International Society of Hypertension
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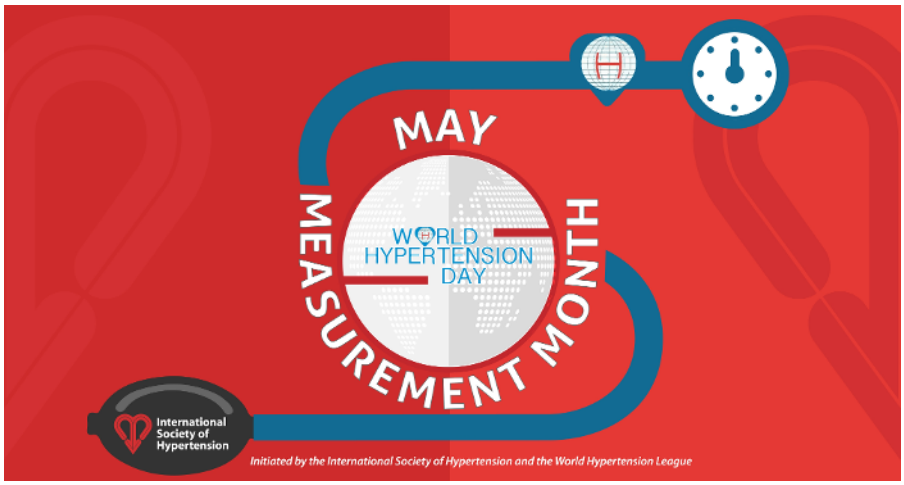

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Notes from the Editor - Lars H. Lindholm

Dear ISH member,

Again, it is a pleasure for me and my colleagues on the editorial team to present a new issue of Hypertension News.

It is indeed a comprehensive issue, this time with a special focus on assessing adherence to prescribed drug treatment, or as Thomas Kahan puts it in his introductory remark on page 13: 'Is Adherence to Medication the Elephant in the Room?' Needless to say, we all need to pay (more) attention to patient adherence to improve blood pressure control. Drug analyses may be one way of doing it! Apart from the introduction, we present three papers on this topic, each with a different focus: one on the use of registries, a second on clinical aspects, and a third on ethics.

In Opus 48, Stephen Harrap and Fadi Charchar wrote a provocative paper entitled: "Genetics of blood pressure - still hoping after all these years". For this issue, we asked Olle Melander (Malmö, Sweden) and Cristiano Fava (Verona) to comment on it (page 22-23). They end their comment with the following strong statement: "Closing doors to the development of genetics of blood pressure would be a betrayal of our children and grand-children. We are not only 'still hoping' as are Stephen Harrap and Fadi Charchar, we are 'very hopeful'. A reply from Stephen Harrap and Fadi Charchar ends the discussion for now (24).

Many ISH members express their (sometimes original) thoughts in Hypertension News and we are very grateful for it. A problem in the past has been the difficulty of referring to papers published in our Newsletter. With the help of Dylan Burger (Ottawa, Canada) we have now registered Hypertension News on an International Standard Serial Number (ISSN 2520-2782). ISSN status is a first step to obtaining Digital Object Identifiers (DOIs). Read more about this important upgrade of Hypertension News on page 28.

In the next issue of Hypertension News (Opus 50) we will report extensively on the May Measurement Month activities. Already, in this issue, you can get some information in the President's address on page 3-4 and you can also hear "The Secretary's Voice" on page 5. As you can see, it has not been an easy project to undertake, but a fantastic one! Somehow it makes me think of what my old army sergeant and corporal said when they tried to teach us how to shoot: "You think this is easy lads – but you just wait until we have explained it to you ..."

Have a good read!

Lars H Lindholm, Editor / lars.h.lindholm@umu.se

PS. Since hypertension and dyslipidaemia often co-exist I recommend that you read Peter Sever's balanced report (page 11-12) on the results of the FOURIER trial, comparing evolocumab and placebo in 27,500 patients with established CVD and recently published in the NEJM.

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

About one third of the way through my Presidency and it would be disingenuous to say anything other than that my focus, and that of several members of the ISH administration and senior management figures, has been May Measurement Month (MMM).

As I write this, we're exactly half way through the month and the momentum is mounting. We have reached the target of getting the active involvement of over 100 countries (albeit by counting the UK as 4 separate countries!) and we are receiving wonderful feedback from all over the world.

On the other hand, there have been glitches – some of them major – which will impact seriously on the numbers screened but we still expect that MMM will be the largest screening programme of any cardiovascular risk factor hitherto, with millions of people entering the database.

We are very grateful to OMRON, who gave MMM an unencumbered donation of up to 20,000 blood pressure measurement machines, of which about 12,000 have been dispatched around the world. However, successful receipt of dispatched machines has been one of our problems, and sadly some machines have yet to reach their destinations!

Last minute ethical issues were raised in some countries, highlighting some of the challenges of carrying out research, despite MMM essentially being an anonymised audit with no real ethical concerns.

World Hypertension Day (May 17) was promoted rather more independently of MMM than I had hoped, but if we (ISH & World Hypertension League) achieve our primary aim of raising awareness of the importance of measuring blood pressure in such a way as to make real beneficial impacts on health priorities regarding blood pressure screening around the world – we shall have succeeded, together or separately!

Looking forward to pulling all the data together from 2 or 3 Apps and several Excel spreadsheets, it seems our data management and statistical support will have a busy summer working towards generating a series of publications (as numbers allow) to supplement the 2 brief papers already published, which "advertised" the MMM campaign (1,2). Thereafter, the work of health economic analyses will be used to promote the benefits of effective blood pressure screening.

Meanwhile, our thanks to the Centres for Disease Control (CDC) and Servier, both of whom have provided grants to facilitate the generation of the data and related publications.

IMAGE: Support from all over the world including; UK, Tasmania, Barbados & Venezuela

Beyond "just" MMM – and as mentioned in my first report, we broke from tradition by bringing the first face to face meeting of the ISH Council forward to March. We met in Dubai and invited not only the Council (the usual participants) but also the leaders of the Regional Advisory Groups (RAGs), the International Forum and the New Investigator Committee (NIC).

It was a very successful meeting and may well provide the blueprint for the future of bringing together the society's officers in one place early in a new President's tenure, to bond and create the strategy for the next 2 years.

Despite the March meeting, we shall also hold a less formal meeting of any/all ISH officers who are attending the ESH meeting in Milan.

My plans following the summer are to visit several hypertension societies around the world to evaluate the potential and challenges for reducing the blood pressure-associated disease burden linked to and beyond the findings of MMM.

Finally, a big thank you to all those who have contributed to MMM and to the other ongoing activities of the various ISH Committees and to our excellent Secretariat!

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- Neil Poulter

The Secretary's Voice:

Maciej Tomaszewski

Dear Readers,

May Measurement Month:

Over the last few weeks the vast majority of efforts and activities within the ISH Council and the Executive Committee have been focused on the May Measurement Month 2017 (MMM2017) initiative. You will see a detailed update on how we have prepared for this key undertaking from our President. I encourage everyone to read news articles on the activities of MMM2017 on the campaign website - www.maymeasure.com and social media platforms: Twitter, Facebook and Instagram. All these social media pages contain most exciting images and data illustrating the global enthusiasm for the MMM2017 project.

Dubai Council meeting:

The ISH Council met in Dubai on 4th March 2017. The meeting was chaired by our President, who highlighted the areas of focus for 2016-18:

i) Increasing the level of awareness among the world's hypertension population,

ii) Improving the level of knowledge about blood pressure among those measuring and managing hypertension, and

iii) Identifying the optimal combination of antihypertensive drugs.

The Council discussed and agreed that some restructuring within the current five Regional Advisory Groups (RAGs) is essential to align their activities with the key mission of the Society and ensure fairer distribution of support and resources among the regions. It has also been agreed that RAGs will have to work more closely with the ISH International Forum (currently chaired by Professor Louise Burrell). Further information will be available in this regard in due course.

IASH-SAHA Mendoza meeting:

I represented the Society and the President at the joint *XXIV National Congress of the Argentinian Society of Hypertension (SAHA)* and the *XXI Biennial Scientific Sessions of the Inter-American Society of Hypertension (IASH)* in Mendoza (20–23.04.2017). This was an exceptionally well-attended meeting with over 3,600 doctors, scientists and health professionals interested in hypertension. Our ISH New Investigator Committee (chaired by Dr Ruan Kruger) contributed to the sponsorship of the Best Poster Awards. You will see detailed reports on this important meeting in this issue of the newsletter - see pages 27-29.

ISH Membership:

Professor Alta Schutte (ISH Vice-President and Chair of the Membership Committee) recently completed an extensive review of ISH membership. One of the aims was to ensure that those members who have consistently not paid their dues for more than two years are marked as resigned on the Society database. The total current number of Society members is 1,232. Of those, 818 are Professional Members, 110 - Affiliated Society Members, 35 - Emeritus Fellows, 11 - Distinguished Fellows, 48 - Emerging Leaders, 6 - Honorary Fellows, 189 - Research Fellows, 5 - Corporate Members (industry partners) and 10 - individual industry members. We are grateful to Professor Schutte and her ISH Membership Committee for all their efforts with recruitment and retention of members of the Society. Please see page 30 of the newsletter for further information on ISH membership.

Refer a colleague to join ISH

If you have a colleague who would like to become a member of ISH please ask them to send their CV to membership@ish-world.com.

Global Hearts Initiative partner meeting:

HEARTS

Technical package for cardiovascular disease management in primary health care

I represented the Society and the President at *The Global Hearts Initiative to Reduce Heart Attacks and Strokes* in Atlanta on 25 April 2017. This important global initiative brings together World Health Organization (WHO), U.S. Centers for Disease Control and Prevention (CDC), CDC Foundation, Pan American Health Organization (PAHO), World Stroke Organization (WSO), World Heart Federation (WHF), ISH, World Hypertension League (WHL) and American Heart Association (AHA), uniting to accelerate national action to prevent and control heart disease and stroke. Two technical packages (HEARTS for cardiovascular disease management and SHAKE for salt reduction) have been developed. Our expertise as a premier professional society in hypertension and the strong membership throughout the world are very much valued by the alliance.

ISH Award Funding Scheme:

I am pleased to confirm that the ISH award funding scheme for mentors and organisations to train research scholars in hypertension in Low-Middle Income Countries now falls under the remit of the Mentorship and Training Committee (currently chaired by Professor Fadi Charchar). The winners of the 2017 awards have been identified in Mongolia, Nigeria and Sudan. The Executive Committee has supported the decision to fund these awards and the winners have been notified. Further information follows on the award winners on pages 20-21 of the newsletter.

Professor Rhian Touyz elected as fellow:

Professor Rhian Touyz (Immediate Past President and Chair of the Women in Hypertension Science Committee) has been elected as a Fellow of the UK Academy of Medical Sciences. I am sure you will join me in congratulating Rhian on this extremely prestigious academic accolade.

ISH Council meeting & Networking and Mentorship social event, Milan June 2017:

The next meeting of the Council will take place in Milan on Saturday 17th June 2017. This will be followed by our annual Networking and Mentorship social event (organised by the Mentorship and Training & New Investigator Committees).

I encourage all of you who wish to attend this hugely popular event to contact our Secretariat to book a ticket. **Please note places are now very limited** and are being allocated on a first come first serve basis, with priority to ISH Research Fellows and Emerging Leaders.

- 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

Is successful renal denervation a function of adherence to antihypertensive medication?

Some 10–15% of all patients attending primary health care with a recorded diagnosis of hypertension and treated with three or more antihypertensive drug classes have uncontrolled hypertension with 140/90 mm Hg or above (often described as *treatment resistant* or refractory hypertension), despite being adherent to prescribed antihypertensive medication [1]. Some of these patients may have unrecognized secondary causes of hypertension. However, with the recent introduction of catheter based sympathetic renal nerve denervation as a possible alternative method for the treatment of resistant hypertension it has become clear that many patients with *apparent resistant* hypertension are poorly adherent to antihypertensive drug therapy [2]. Thus, medication adherence may be an important contributor to the reported highly variable response to renal denervation therapy.

Recently, de Jager and associates reported on the SYMPATHY trial and on the impact of medication adherence on the effect of renal denervation in apparently resistant hypertension [3]. This multicentre study in the Netherlands randomized patients with resistant hypertension, defined as an average daytime systolic ambulatory blood pressure of 135 mm Hg or above despite three or more blood pressure lowering agents (or with documented intolerance to two or more agents), by 2:1 to renal denervation in addition to usual care, or usual care only, stratified for site and estimated glomerular function. Blood samples were collected on the same day as blood pressure was assessed. Primary outcome was change in average daytime systolic ambulatory blood pressure at six months.

There were 95 patients randomized to renal denervation and 44 to usual care; however four declined renal denervation and eight (five in the intervention group) withdrew their participation. Mean age was 61 years, about one third were male, average daytime ambulatory blood pressure was 160/93 mm Hg, and the participants were on an average of 3.4 antihypertensive drug classes. Mean average daytime ambulatory blood pressure was reduced by six months. However, in confirmation of other randomised controlled studies on renal denervation [4], the difference (mean values and 95% confidence values) between the study groups in average daytime systolic and diastolic ambulatory blood pressures were small, +2 (–6 to +10) and +1 (–7 to +9) mm Hg, respectively.

For the assessment of medication adherence, liquid chromatography combined with tandem mass spectrometry was used to screen for antihypertensive drugs in blood samples collected on the same day as blood pressure was assessed. Patients were characterized into adherent, poorly adherent, and non-adherent, corresponding to more than 80%, 20–80%, or 0% of the prescribed drugs present in the samples, respectively. Data for 78 patients at both baseline and follow up were available. On both occasions 80% were poorly adherent or completely non-adherent, and one third of the participants changed from one adherence category to another during the course of the study. The highest blood pressure values were observed in patients completely non-adherent. In patients within the same adherence category at baseline and at follow up, daytime and 24 h systolic ambulatory blood pressure, and office systolic blood pressures were lower (–3, –5, and – 14 mm Hg, respectively) in the intervention group, as compared to usual care.

While SYMPATHY [3] confirms previous observations of small effects by renal denervation on ambulatory blood pressure by renal denervation [4], it extends our knowledge on renal denervation in resistant hypertension and medication adherence. First, poor medication adherence is common in resistant hypertension, is associated with higher blood pressure values, and may contribute to apparent treatment resistant hypertension. Second, patients with better medication adherence appear

to respond to renal denervation with a greater reduction in blood pressure. This emphasizes the importance of improving medication adherence in patients with hypertension.

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- Thomas Kahan

Hot Off the Press

Antoine Caillon

Post-doctoral Fellow, Vascular and Hypertension Research Unit, Lady Davis Institute for Medical Research, Montreal, Quebec, Canada

From RAG to Riches And Back Again: always keep an eye on our mice models

Kathryn Sandberg and her team very recently conducted a study[1], to be published in the June 2017 issue of Hypertension, focusing on the loss of resistance to angiotensin II–induced hypertension in Recombination-Activating Gene 1 knockout mice (Rag1-/-) on the C57BL/6J background (Jackson Laboratory). This mouse model is deficient in functional T and B cells due to the lack of the V-D-J recombination enzyme, and has been used by several groups in the past decade to explore the involvement of the adaptive immune arm in hypertension.

In 2007, Guzik et al.[2] were the first to demonstrate a role for T cells, and not B cells, in angiotensin II- and DOCA-salt-induced blood pressure elevation and vascular remodeling. In Rag1-/- mice, they showed that repletion via tail-vein injection with T cells, but not B cells, from a wild-type source rescued the otherwise blunted hypertensive response to angiotensin II and DOCA-salt. This study prompted the extensive use of this model to further explore the role of various T cell subsets in hypertension.

However, since 2015, Rag1-/- mice seem to have lost protection against angiotensin II-induced blood pressure increase. This observation was reported by different independent laboratories previously, and addressed in detail in the present study. The authors showed that glomerular angiotensin type 1-receptor binding was higher in recently purchased Rag1-/- mice, suggesting that blood pressure protection as a result of the lack of T cells is lost due to an increase in renal angiotensin type 1-receptor activity. They stressed that spontaneous genetic drift due to mutations lead to phenotypic change in all animals, including inbred mouse strains, because of the universal drive to increase genetic variation.

The gradual loss in blood pressure protection in Rag1-/-

mice can be traced over time as evidenced by increasingly contrasting observations made by us and others since the initial study by Guzik et al. In a study published last year[3], our lab showed that angiotensin II infusion caused a similar rise in systolic blood pressure in Rag1-/- and wild-type C57BL/6J mice; only diastolic blood pressure was blunted in Rag1-/- mice. This is different from the Guzik study in which both blood pressures were significantly blunted in these mice.

These observations illustrate the importance of including experimental details about the location and time period over which animals are bred in publications involving animal studies. This will promote rigor and reproducibility in the scientific literature.

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- Antoine Caillon

New Investigator Spotlight Features for March - June 2017

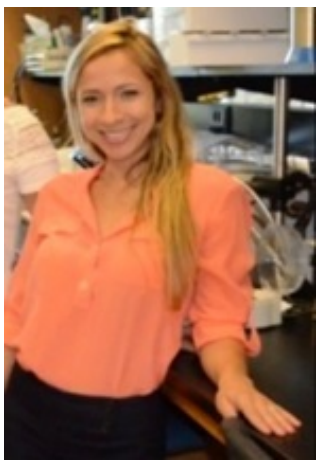
March spotlight of the month

Yolandi Breet

Postdoctoral Research Fellow,
Hypertension in Africa Research Team (HART),
North-West University,
Potchefstroom Campus,
South Africa

Read an interview

April spotlight of the month



Camilla Ferreira Wenceslau

Research Scientist
Department of Physiology,
Augusta University,
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Augusta, GA 30912-3000. USA

Principal Investigator:
"Intrarenal arteries sense trauma-derived mitochondrial N-formyl peptides leading to kidney injury in SIRS".

Read an interview

May spotlight of the month

Shani Botha

Senior Lecturer and Researcher
Medical Research Council Unit for Hypertension & Cardiovascular Disease,
Hypertension in Africa Research Team (HART)
North-West University,
Potchefstroom, South Africa

Read an interview

June spotlight of the month

Debbie Ona

Clinical Associate Professor,
Section of Hypertension,
Department of Medicine,
University of The Philippines, Philippine General Hospital, Taft Avenue, Manila, Philippines

Read an interview

Hot Off the Press

Matthew Sparks, MD

Assistant Professor, Associate Program Director, Nephrology Fellowship, Director of Medical Student Research, Department of Medicine, Duke University School of Medicine, USA

Podocyte specific APOL1 risk variant overexpression in mice induces proteinuric kidney disease

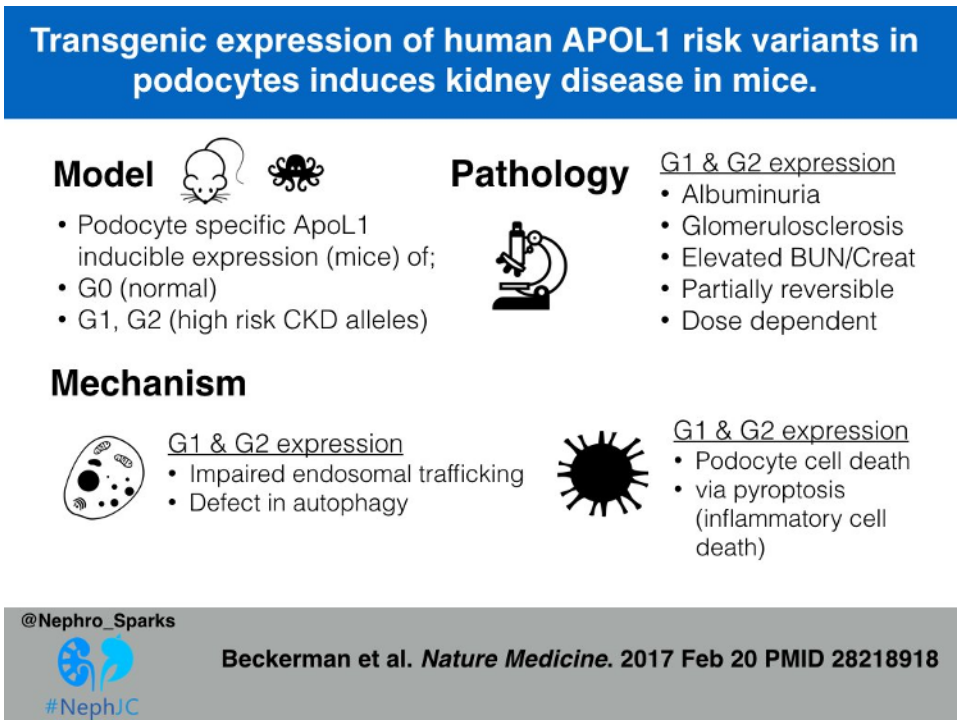
Beckerman *et al.* (2017) *Nature Medicine*

The presence of 2 APOL1 risk alleles (risk alleles termed G1 and G2, with G0 being normal) emerged as a huge story back in 2010 after Genovese et al reported their findings in *Science* that the presence of these risk alleles were associated with FSGS and hypertension attributed ESKD in African Americans. Interestingly, they described how the high risk alleles function as a serum lytic factor for *Trypanosoma brucei rhodesiense*. This is important because this particular subspecies is able to evade lysis from the G0 allele. Since the seminal observation a number of investigations have associated these risk alleles with several kidney diseases in African Americans (HIVAN, FSGS, hypertension associated ESKD, and Lupus).

This paper from Beckerman et al, reported in the journal *Nature Medicine,* examines the effect of APOL1 risk alleles specifically in the podocyte using a mouse model. First, it is important to note that mice and rats do not have APOL1, nor do they have an analog. Therefore, it was necessary to not only overexpress the risk alleles (G1 and G2) but also the normal allele (G0) in order to examine their function in vivo. This group of investigators overexpressed all 3 alleles only in podocytes with a doxycycline inducible system (Nephrin-rtTA).

They report in the supplemental data that nephron specific APOL1 risk allele expression does not induce kidney alterations. After verification of podocyte specific expression they examined the kidney for signs of pathology. After inducing podocyte specific APOL1 transgene expression in adult mice they found a higher amount of albuminuria, glomerulosclerosis, and elevated BUN/Creatinine in G1/G2 mice compared to G0. They also demonstrated that albuminuria was partially reversible after stopping APOL1 G1/2 transgene expression (by withholding doxycycline). The degree of albuminuria also correlated nicely with APOL1 G1/2 expression and not with APOL1 G0. The mechanism of G1/G2 induced kidney disease was linked to impaired podocyte endosomal trafficking. Thus, this defective trafficking results in altered autophagy, and ultimately podocyte cell death via pyroptosis.

These data demonstrate the central role of the podocyte to kidney disease and could provide important avenues targeting these pathways in APOL1 associated kidney disease. To read more about this paper and view the online discussion go to NephJC.



- Matthew Sparks

Lipid Lowering in the Hypertensive Patient

Peter Sever

International Centre for Circulatory Health

National Heart and Lung Institute

Imperial College London, UK

Hypertension and dyslipidaemia frequently co-exist. It is not surprising, therefore, that the majority of hypertensive patients warrant consideration for concomitant lipid-lowering therapy. The most recent meta-analyses published by the Cholesterol Treatment Trialists Collaboration, reported that the lowering of LDL-cholesterol by approximately 1mmol/L, was associated with a reduction in vascular events of about one quarter.[1] This meta-analysis demonstrated that in virtually all subgroups of patients studied, the relative risk reductions were consistent, including patients with hypertension.

Two hypertension trials specifically evaluated the effects of lipid-lowering with statins in patients with hypertension. In the Anglo-Scandinavian Cardiac Outcomes Trial,[2] over 10,000 hypertensive patients with a total cholesterol less than 6.5mmol/L, were randomised to atorvastatin 10mg or placebo. The primary endpoint of fatal and non-fatal myocardial infarction was reduced by 36% in those assigned a statin, and there was a reduction in a composite secondary endpoint of combined cardiovascular events. In the Antihypertensive and Lipid-Lowering Heart Attack Prevention Trial,[3] a subgroup of hypertensive patients were randomised to pravastatin 40mg or "usual care". In this study there was a non-significant (9%) reduction in myocardial infarction - a reduction that was compromised by the fact that statin treatment was common in those assigned "usual care"- and the difference achieved in cholesterol between the two treatment groups (9%) was therefore minimised. However, based on the CTTC meta-analysis, it can be concluded from the substantial evidence base, that statin treatment is effective in hypertensive patients and, for those at high absolute risk, the concomitant use of statins should be considered mandatory.

I wrote about the FOURIER trial in one of my earlier commentaries to the ISH Hypertension News and the trial has now completed. The first report was presented at the American College of Cardiology in March this year, and published simultaneously in the New England Journal of Medicine.[4] The identification of proprotein convertase subtilisin/kinase type 9 was first reported in 2003 and within 14 years, the first major morbidity and mortality trial has been completed.

FOURIER was a randomised, double-blind, placebo controlled trial of over 27,500 patients with established cardiovascular disease and an LDL-cholesterol level of less than 1.8mmol/L. All patients were receiving concomitant statin therapy in optimal or best tolerated doses. Patients were randomly assigned either evolocumab or placebo, which was administered as a subcutaneous injection. The primary endpoint was a composite of cardiovascular (CV) death, myocardial infarction, stroke and hospitalisation for unstable angina or coronary revascularisation. The key secondary endpoint was a composite of CV death, non-fatal myocardial infarction or non-fatal stroke. The study was concluded after a median follow-up period of 2.2 years.

During the trial, LDL-cholesterol levels were reduced by almost 60% from a baseline of 2.4mmol/L to 0.78mmol/L. Active treatment reduced the primary endpoint by 15% and the key secondary endpoint by 20%. Both of these relative risk reductions were highly significant and were consistent across all key subgroups. Importantly, 80% of the patients recruited into FOURIER had a history of hypertension, and benefited to the same extent as the total trial population. There were no differences between evolocumab and placebo in any adverse events.

A further analysis of the endpoints revealed that, whilst there were clear reductions in myocardial infarction and stroke, there were no reductions in either CV death or all-cause mortality. It is, however, important to point out that the trial was stopped, as pre-specified, when 1,630 key secondary endpoints had been reported. It was not expected that, with this duration of follow-up, a reduction

in CV death would have occurred and, in previous trials comparing more versus less lipid- lowering treatment, there was also no reduction in CV mortality.[5]

A time-dependent analysis of the results of FOURIER suggested that there was a delay in the achievement of the maximal benefit from lipid-lowering, with approximately half the risk reduction observed in year 1 compared with year 2. Whether a longer duration of trial would have demonstrated a reduction in CV mortality is conjectural.

These are important results, which are in line with predictions based on the CTTC meta-analyses, and confirm the benefits of adding evolocumab to statins in the prevention of further CV events in patients with established vascular disease.

In an important sub-study of FOURIER, the EBBINGHAUS Trial, the effect of evolocumab compared with placebo was assessed using a battery of tests of cognitive function. Concern had previously been expressed, based on some observational studies, that statins adversely affected cognitive function. This was highlighted by the MHRA (2009) and the FDA (2012) and led to an addition to the statin label of potential adverse effects on cognitive function. However, in double blind, randomised controlled clinical trials, no such adverse effects on cognitive function had been reported. In some short term trials with monoclonal antibodies to PCSK9, there were reports of adverse effects of these drugs on cognitive function. This stimulated the need for a more comprehensive evaluation of these drugs on cognitive function. EBBINGHAUS incorporated a highly sophisticated range of cognitive function tests (CANTAB, http://cambridgecognition.com). Almost 2,000 patients were randomised and followed-up for an average of just over 2 years. In a non-inferiority analysis, there were no differences in any of the outcome assessments for cognitive function.

Committees formulating new guidelines, and healthcare providers, will now assess the place of evolocumab and other monoclonal antibodies to PCSK9 in future treatment strategies. The SPIRE trial of bococizumab,[6] another monoclonal antibody to PCSK9, was stopped prematurely on account of the development of antidrug antibodies, and an attrition of the effects of the drug on lowering cholesterol. For those assigned to SPIRE 2 - the sub study that recruited patients with prior vascular disease - a reduction in CV events was also seen with active treatment versus placebo. Thus these findings support the results of FOURIER. Importantly, these studies also demonstrated that achieving very low levels of LDL-cholesterol was not associated with the emergence of any untoward adverse events.

Cost effectiveness studies will provide guidance on the future use of evolocumab in high risk patients with CV disease and, more specifically, in those who have not reached target levels of LDL-cholesterol with statin treatment. Costs for the drug vary enormously, from around $14,000 per year per patient in the USA to around £2,000 per year, the discounted price to the NHS, in the UK. Cost effectiveness analyses will therefore be substantially influenced by the annual cost of the drug.

It is worth noting that the potential patient population for whom evolocumab would be advantageous is large. In the latest EUROSPIRE programme (2016), approximately 80% of patients with a previous history of myocardial infarction had an LDL-cholesterol of greater than 1.8mmol/L on existing statin treatment, with 40-50% having an LDL-cholesterol of greater than 2.5mmol/l. Many of these patients would not have been on optimal statin treatment, however.

Perhaps one of the most important implications from the results of FOURIER is that there are real benefits of achieving much lower levels of LDL-cholesterol and that these are safe and not associated with any untoward side effects. This should stimulate clinicians to ensure their existing patients are treated with optimal doses of the more effective statins (which is not the case in clinical practice).

Many will argue that the numbers needed to treat (NNT) are high. Approximately 50 patients have to be treated for 3 years to prevent one major CV event. The critics highlight the other 49 who do not benefit! Many will recall similar arguments being levelled at treating mild hypertension.

The final decision must await the outcome of cost effectiveness studies, but for many patients, particularly those with high residual levels of LDL-cholesterol on optimal doses of statins – particularly those with familial hyperlipidaemias - the benefits are real, and the outcome of the FOURIER trial is a major advance in our knowledge of the benefits and safety of a new form of lipid- lowering treatment.

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- Peter Sever

Introduction: Is adherence to medication the elephant in the room?

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Most medications act best when patients take them; and this appears to be the case also for antihypertensive drugs. Unfortunately, there is evidence that patients stop taking treatment that is intended to be taken lifelong. This is unfortunate and will reduce the potential preventive effects of their medication. Thus, adherence to antihypertensive medication is inversely related to cardiovascular outcomes [1]. Similar findings have been demonstrated in other chronic disease conditions with high cardiovascular risk, such as diabetes [2] and coronary heart disease [3]. Adherence to medication is generally greater in secondary prevention of cardiovascular disease (approximately two thirds adherent) than in primary prevention (approximately one half adherent) [4]. Of note, adherence to cardiovascular preventive medication is generally not related to drug class, suggesting that other factors than side effects are important [4].

There are several ways to assess adherence in clinical practice. They all have their advantages and disadvantages, and no way is perfect. Tablet counts, often used in clinical studies, and questionnaires, such as the commonly use Morisky adherence questionnaire, are often used but of limited value. Other methods, which appear to provide better information, include the combined use of electronic health records, data registries, and data on dispensed drug prescriptions; electronic pill containers recording opening and closing of the container; observed therapy units; and monitoring of drug concentrations in blood or urine. However, there are important ethical considerations to the assessment of adherence to treatment that should be considered.

Lack of adherence to medication is the elephant in the room. In order to improve blood pressure control we need to pay more attention to patient adherence to antihypertensive medication. The essays presented below will hopefully contribute to this.

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- Thomas Kahan

Registries – the golden standard for assessment of adherence to antihypertensive treatment?

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There is no perfect way to measure patient adherence. Methods that rely on patients' self-reporting are biased and those based on measurements taken during a consultation are subject to "white-coat adherence", i.e. improved adherence before a scheduled visit to the clinic or laboratory. One opportunity is to use registries increasingly available in healthcare since they may provide large samples of patients with hypertension, followed over long time with minimal risk for bias.

We live in the era of digitalization in healthcare. During the last decades, progress in computer technology allowed rapid access to data that in the past were very time consuming to collect and compile. During the 70s the first databases based on administrative claims data were established in North America and Europe. Today, an increasing number of healthcare organizations in North America, Europe and Asia have established large registers on diagnoses and dispensed prescription drugs—in many cases with the possibility of linkage to clinical data[1-4]. The potential for analyzing drug utilization has further developed with the introduction of electronic health records containing not only prescription drug data but also clinical parameters, such as diagnosis, vital signs, laboratory data and more or less structured clinical notes.

Adherence research has been confusing due to the lack of universally accepted standards regarding terminology and methods. A few years ago, Vrijens et al, proposed an analytical framework where adherence consists of three different components[5]; *initiation* of the treatment (if the patient takes the first dose), *implementation* of the dosing regimen (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen) and *discontinuation* of therapy (if patient stops taking the prescribed medication). *Persistence* may be defined as the length of time between initiation and discontinuation of therapy. Registers may be useful to measure all these components of adherence. Electronic medical records recording prescriptions issued by physicians can be linked to dispensing databases to assess the proportion not filling their first prescription, i.e., failure in the initiation of therapy. Longitudinal analyses of pharmacy dispensing data can be used to monitor implementation over time and to identify if the patient discontinues. Dispensing databases is a rather rough measure of implementation since it only allows for analyses of appropriate volumes dispensed according to the prescribed regimen and not to what extent patients actually take medications as prescribed. However, given the large unbiased samples of data closer to patient behavior than the medical records, dispensing data is considered as the golden standard in analyses of medication persistence[5].

Today, a majority of all studies on adherence in hypertension uses data from registers[6]. Originally, there were limited opportunities linking dispensing data to clinical information. During the last decades, these opportunities have grown in many countries. We have used Swedish registry data and linked electronic medical records from 48 primary healthcare centers with national registers on sociodemography and dispensed prescription drugs to create a database for hypertension research, the Swedish Primary Care Cardiovascular Database (SPCCD)[7]. In a study on persistence to antihypertensive therapy we showed that only two percent of patients did not visit the pharmacy to claim their first prescription. However, many patients discontinued treatment early, with one sixth of all patients discontinuing directly after they purchased their first prescription, and one third had discontinued their medication after two years[8].

There is a large range in persistence rates found in different studies (see Figure). This variation is not

surprising given the large discrepancies between studies in populations studied, ranging from elderly male American veterans with cardiovascular comorbidity to young patients in Italy being diagnosed with hypertension in primary care for the first time in life. It is also important to acknowledge the large differences in methods with, e.g., some studies having a diagnosis of hypertension as inclusion criteria while others include all patients initiated on antihypertensive drugs regardless of the underlying diagnosis. Furthermore, some studies assess therapy persistence (the proportion remaining on any antihypertensive therapy) while others assess class persistence (the proportion remaining on a specific drug class). Finally, there are inconsistencies in how exposure is measured and the gap applied on dispensing patterns to define discontinuation. It is important to critically assess the methods applied since they may introduce bias in analytical studies assessing differences in adherence between different pharmacological groups.

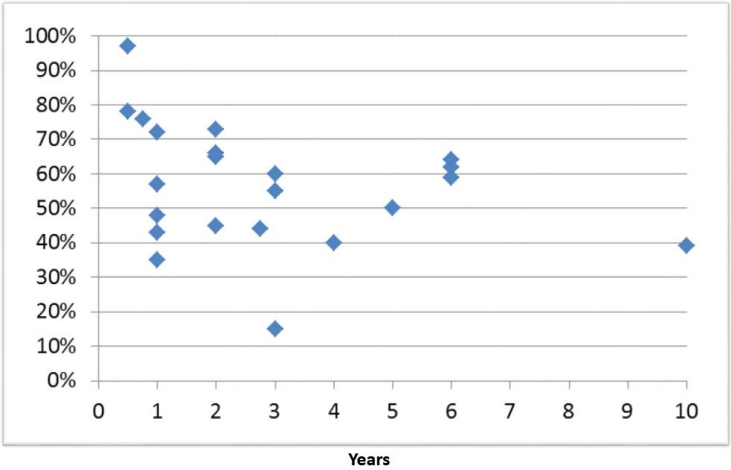

Figure legend: Therapy persistence rates in 20 studies on antihypertensive drugs. Studies from Europe, Australia and North America published 2002-2016

Many patient, provider or health system characteristics may influence adherence and persistence. A majority of studies include age, sex and comorbidity in the analyses. Others have analyzed adherence and persistence in relation to patient characteristics such as income, living area, ethnicity, social insurance, health status, education and marital status or provider characteristics such as organization of the clinic or physician education specialty and qualifications. In our studies we found the major determinants of discontinuation of antihypertensive drug treatment to be male sex, young age, mild-to-moderate systolic blood pressure elevation, and birth outside of Sweden [8,9]. Furthermore, we found no major differences in persistence between different drug classes[9]. Our conclusions on key determinants are in agreement with many other studies, but there are also studies showing the opposite. Studies assessing difference between antihypertensive drug classes have also shown conflicting results. Unfortunately, we believe that this could partly be explained by methodological flaws and the fact that factors known to be associated with poor persistence are not taken into account.

Registers will continue to be important tools for research on adherence and persistence in hypertension. Future studies would benefit from applying a common terminology, improving the clarity in the methods section to enable critical assessment, conducting appropriate adjustment for potential confounders and including sensitivity analyses to assess the robustness of the study design. Finally, it is important to acknowledge the limited information available in registers about life style and attitudes to treatment among patients and physicians. The opportunities to acquire such information will increase substantially the coming years as a result of the increasing use of electronic patient surveys, smartphones monitoring patients' activity and real-time alerting medical devices.

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- Björn Wettermark & Miriam Qvarnström

Clinical aspects of screening for non-adherence to antihypertensive medications

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Non-adherence is defined as "the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider". {1789 World Health Organisation 2003[1]}

The term "compliance" was commonly used in the past to define non-adherence, but its use is not favoured now due to its negative connotation of the patient–doctor relationship.[2] Non-adherence is very common; around 5% of patients never initiate their treatment and 50% have a low persistence. The latter is defined as the period (measured in days/months) between the initiation and the subsequent non-adherence.

There are various measures that can be used to assess non-adherence in clinical practice. Physicians' perception is considered to be no better than tossing a coin, and patient-reported questionnaires such as the commonly-used Morisky Adherence Questionnaire (MAQ), although inexpensive, generally tend to over-report adherence by up to by one fifth due to patients' desire to appear to be "doing the right thing".

Prescription refill rates are inexpensive and have the added benefit of providing information on persistence. Their accuracy depends on patients attending a single heath system with seamless electronic records.[3] Furthermore, the records may not reflect a patient's current disease status or medication-taking behaviour. Medication event monitoring systems (MEMS) record dispensation of medicines. They are accurate, provide detailed data on dosing times and patterns of non-adherence but are expensive and can suffer from malfunction. A majority of these devices are also currently limited to recording a single medication per container.

All these above methods suffer from a key limitation in that they are surrogate measures which do not equate to ingestion of medication. Hence, direct objective measures such as directly observed therapy (DOT) clinics have been used. In DOT clinics, patients ingest their antihypertensive medications sequentially at intervals under continuous observation by a nurse. This is an expensive process and can be potentially dangerous due to symptomatic hypotension developed by non-adherent patients further

to taking several powerful blood pressure lowering medications.[4]

Digital pills are a recent new innovation. These pills, developed by the company Proteus, are licensed for use in Europe and USA. The pills contain ingestible sensors that are activated by gastric juices in the stomach and a signal is emitted which is detected by a patch worn by the patient. The information can then be transmitted wirelessly. These are expensive and are currently in very limited use, and patient acceptance of this method is unclear.

We and others have developed a biochemical method using high performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) to assess non-adherence to antihypertensive medications in urine or blood.[5-8] Non-detection of medication in urine implies that it has not been ingested for at least four half-lives prior to the sample collection and for the majority of anti-hypertensive medications this is greater than 24 hrs. The impact on persistence is unclear and the method may be susceptible to tooth-brush adherence - i.e. patient taking the medications just prior to the clinic visit (akin to the behaviour of brushing teeth prior to a dental visit).

We set the method in 2011, starting with a test for a single medication, and sequentially expanded to the current full screen of more than 40 antihypertensive medications.[5] We receive samples from around 20 centres across the UK and have analysed more than 2000 samples to date. The method is reliable, robust and objective, being derived from forensic medicine. Our method requires 5-10mL of a random urine sample which can be transported by routine post and kept frozen until analysis. Samples are analysed in batches of 20.

There is a pre-analytical sample preparation step that requires around two hours of time for a mid-level laboratory technician. This is followed by analysis on HPLC-MS/MS. The run time is 30-40 minutes per sample (to detect all analytes). Subsequent to this, the results are interpreted by a senior technician and then authorised by a Laboratory Medicine Physician (Chemical Pathologist). The method requires relatively expensive instrumentation (~£200,000-£250,000) and significant technical expertise.

In our clinic, we request a urine sample from the patient on the day of their visit after verbal consent. The results are then discussed with the patient at their subsequent visit. We find that the objective result allows an open and non-confrontational discussion. It brings to the fore the patient's concerns about medication side effects and/or their beliefs that medications are not required given the asymptomatic nature of hypertension. We also address issues like polypharmacy, and address forgetfulness by recommending dossette boxes.

The test is repeated at subsequent visits and in our experience this improves the adherence status of the majority of patients in only two to three visits. Our experience for the last 5 years has been that there is widespread acceptance of the test by patients. The HPLC-MS/MS-based test is particularly useful to confirm non-adherence in patients with suboptimal blood pressure response to medications. We have demonstrated the utility of this test early in the diagnostic pathway to resistant hypertension to prevent unnecessary and expensive investigations.[9]

In summary, non-adherence needs to be routinely assessed in patients especially those with suspected pseudo-resistance. Objective methods are to be preferred and we suggest that biochemical testing if available, be used as the method of choice.

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- Pankaj Gupta, Prashanth Patel, Bryan Williams and Maciej Tomaszewski

Monitoring antihypertensive treatment by drug analyses – critical issues and ethical concerns

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Poor adherence to prescribed drug therapy is a common and potentially modifiable reason for inadequate treatment effects, not least in chronic and (usually) asymptomatic conditions like hypertension [1,2]. The introduction of invasive treatment by renal denervation for patients with resistant hypertension has prompted the need for exclusion of modifiable causes behind the persistently elevated blood pressures before subjecting the patient to the risks associated with renal denervation. Before considering renal denervation in a presumably resistant hypertensive patient the possibility to control the patients´ blood pressure with a regimen consisting of at least three drugs from different classes at optimal dosages should be ruled out whether the clinical setting is a trial or routine care. Adherence is an important issue in this context [1-4].

Long-term adherence to a complex treatment regimen is notoriously difficult to document. Interviews, pharmacy claims and electronic pill boxes are tools that yield some information but none of them actually prove that the drugs are taken as prescribed by the patient. Screening of the prescribed drugs or their metabolites in serum/plasma or urine has therefore evolved as an "objective" method for verifying adherence [3,4]. Finding drug/metabolite levels compatible with intake of appropriate dosages of the drug despite persistently elevated blood pressures would then support the contention that there is resistance to treatment. Absence of any of the analytes sought in the sample would argue for poor adherence as a causative factor behind the "resistant" hypertension. However, it is important to know the robustness of a negative result (drug levels missing or too low) and what the positive predictive value of a positive result (all drugs found) is. Furthermore, there are ethical issues that need consideration and which may also influence the meaningfulness of the testing.

An important issue is the "time window" that the drug/metabolite analysis covers. This is for most antihypertensive drugs rather short – probably one or a couple of days depending on the drug/metabolite in question, its excretion pattern in the patient (which can vary) and the sensitivity of the assay. In drugs of abuse testing urine samples are preferred (although the samples can be adulterated to hide drug intake) since measurable levels persist longer in urine than in blood. What are the detection times in blood or urine (with confidence limits) for the drugs tested, taking both the dosing and the interindividual variability in pharmacokinetics into consideration? Is urine or blood the best matrix for the analysis? The time windows will be rather short and the analysis will provide information of a "snap shot" nature rather than proving that the patient is adherent in the therapeutic sense. The "tooth brush" effect, i.e. taking the prescribed treatment before a visit to the doctor, is a well-known phenomenon which cannot be excluded with assays that measure recent drug intake only. Long term information could be obtained by repeated measurements, but the tooth brush effect will probably be encouraged upon repeated monitoring. The best method for bioanalytical documentation of long term adherence would be to measure drug/metabolite levels in hair, which would cover a time frame of months, but I do not know if that is feasible.

How should the patient be informed about the drug testing? Informed consent is mandatory whenever this is possible in a research project [5]. Should this not be the case also in routine health care? Using a sample for

reasons other than those disclosed to the patient is unethical and confrontation of patients with negative test results will no doubt endanger the patient´s trust of the doctor responsible for clandestine testing and, in the worst case, perhaps even of health care in general. A falsely negative result would be disastrous. If informed consent is obtained, when should this be? After sampling but before the analysis? Or before the sampling? In the former case the patient may feel that it is difficult to withdraw consent when the sample has already been taken. Regardless of the timing of the information, the possibility to obtain samples from unprepared patients will disappear after the first sampling. Most patients with "resistant" hypertension due to poor adherence will probably anticipate renewed testing and take their drugs before future visits, thereby avoiding negative test results even if they do not follow the therapeutic regimen between visits. The value of monitoring adherence by drug/metabolite analyses is thus limited for both analytical (detection periods) and ethical (informed consent) reasons. What are then the alternatives?

The key to good adherence and long-term persistence in a patient with hypertension lies in convincing the patient that taking the treatment as prescribed is in his/her best interest. The patient could become his/her own doctor and monitor the therapy with home blood pressure measurements. Electronic devices such as the MEMS monitor can be helpful for pedagogical purposes and pill boxes that remind the patient or a Dosette with dispensed medicines can help the patient remember to take the drugs. Repressive measures such as witnessed drug intake and monitoring drug intake by bioanalytical techniques should be handled with great care. Most importantly, the integrity of the patient should be respected by informing him/her adequately about the purpose of sampling and at the same time the doctor should recognize the limited value of "snap shot" testing, especially if it is performed repeatedly.

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- Paul Hjemdahl

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Award Winners: ISH Funding for Mentors and Organisations to Train Research Scholars in Hypertension Research

Fadi Charchar PhD FAHA

Chair, ISH Mentorship and Training Committee

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.

There is a critical need to establish and support high quality training programmes within low/middle income countries that can enhance the early careers of researchers in the basic science, clinical and public health areas of hypertension. To help meet this need, in 2016 the Society advertised that awards would be made available to mentors and organisations in low/middle income countries with the expertise and resources to offer fellowship training in hypertension disciplines to young investigators.

Further information on the application process can be viewed in the news section of the ISH website. **Click here**.

We are delighted to announce that ISH funding has been awarded to the three following projects for a maximum of two years.

ISH members who are leaders in the field have volunteered to support the mentors and mentees over the funding period. We would like to thank these mentors on this noble task. We are looking for another volunteer for project 2 and welcome the involvement of ISH members.

(1)

Project title: **Genetic risk factors of hypertension in Mongolia**

Mentor: Professor Tsolmon Unurjargal

Host organisation: Mongolian National University of Medical Sciences, Ulaanbaatar, Tuv, **Mongolia**

Scholar: Dr. Bolortuul Byambatsogt

ISH International mentor: Professor Brian Morris, University of Sydney, Australia

Dr. Bolortuul Byambatsogt

Professor Tsolmaon Unurjargal

(2)

Project title: **Role of mineralocorticoid receptor in experimental pre-eclampsia model**

Mentor: Professor Lawrence Olatunji

Host organisation: University of Ilorin, Ilorin, **Nigeria**

Scholar: Dr. Taofeek O. Usman

ISH International mentor: We are searching for expression of interests from international mentors. Please contact secretariat@ish-world.com should you be interested.

Professor Lawrence Olatunji & Dr. Taofeek O. Usman

(3)

Project title: **Identification of hypertension-susceptibility genes and pathways by a systematic multiple candidate gene approach: Sudan whole exome sequencing project for hypertension**

Mentor: Professor Dina A. H. Ibrahim

Host organisation: Central Laboratory, Ministry of Higher Education and Scientific Research, Khartoum, **Sudan**

Scholar: Dr. Wissal Ahmed Elhanbali

ISH International mentor: Professor Patricia Munroe, Queen Mary University of London, UK

Dr. Wissal Ahmed Elhanbali

Professor Dina A. H. Ibrahim

Our sincere thanks to the application reviewers from the (1) New Investigator Committee, (2) Mentorship and Training Committee and (3) Research, Science and Education Committee, to include: *Claudio Borghi (Italy), Sofie Browers (Switzerland), Fadi Charchar (Australia), Fady Hannah-Shmouni (USA), Krasimira Hristova (Bulgaria), Vanja Ivkovic (Croatia), Ruan Kruger (South Africa), Francine Marques (Australia), Daniel Piskorz (Argentina), Cesar Romero (USA), Richard Wainford (USA), Jiguang Wang (China), Michael Weber (USA), Brandi Wynne (USA) and Thomas Unger (Netherlands)*

- Fadi Charchar

Comment and reply on the article "Genetics of Blood Pressure – Still Hoping After All These Years" written by Stephen Harrap & Fadi Charchar

Conclusion of article: 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.

Comment

Olle Melander 1,2 (pictured left)

and

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In the February issue of Hypertension News, Stephen Harrap and Fadi Charchar launched a provocative paper entitled: "Genetics of blood pressure – Still hoping after all these years". The authors are well-known for their impressive mass of studies about the genetics of blood pressure and hypertension but in an in-depth analysis of the history of the genetics of hypertension underline all the unfulfilled promises of this research field in the genomic era concluding that "Hypertension is still waiting for genetics to deliver something really useful".

Even if all their criticisms are well-posed, and probably all the researchers in the field agree with many of their statements, the same authors respond to their own provocative criticisms by suggesting possible solutions: use molecular biology and physiology to dissect the mechanisms underlying the genetic associations now discovered with GWAS.

We could not agree more. However, what the authors forget to acknowledge is that delivery of almost one hundred blood pressure gene variants has provided us all (Harrap and Charchar included) with the keys to many completely novel physiological and pathophysiological pathways of blood pressure and hypertension *in humans*. Importantly, most of these physiological pathways, which are common in the population and could alter our hypertension susceptibility throughout life, had never been possible to identify with only physiological and molecular biology studies (in animals or humans)! Thus, exactly because of the unbiassed and unrestricted genome wide search, which Harrap and Charchar criticizes for not having delivered, genetics - and the GWAS in particular - has in fact fulfilled its promise in identifying completely new keys to mechanisms behind blood pressure regulation and hypertension susceptibility in humans.

Nonetheless, it is true that each of the individual gene variants confer very small effects on blood pressure. Could zooming in on the mechanism underlying single gene variants really be of any clinical utility at all given that the genetic effect is less than 1 mmHg per variant? Definitely yes. Let us rely on evidence from another cardiovascular risk factor, i.e. LDL cholesterol. In GWAS with identical strategy as those performed for blood pressure, 30 loci associated with LDL cholesterol were reported in 2010, one of which was a common variant of the

hydroxy-3-methylglutaryl coenzyme A reductase gene (HMGCR) [1]. The effect size of that variant was as miniscule as typical for blood pressure GWAS variants, in this case ~0.07 mmol/L of LDL cholesterol. However, had not statins already been discovered, it would have been an unforgivable and historical medical mistake not to mechanistically follow up the GWAS-guided HMGCR pathway as it, now proven, was a "genetic drug target key" for statins. Similarly, any of the small effect size GWAS signals for blood pressure, which Harrap and Charchar dismisses as clinically meaningless, could be genetic keys for a novel drugs with huge effects on blood pressure and cardiovascular risk, even if the genetic effect that guided us there was miniscule. This is certainly emphasized by Harrap and Charchar in arguing for more mechanistic studies of what we now have, but again, the multiple novel pathways highlighted by GWAS for blood pressure calls for some humbleness for the years of well-invested efforts by researchers who identified the variants in question.

Has too much money been invested in GWAS? In our opinion no. GWAS is, compared to many techniques, a cheap one. Collecting and phenotyping the cohorts that allowed GWAS to be applied on the blood pressure phenotypes have been much more expensive, but we believe Harrap and Charchar agree that collecting and phenotyping the underlying cohorts was worth every penny. GWAS itself must be considered as an extremely cost-effective use of tax payers and donors' research grant money. The cost-effectiveness was further optimized by some of the greatest investigator initiated world-wide collaborative networks that we have ever seen. One may ask if the individual contribution of each author in the resulting consortium papers is equal to an individual contribution of a regular paper with 5-6 authors or not. However, it is clear that these large and investigator-initiated collaborative studies with focused aims and clear methods were much more fruitful and cost-effective than many of today´s funding body-initiated networks with vague aims and large costs.

What about exome sequencing in large samples? Is it a repeated mistake, as Harrap and Charchar seem to indicate, or a natural next step? Without giving a firm opinion on that, let´s just parallel lipid genetics again. Identification of rare variants of the PCSK9 gene, which lower LDL-cholesterol and reduce risk of coronary heart disease (CHD), was the fundament for identification and development of PCSK9 inhibitors, now shown to protect against CHD [2, 3]. In addition, triglyceride lowering rare genetic variants of the LPL-inhibitor ANGPTL4 also associate with lower CHD risk, suggesting that ANGPTL4 inhibitors as a completely novel drug target [4]. Could exome sequencing studies of blood pressure be equally fruitful? Maybe and maybe not but giving up methods that have proven successful in related fields does not seem appealing to us.

Is the unfulfilled promise of genetics to be clinically relevant for the prediction of hypertension or cardiovascular events destined to be forever discarded? It is true that blood pressure genetic risk scores, as we define them today, even if strongly associated with BP and cardiovascular events, cannot add to the prediction and discrimination of hypertension or the consequent events. But we can object that, we could finally reject this still fascinating prospective, only after most of the genetic variants are discovered (both common and rare) together with the specific context where they act, their relative weight and their possible interactions with environment.

Indeed, myriads of well-known factors: baroreceptors, chemoreceptors and the macula densa, located at different sites in the circulation and endocrine, paracrine and even autocrine actions contribute to blood pressure variation inside the body. Moreover, profound environmental effects such as salt intake, diet (both quantity and quality), alcohol consumption, sleeping behavior, coffee intake, and emotional stress contribute to the complexity and we already have several classes of efficient antihypertensive drugs. Still, hypertension is one of the greatest contributors to premature mortality world-wide. Hypertension research must solve this. We are the first to agree with Harrap and Charchar that it is prime time for mechanistic and physiological studies to take advantage of the novel knowledge that GWAS has contributed with. However, we also believe that exome and whole genome sequencing in large samples must follow. Also implementing a better phenotyping process, by using more accurate methods to measure BP such as ambulatory blood pressure monitoring (ABPM), not only can lead us closer to the "real" individual blood pressure but can help genetics to improve its potential of discovery [5]. Closing doors to the development of genetics of blood pressure would be a betrayal to our children and grand-children. We are not only "still hoping", as Harrap and Charchar, we are very hopeful.

Continued on next page..

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-Olle Melander and Cristiano Fava

Response

Stephen Harrap[A] (Pictured above left)

and

Fadi Charchar[B] (Pictured above right)

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We appreciate that Olle Melander and Cristiano Fava took the time and effort to comment on our recent contribution to the ISH Hypertension News. Let's hope, with support and encouragement from our Editor Lars Lindholm and contributions from those prepared to enter into debate that the ISH Hypertension News might become a popular forum for open discussion on contemporary topics of interest in the world of blood pressure and cardiovascular disease.

In this spirit, we'd like to respond briefly to some key points raised by Olle and Cristiano. We'd hate to be seen as "closing doors" on genetic research. For us, it's a future of opening the right doors. We have opened the GWAS door and revealed a room full of potential riches. Reopening this door is adding little to our wealth. Let's pause to look closely at what we have found and try and really understand what it means. For example, in 2009 both the CHARGE[1] and Global BPGen[2] studies identified markers near the gene encoding cytochrome P450 17A1 (*CYP17A1*). This is a fabulous candidate for further study. But what have we learnt in the 8 years since? Sequencing around *CYP17A1* in 2014 confirmed the association with blood pressure and identified an upstream variant (rs11191416).[3] Yet there is still much uncertainty. What genomic and physiological functions does this polymorphism perturb? Other data suggests it alters expression in whole blood of a gene *NT5C2*, but its role in blood pressure remains entirely mysterious. Why are we not capitalising on such strong existing GWAS clues? The trickle of explanatory research stands in stark contrast to the ongoing flood of GWAS clues that now number in their hundreds. Perhaps blood pressure can learn something from lipid research, for it is from this domain that Olle and Cristiano had to turn for examples of adding real value to GWAS discoveries.

The transition from circumstantial evidence to proof is by no means easy. But with a redirected enthusiasm and appropriate allocation of resources we should be able to define the novel mechanisms by which hypertension develops and proffer new approaches to prevention and treatment.

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- Stephen Harrap and Fadi Charchar

Council's Corner: Hypertension Issues - a personal view

Nadia Khan

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Expanding the Workforce in Hypertension: A Focus on Pharmacists

Hypertension awareness and control remains sub-optimal globally, even in developed countries with universal access to health care and subsidization of medications[1,2]. The reasons for low awareness of hypertension and sub-optimal control of blood pressure are multifactorial and include limited access to health care[3]. Antihypertensive prescribing and hypertension management rests largely on the shoulders of primary care physicians. From the global health authority, physician to patient ratios range from as low as 0.02 physicians in Niger to 4.42 physicians per 1000 in Norway with 44% of WHO countries having <1 physician per 1000 patients[4]. Other key barriers include physician inertia and reluctance to treat the elderly to target, increasing comorbidity and complexity of patients, and patient non-adherence[3]. Physicians have limited time with patients to measure BP, evaluate for medication non-adherence, lifestyle modification counseling and institute medication changes. Novel approaches are needed to more efficiently and effectively improve BP control and expanding the hypertension work force is a strategy worth considering.

There is emerging evidence that optimizing the full scope of care of other health care professionals including pharmacists for team-based care may offer a solution to improving hypertension control. In North America, patients visit pharmacists 5 to 7 times more frequently than physicians, positioning pharmacists and community pharmacies as additional points of health care contact[5]. In a meta-analysis by Santschi et al., of 39 RCTs (n=14244 patients), pharmacist interventions were compared with usual care in the control of blood pressure[6]. The majority of trials evaluated pharmacy-led patient education, feedback and suggested medication changes to physicians, and medication management. Interventions were led by pharmacists in 23 of the 39 trials and conducted in collaboration with other health professional teams usually including physicians (16 trials). Patients were followed at outpatient clinics or by GPs. Overall, pharmacist interventions were associated with small to moderate lowering of blood pressure -7.6 mmHg (95%CI: -13.9 to -1.4mmHg) /3.9mmHg (95%CI: -9.9 to 2.0 mmHg). However, there was substantial heterogeneity in magnitude of BP lowering effect between studies and evidence of publication bias. In analyzing sources of heterogeneity, pharmacist-led care was associated with a greater magnitude of blood pressure lowering compared with collaborative care (-8.5 vs. -6.3 mmHg, p=0.046) but no difference in diastolic pressure.

A recently published trial further examined the effectiveness of a fuller scope of pharmacy interventions in 340 patients with diagnosed hypertension in Canada[7]. Patients were randomized to specially trained pharmacists who were able to independently prescribe antihypertensive therapy using the Hypertension Canada guidelines, in addition to counseling and reviewing medications compared with usual care. The primary care physician was always notified of any medication changes and patients continued to access their primary care physician. Pharmacists were responsible for follow-up and monitoring lab values. At 6 months, the mean difference in BP was 6.6mmHg (+/-1.9mmHg)/3.2

(+/-1.3 mmHg). More patients achieved target BP in the pharmacist intervention strategy compared with usual care (58% vs. 37%). These studies and others in middle-income countries[8], collectively indicate that expanding the hypertension workforce using team-based care is a promising strategy for improving hypertension control. Moreover, cost effectiveness analysis also indicates that team-based care with full scope pharmacy support is cost effective[9].

Challenges and Opportunities

Although these benefits were known for several years, incorporating widespread use of team-based care for hypertension has been challenging. Several countries, the Netherlands, Canada, and US for example, adopted expanded roles for pharmacists ranging from educating patients, medication reconciliation to independent prescribing, but uptake has been slow. Limited uptake of shared care is ascribed to lack of trust among physicians for pharmacists to expand their role, lack of experience and expertise by pharmacists in clinical care, insufficient environments for private patient examination, poorly defined prescribed roles for pharmacists, inadequate remuneration or time constraints of pharmacists to take on a health care role as they transition from product-centered to patient-centered activities[10].

Several strategies may help to mitigate these barriers and create sustainable team-based care. These strategies include ensuring sufficient communication and clinical training in pharmacy degree programs, development of hypertension curriculum and training programs for community pharmacists, achieving buy in and greater collaboration with the primary care community, development of platforms to improve sharing of health records between pharmacies and physician offices and ensuring appropriate remuneration for these activities[11].

Hypertension prevalence is growing globally and we need to implement new strategies to improve blood pressure control. Team-based models of care that leverage the full scope of pharmacists' and other health professionals' skills are an untapped solution whose time has come.

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- Nadia Khan

View Women In Hypertension Spotlight features

Joint Meeting of the Argentine Society of Hypertension (SAHA) and the Inter-American Society of Hypertension (IASH) is co-sponsored by the ISH, the Hypertension Council of the AHA and the American Foundation for Hypertension Research & Education.


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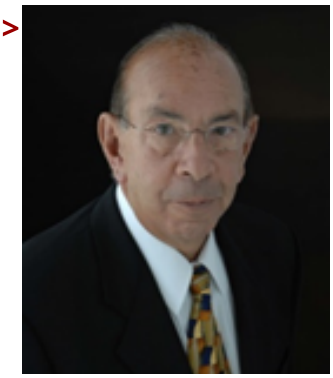

(3) >


(4) >

(1) Agustin Ramirez - ISH Council member & Chair Central & South America Regional Advisory Group, Buenos Aires, Argentina

(2) Cesar Romero - ISH New Investigator Committee Lead - Media & Communications , Troy, Michigan, USA

(3) Carlos M. Ferrario - President, IASH, Winston Salem, North Carolina, USA

(4) Nicolas Renna - IMBECU-CONICET Hospital Español, Mendoza, Argentina, Organizing Committee President

The annual scientific meeting of the Argentine Society of Hypertension (SAHA) was held in the city of Mendoza, Argentina from April 20th-23rd 2017. In the foothills of the Andes, the city of Mendoza and its surrounding areas are known worldwide as the gateway for climbers and mountaineers seeking to reach the slopes of the Aconcagua, the highest mountain in the Western and Southern Hemispheres. Equally important, Mendoza's gentle climate and fertile soil accounts for this area becoming the largest wine-producing region in Latin America.

Organized by Dr. Nicolas Renna (Organizing Committee President) and Dr. Roberto Miatello (Scientific Committee President) the meeting was an outstanding success, attracting a record of over 3,400 attendees representing all areas of cardiovascular medicine including practicing physicians, basic and clinical investigators, and nurses. The participation of the Inter-American Society of Hypertension (IASH) as the scientific co-sponsor of the meeting enriched the academic and clinical objectives of the SAHA's Congress by covering the travel expenses of 12 international leading clinical and basic science investigators from the USA, Canada, Mexico, Chile and the United Kingdom, and the granting of monetary awards to the three best posters presented by young Latin American investigators.

An international symposium, jointly organized by SAHA, the IASH and the ISH provided a venue for an up-to-date discussion of the merits of intensive blood pressure control based on the recent findings of the SPRINT Trial. The SAHA-IASH-ISH joint symposium, chaired by Dr. Daniel Piskorz (Argentina) and Dr. Agustin Ramirez (Argentina), had Dr. William Cushman (Memphis, TN, USA) as the leading presenter of the SPRINT Study. Dr. Cushman's presentation was followed by a further discussion of the SPRINT Trial Results in Special Populations by Dr. Henry Punzi (Dallas, TX, USA). Dr. Luis Juncos (Córdoba, Argentina) addressed the Impact of Intensive Control in Arterial Hypertension with a focus on Chronic Kidney Disease while Dr. Luis Alcocer (México City, México) discussed whether the findings of the SPRINT Trial are applicable in Latin America. Drs. Gabriel Waisman (CABA, Argentina) and Ernesto Schiffrin (Montreal, Canada) then presented the current status of therapeutic guidelines recommended by SAHA, the Canadian and ISH Hypertension Societies respectively. The superbly exciting symposium closed with a focus presentation by Dr. Maciej Tomaszewski (Manchester, UK) who outlined the factors associated with lack of adherence to antihypertensive treatment. The symposium was a great success; the highly lively discussion that followed the presentations provided a testimony to the potential importance of aggressive blood pressure control in terms of their applicability to Latin-American populations.

As part of the program, the IASH also co-sponsored with SAHA a symposium focusing on Tissue Hormone Systems

Implicated in Cardio Renal Remodeling. This symposium included presentations from Drs. Prieto (Tulane University, New Orleans LA, USA), Maria P. Ocaranza (Catholic University, Santiago, Chile), Jasmina Varagic (Wake Forest University, Winston Salem, NC, USA), Robson Santos (Federal University of Minas Gerais, Belo Horizonte, Brazil), Mariela Gironacci (Faculty of Pharmacy and Biochemistry, University of Buenos Aires, CABA, Argentina), Oscar Carretero (Henry Ford Hospital, Detroit, MI, USA), Gregory Fink (Michigan State University, Lansing, MI, USA) and Carlos M Ferrario (Wake Forest University, Winston Salem, NC, USA). The two sessions of this symposium were well-attended. Non-restricted grants provided by the AHA Hypertension Council, the American Foundation for Hypertension Research & Education and the ISH to the IASH provided the financial resources to accomplish this educational activity.

Altogether, more than 110 original abstracts were presented during the SAHA meeting, 35 of which were in an international competition organized by SAHA-IASH, AHA and ISH. Young investigators coming from Argentina, Brazil, Uruguay, Chile and the USA presented their work in an original electronic screen poster competition. Drs. Alexis Gonzales (Valparaiso, Chile), Cesar Romero (Detroit, MI, USA) and Diahnn Perdicaro (Mendoza, Argentina) received travel awards from the IASH as the best posters presented at this session. We congratulate all the participants. In addition, Dr. William Cushman was honored with the 2017 Lifetime Achievement Award by the IASH.

The proven collaborative efforts between the organizers of the SAHA meeting in Mendoza and the IASH sets a new example for future educational efforts whereby the activities of local hypertension societies are enriched through the participation of international scientists for whom the IASH, working in cooperation with the ISH, the Hypertension Council of the AHA, and the American Foundation for Hypertension Research & Education provide the financial resources to achieve these tasks. The experience gained from the Mendoza meeting underscores the vital role of the ISH in achieving these goals.

In Mendoza, Dr. Judith Zilberman was elected President of the SAHA for the next two years. She is the first woman to be elected to this position in the SAHA history. Dr Zilberman is a regular member of our society and an active member of the ISH research network "*Women in Hypertension*". We congratulate Dr. Zilberman and we wish her great success in this role.

Dr Judith Zilberman

President, SAHA

Sociedad Argentina de Hipertensión Arterial

- Agustin Ramirez, Cesar Romero, Carlos Ferrario & Nicolas Renna

Hypertension News is now registered to an ISSN

Dylan Burger

Canada

The editorial board is pleased to announce that Hypertension News is now registered to an International Standard Serial Number (ISSN) and can now be identified by the number "**2520-2782**". For those unfamiliar with the ISSN designation, it is an internationally recognized code that identifies Hypertension News as a serial publication. ISSN status provides several benefits to Hypertension News. Most critically, it registers our publication for easy identification worldwide which will increase exposure and assist libraries in cataloguing and archiving our content.

The ISSN can also be used as part of a citation for Hypertension News content. For example, to cite Prof Harrap and Prof Charchar's article from the February edition of Hypertension News:

Harrap S. and Charchar F. "Genetics of Blood Pressure: Still Hoping After All These Years." *Hypertension News*. 48. (ISSN: 2520-2782).

Finally, ISSN status is a first step to obtaining digital object identifiers (DOIs), alphanumeric codes that will provide a persistent link to all Hypertension News content. Establishing DOIs for Hypertension News contributions would greatly improve accessibility and better facilitate sharing of material. Accordingly this is a long-term goal of the Hypertension News editorial board.

For more information on ISSN registration visit: http://www.issn.org/

For more information on DOIs visit: https://www.doi.org/

Inter-American Society of Hypertension (IASH) joins ISH in Promoting Educational Activities in Argentina

Carlos M. Ferrario, MD, FAHA, FASH, FACC

President, IASH

The joint XXIV National Congress of the Argentinian Society of Hypertension (SAHA) and the XXI Biennial Scientific Sessions of the Inter-American Society of Hypertension (IASH) were held April 20– 23, 2017 in the city of Mendoza, Argentina, the gateway to the longest continental mountain range globally, the Andes. Carlos M Ferrario (IASH President), and Drs. Nicolas Renna (Organizing Committee President) and Roberto Miatello (Scientific Committee President) of the SAHA labored intensively to provide a joint program reflecting the common scientific and programmatic objectives in terms of fostering medical education and stimulating the incorporation of younger professionals aspiring to better serve patients through enhanced knowledge and medical research.

IASH, sponsoring an international session focusing on the SPRINT TRIAL and consequent revision of hypertension management guidelines, highlighted IASH's goal to facilitate educational access for international leaders in the field of hypertension and cardiovascular disease. The accompanying sessions, focusing on new developments in basic science and its applicability to clinical medicine, complemented IASH's objective of providing the best scientific learning experience to those wishing to expand their knowledge of hypertension mechanisms.

In accomplishing these educational goals, IASH is permanently indebted to the members of the ISH who through the award of traveling grants permitted the IASH to bring to the Mendoza meeting 12 international leaders in the fields of clinical and basic science research. With the collaborative active support of Dr. Maciej Tomaszewski (Manchester, UK), several hundred attendees participated in a joint session of the three sponsoring societies whereby the issue of intense blood pressure control in preventing cardiovascular events and renal damage were debated by Drs. William Cushman (Memphis, TN, USA), Henry Punzi (Dallas, TX,USA), Luis Juncos (Córdoba, Argentina), Luis Alcocer (México City, México), Gabriel Waisman (CABA, Argentina), and Ernesto Schiffrin (Montreal, Canada).

A timely analysis of Tissue Hormone Systems Implicated in Cardio Renal Remodeling was the subject of another two-day Symposium in which the joint efforts of the IASH and the ISH, together with support from the AHA-Hypertension Council and the American Foundation for Hypertension Research & Education, permitted leading investigators from the USA, Chile, Argentina, and Brazil to present their most important research discoveries in the field of cellular hormones. This Symposium included presentations from Drs. Prieto (Tulane University, New Orleans, LA, USA), Maria P. Ocaranza (Catholic University, Santiago, Chile), Jasmina Varagic (Wake Forest University, Winston Salem, NC, USA), Robson Santos (Federal University of Minas Gerais, Belo Horizonte, Brazil), Mariela Gironacci (Faculty of Pharmacy and Biochemistry, University of Buenos Aires, CABA, Argentina), Oscar Carretero (Henry Ford Hospital, Detroit, MI, USA), Gregory Fink (Michigan State University, Lansing, MI, USA) and Carlos M Ferrario (Wake Forest University, Winston Salem, NC, USA).

In addition, with the active participation of Dr. Maciej Tomaszewski, IASH and ISH granted Drs. Alexis Gonzales (Valparaiso, Chile), Cesar Romero (Detroit, MI, USA), and Diahnn Perdicaro (Mendoza, Argentina) with travel awards for the best posters from a total of 34 competing for these awards.

As IASH continues to pursue its educational mission across the American continents, the generous commitment of the ISH to assist us in the achievement of a common mission set an example in Argentina of how our two organizations could play a vital role in enhancing the academic and medical knowledge that is offered by local Societies with more limited financial resources. This partnership allows physicians and basic scientists in Latin America to have direct access to the knowledge possessed by leading clinical and basic scientists on a first-hand basis.

In the name of all the Organizing members of the joint scientific sessions of the SAHA and the IASH, we thank the ISH for their generous contribution to enhancing knowledge of hypertension.

- Carlos M. Ferrario

Facts about ISH membership

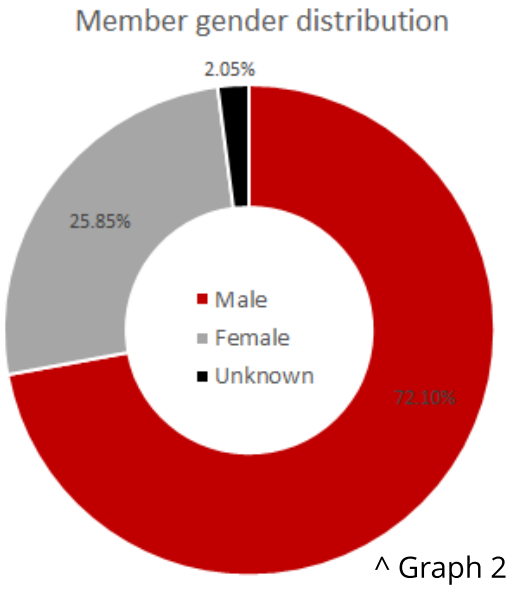
(updated 31.05.2017)

Graph 1 --->

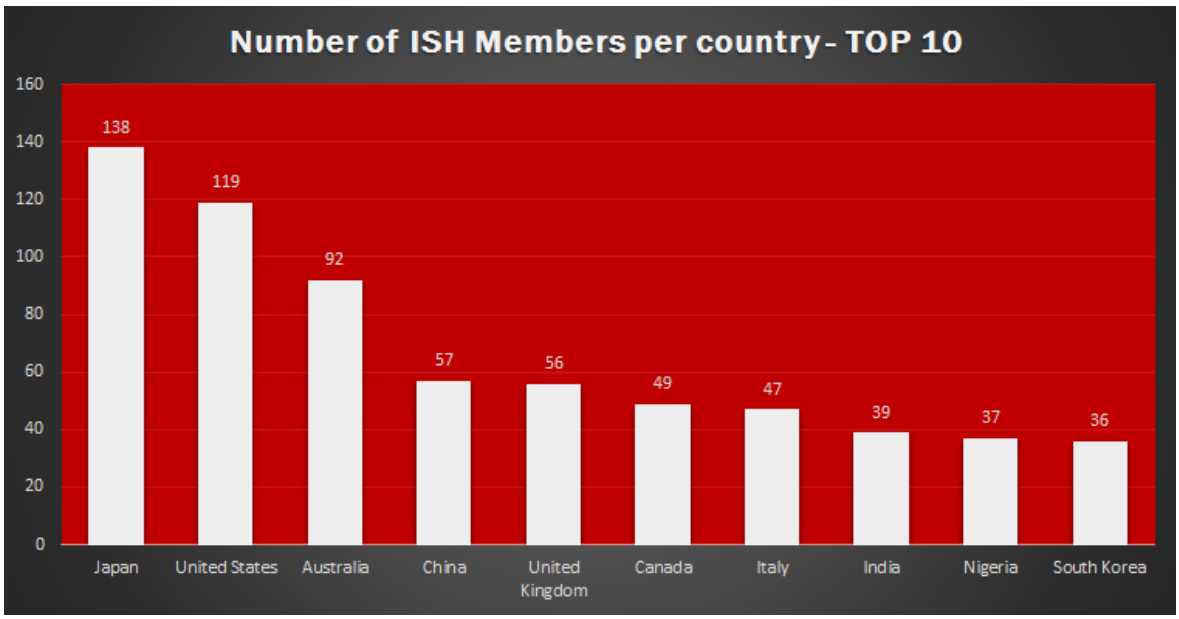
As mentioned in the Secretary's report on page 5, we thought it would be interesting for our readers to view more information on ISH membership statistics.

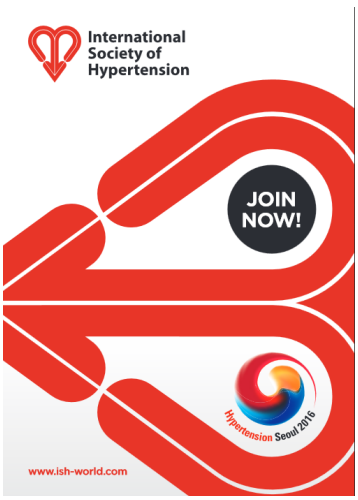
- Graph 1 shows the total number of members from 2016 - present (31.05.2017)
- Graph 2 shows the breakdown of ISH members by gender, indicating a quarter of our members consist of women.
- Graph 3 shows the top 10 countries in which our members reside

If there are any other statistics you would be interested in seeing in the next issue, please email membership@ish-world.com.



^ Graph 2





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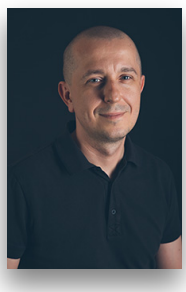

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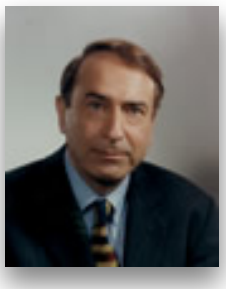

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China

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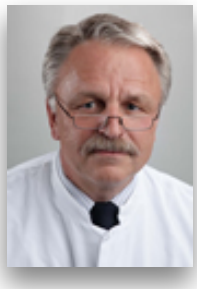
ISH Council members 2016 - 2020 continued

Ordinary Members of the Council

Claudio Borghi
Italy

Hermann Haller
Germany



Sadayoshi Ito
Japan

Nadia Khan
Canada

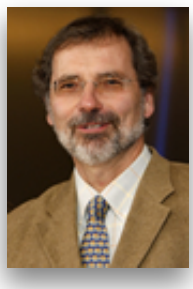
Cheol-Ho Kim
Korea

Yoshihiro Kokubo
Japan

Agustin Ramirez
Argentina

Markus Schlaich
Australia

Roland Schmieder
Germany



Thomas Unger
Netherlands

Richard Wainford
U.S.A

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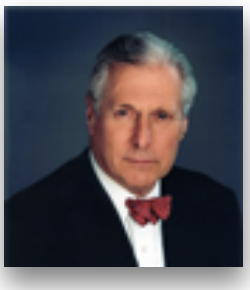
Ex-Officio Members of the Council

Louise Burrell
Australia

Daniel Lackland
U.S.A

Lewis Landsberg
U.S.A



Lars H. Lindholm
Sweden

Trefor Morgan
Australia

Josep Redon
Spain

Alberto Zanchetti
Italy

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ISH Corporate Members

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

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