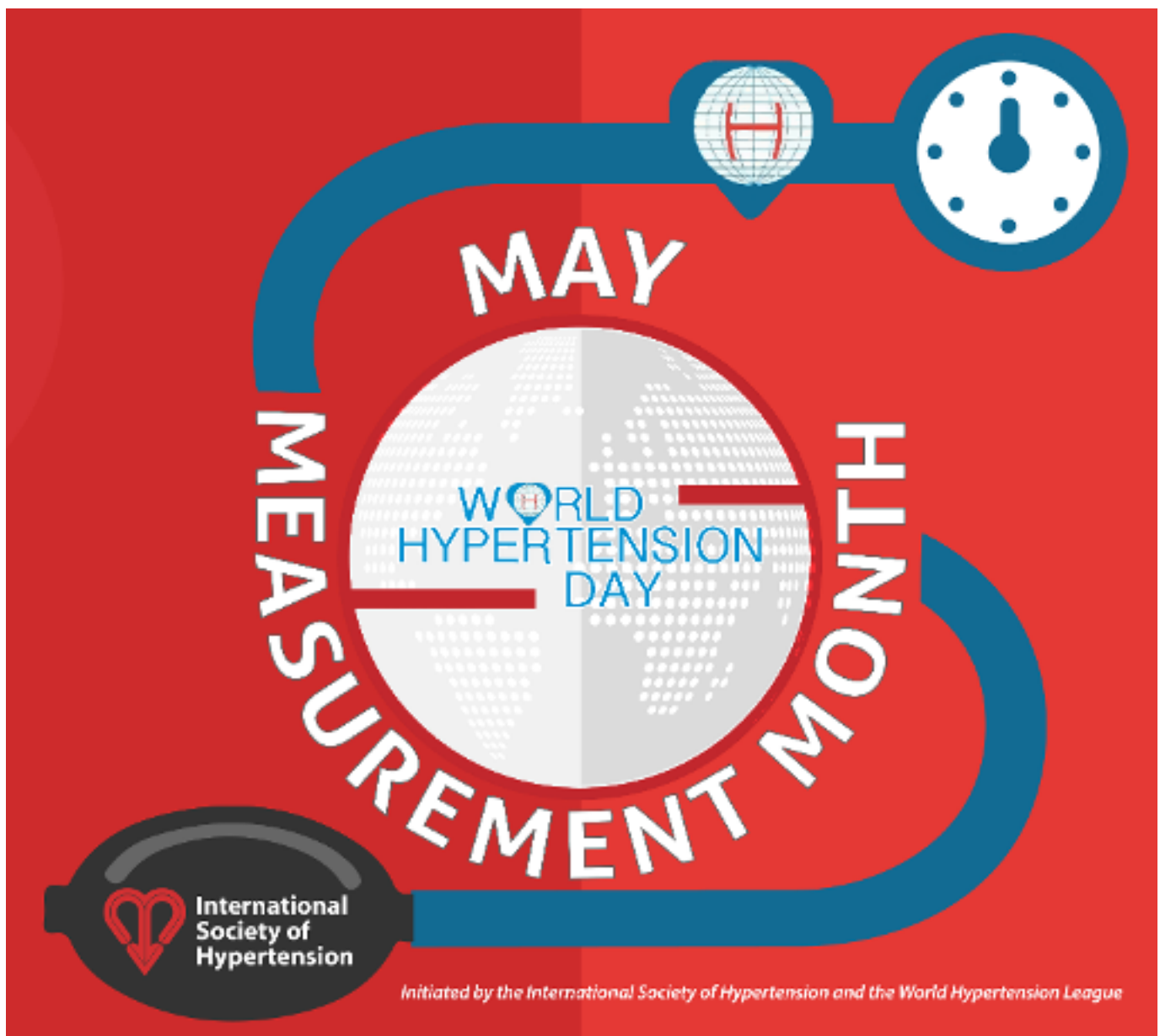
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-Omar Al Dhaybi and George Bakris



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