International Society of Hypertension
HYPERTENSION NEWS
September 2015, Opus 42

Notes from the Editor
- Lars H. Lindholm

Again, it is my pleasure to present a new issue of Hypertension New to you, this time Opus 42, which is a rather comprehensive one. Let me first express my sincere thanks to all our contributors. This newsletter would not exist without your help!

Our policy is to edit your texts as little as possible and to keep your different spellings of English (e.g. British, American, or Australian) intact. However, sometimes I am afraid I have to shorten the texts..... Moreover, we do not include full papers published elsewhere. Instead, we comment on them under the heading "Hot off the Press".

The "Hot off the Press" section in this issue has six parts, two longer - on baroreceptor activation treatment and basic science - and four shorter ones. One of the latter is on the first communication from the Lancet's Hypertension Commission, where new voices are to be heard (page 5). Another on the impact of blood pressure of grief when the Australian cricketer Phillip Hughes was buried (page 6).

In every issue of Hypertension News, we have an Institute Focus. This time it is on Professor Enrico Agabiti Rosei and his excellent group in Brescia, Italy (pages 7-9). We also present four commissioned papers on i) Hypertension in Pregnancy (pages 11-13), ii) Statins and Myalgia: Fact or Fiction? (pages 13-15), iii) Pulmonary Hypertension (pages 15-16), and iv) Biochemical Testing for Non-Adherence to Antihypertensive Medications (pages 17-18).

On June 12-15, the European Society of Hypertension (ESH) organised their annual meeting, this time in Milan, Italy. The meeting was, as always, well run under the professional leadership of Professor Giuseppe Mancia and his group. In this issue of the Newsletter, he presents a report on the meeting (page 21-22) followed by two short reports from young ISH investigators, drs Ruan Kruger, Potchefstroom, South Africa (page 22) and Sofie Brouwers, Brussels, Belgium (page 23). There were about 3,500 participants at the ESH meeting and attendance was high. On page 24, we give an overview over the attendance at ISH meetings from 1982. We have extracted the figures from the ISH files with the help of Helen Horsfield at the ISH Secretariat. To me, it is obvious that at recent meetings the attendance was highest when the ISH and the ESH have had joint meetings!

Lars H Lindholm,
Editor, Hypertension News

Join us at the ISH Biennial Scientific Meeting in Seoul in 2016!

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From the ISH President - Rhian Touyz

ISH continues to be as busy as ever. Since our last newsletter, there have been a number of new initiatives and projects that I would like to share with you.

1. The ISH / Asian Pacific Society of Hypertension (APSH) Summer School that took place in Beijing, China was a great success, with more than 30 scholars in attendance from the region. Our hosts in China were very gracious and the ISH faculty (including Immediate Past President, Dr Ernesto Schiffrin, and New Investigator Committee representatives Dr Sofie Brouwers and Prof Fadi Charchar) were made to feel most welcome. This issue of the newsletter highlights the activities at the Summer school and already there are discussions about the 2016 Asia Summer School. Please see event reports on pages 19-21.

2. The new ISH committee related to 'Women in Hypertension Research' has now been officially created and in the next few months you will learn more about this very exciting programme.

3. The Africa Regional Advisory Group (RAG) under the leadership of Professor Basden Onwubere, will participate in an ISH-sponsored session on hypertension in the Pan-African Society of Cardiology (PASCAR) meeting in Mauritius later this year. Professors Alta Schutte and Brian Rayner, together with Professor Onwubere, will represent ISH. The Africa RAG is working on the 2016 Africa Hypertension teaching seminar, which hopefully will take place in Maputo early next year.

4. I represented ISH at the Global Meeting on Prevention of Cardiovascular Disease, recently held at the European Society of Cardiology (ESC) meeting in London. The meeting, organised by the World Heart Federation, discussed strategies for the 25:25 mission, and hypertension was identified as a top priority. As such ISH has a major role to play in helping to reduce cardiovascular disease by 25% by 2025. This will be further discussed in future ISH newsletters.

The current issue of Hypertension News provides further details of our recent activities. As you can see your leadership continues to work hard in realising the mission of ISH. We encourage feedback from our membership, so please contact us if you would like to contribute to future issues of the newsletter.

- Rhian Touyz

Membership Subscriptions 2015

Please note (as stated in the constitution): Membership shall automatically cease upon failure to pay the annual subscription fee for two consecutive years.

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Hot off the Press

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

Beneficial effects of baroreceptor activation treatment in chronic heart failure

Antihypertensive drugs lower blood pressure and reduce complications. However, many patients do not reach target blood pressure and non-pharmacological techniques to reduce blood pressure have attained recent interest. There is longstanding evidence both from experiments in animals and in humans to show that disruption of renal sympathetic nerve activity will reduce blood pressure [1]. More recently, early studies of catheter-based endovascular renal sympathetic denervation in patients with treatment resistant hypertension showed marked and sustained reductions in office blood pressure [2]. However, the evidence from randomised controlled studies to reduce blood pressure by renal denervation remains equivocal [3].

Another non-pharmacological means to reduce blood pressure in man is to interfere with autonomous vascular control by baroreceptor stimulation (baroreflex activation therapy) [4]. Typically, electrical stimulation technology is delivered by a device similar to a cardiac pacemaker implanted by a vascular surgeon on the carotid sinus on one side, which reduces sympathetic nerve activity and increases parasympathetic activity. A randomized placebo-controlled double-blind study with the first generation of such a device appeared to reduce blood pressure long term but the trial design and device methodology resulted in the study not achieving the prespecified endpoints for short-term safety and efficacy [5]. The next generation of baroreflex activation therapy system was designed to provide a simpler device and implantation procedure, and has been examined in hypertensive patients in only one open uncontrolled study of patients with resistant hypertension [6].

Chronic heart failure is another cardiovascular disease characterized by increased neurohormonal activation. Blockade of sympathetic and other neurohormonal mechanisms by drug therapy has been shown to translate into improvement in symptoms and prognosis. Thus, the report earlier this year by Abraham and collaborators on baroreflex activation therapy in heart failure is of great interest [7]. The study randomized 146 patients with New York Heart Association class III chronic heart failure and reduced ejection fraction to baroreceptor activation therapy and guideline directed medical treatment or to guideline directed medical treatment alone for six months and evaluated a primary safety endpoint (event-free rate of all system-related and procedure-related major adverse neurological and cardiovascular events) and primary efficacy endpoints (changes in New York Hear Association class, quality of life score, and six minute walk test). Patient characteristics were typical for subjects with advanced heart failure with reduced ejection fraction, and all patients were well treated. The mean age of the study population was 65 years, 14% were women, and co-morbidity with hypertension, atrial fibrillation, diabetes, and chronic kidney disease was common.

The system-related and procedure-related event-free rate was 86% and all but one event occurred within a week of the intervention and resolved with no remaining effects. The overall major adverse neurological and cardiovascular event-free rate was 97%. Patients tolerated baroreceptor activation therapy well. At six months New York Heart Association class, quality of life, and six minute walk test distance all clearly improved in the group with baroreceptor activation therapy, as compared to the control group (all $P < 0.005$). Also NT-pro-brain natriuretic peptide improved, and hospitalizations tended to be reduced favourably for the actively treated group. Important limitations of this study include the small study population and limited duration, and subsequently no statistical power to study cardiovascular outcomes. Furthermore, the study was not blinded, which may be of importance [8].

This well conducted study shows that baroreceptor activation therapy appears safe and well tolerated in patients with heart failure, similar to what has been observed with the second generation baroreflex activation therapy system in patients with resistant hypertension [6]. Furthermore, symptoms and signs, all shown to be associated with prognosis, improved by baroreceptor activation therapy. Of note, quality of life is a strong independent risk marker of prognosis in chronic heart failure [9].

These promising results in patients with chronic heart failure warrant further randomized controlled studies in patients with difficult to treat hypertension. The CVRx Barostim Hypertension Pivotal Trial has been registered with safety and reduction in office blood pressure at six months as primary outcomes. The results of some 310 patients randomized to baroreflex activation therapy and optimal medical treatment, or optimal medical treatment alone, are expected by the end of this year. The Nordic BAT Study is a randomized single-blinded controlled study in patients with resistant hypertension in the Nordic-Baltic countries with changes in ambulatory blood pressure at six months as primary outcome. Study recruitment started this year. The results of these and other studies are awaited.

- Thomas Kahan

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Hot off the Press

Bo Carlberg

Department of Public Health and Clinical Medicine,
Umeå University, Umeå, Sweden

The Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning Trial (DANTE)

There are very few (if any?) randomised controlled trials studying the effects of stopping antihypertensive treatment. Despite this, it is common to stop antihypertensive treatment in elderly patients, in particular in patients with cognitive impairment where low blood pressure could have theoretical adverse effects on cerebral function. However, the effect of stopping treatment has not been previously studied.

The Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning Trial (DANTE) included 385 patients above 75 years with mild cognitive impairment and treatment for hypertension with a SBP below 160 mm Hg. They were randomized to continue their treatment (control) with antihypertensive drugs or to a less intensive treatment (intervention). The study continued for 16 weeks. Blood pressure was 7.4/2.6 mm Hg higher in the intervention arm at the end of the study.

Discontinuation of antihypertensive did not improve any measures of cognitive functioning or functional status.

This is a study of short duration with negative results. It is possible that a larger study with longer follow-up could show different results. Importantly, a longer follow- up period is also necessary for studying the adverse effects of discontinuing antihypertensive drugs, like heart failure and other potential cardiovascular risks.

In clinical practice, antihypertensive drugs are often stopped in elderly people because of potential future risk for the patient. However, the benefits and risks of such actions are completely unknown. Hopefully, this study will inspire researchers to carry out randomized controlled trials of stopping treatment with cardiovascular drugs in the elderly.

- Bo Carlberg

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Hot off the Press

Bo Carlberg

Take the Pill!

A recent large case-control study, published in Hypertension, investigated the relationship between adherence to antihypertensive drugs and hospitalisation for heart failure. Patients were included when their first prescription of an antihypertensive drug was on dispensed. Adherence was calculated from PDC (proportion of days covered by treatment) during up to 7 years of follow-up. Thus, the number of days covered by dispensed drugs divided by the total number of days of follow up was calculated. High adherence was defined as a patient who was on dispensed antihypertensive drugs for more than 75% of the days. Very low adherence was defined as a patient who was on dispensed drugs for less than 25% of the days etc.

The cohort included 76,017 patients of whom 622 had been hospitalised for heart failure. Adherence to prescribed treatment was remarkably low. About 60% of the patients were on dispensed drugs for less than half of the days.

Table. The odds for being hospitalised for heart failure decreased with increasing adherence.
PDC: Proportion of days covered by antihypertensive treatment.

Adherence to antihypertensive drugs, PDC %	Distribution of cases with heart failure (%)	Odds Ratio for Heart Failure	95% CI
Very Low (≤ 25%)	46 %	1.0	Reference
Low (26-50%)	15 %	0.83	0.63-1.10
Intermediate (51-75%)	13 %	0.73	0.55-0.98
High (>75%)	26 %	0.66	0.52-0.83
		P trend < 0.001	

It is obvious that adherence to treatment is one of our most important challenges in drug treatment of hypertension. We have drugs. We know the effects. Take the pill!

- Bo Carlberg

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Hot off the Press

Lars H. Lindholm

Editor, Hypertension News

New voices to be heard on high blood pressure

The Lancet Commission on Hypertension

The Lancet has taken the initiative to launch a "Commission on Hypertension" with the aim of revaluating our understanding and treatment of high blood pressure [1]. This is a brilliant initiative! As far as I understand, there will be no sacred cows and previous dogmas will be challenged.

The Commission, which comprises about 20 young scientists from around the world, is led by Professor Michel Hecht Olsen from the University of Odense in Denmark. The Commission is not expected to produce new hypertension guidelines - we have more than enough of those already! The group has met twice and is expected to complete its report within a year. The Lancet recently appointed four very senior advisors and, needless to say, the report (about 25,000 words) will be thoroughly peer-reviewed before publication.

To me, the exciting part of this is that the members of the Commission can do this unencumbered by previous vested interest. Turning the stone, may reveal some surprising opportunities! We wish them the best of luck. It is quite a job they are undertaking.

- Lars H. Lindholm

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Hot off the Press

Lars H. Lindholm

Impact of grief on blood pressure

In a recent short report in The Medical Journal of Australia (MJA), Anastasia Mihailidou, Thomas Buckley, Alexandra Bunes, and Geoffrey Tofler from Sydney report on two female patients referred independently for ambulatory blood pressure (ABP) monitoring, as part of their clinical management [1]. Both watched the funeral of the Australian cricketer Phillip Hughes on TV whilst sitting down and wearing an ABP device. Although they had never met him, they reported "an emotional response" to the broadcast. One of the patients was treated with an Angiotensin II receptor blocker and the other with a beta blocker. Both had a systolic blood pressure (SBP) increase of 25 mm Hg during the funeral. Such increase of SBP – which reflects overall changes in the cardiovascular system at the time of emotional stress - is associated with increased cardiovascular risk. Interestingly, the first patient got a similar increase in SBP about one hour after the funeral when her dishwasher fell over.

Hence, emotions can increase SBP also if you are on blood pressure lowering treatment. Moreover, beta blockers don't block stressful stimuli as well as people often think. This report also highlights the potential health impact of grief delivered via media and is well worth reading and thinking about!

- Lars H. Lindholm

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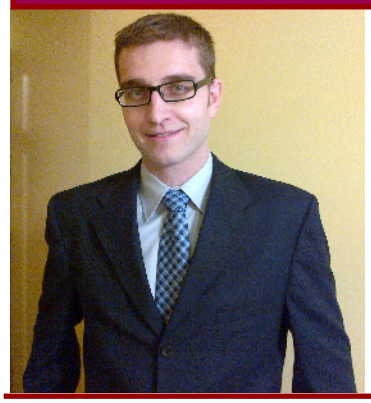
Hot off the Press



Dylan Burger

Ottawa, Canada /New Investigator and Communications Committee Member

Increased phosphorylation of the renal Na+-Cl- cotransporter in male kidney transplant recipient patients with hypertension: a prospective cohort

Rojas-Vega L et al. (2015) Am J Physiol Renal Physiol

While calcineurin inhibitors (i.e. cyclosporine, tacrolimus) are highly efficacious agents that reduce acute rejection rate in renal transplantation, their use is also associated with risk of developing hypertension [1]. These side effects often resemble familial hyperkalemic hypertension (FHH), a genetic disease arising from mutations in WNK kinases and characterized by overactivity of the renal sodium chloride cotransporter (NCC). Consistent with this, experimental evidence suggests that alterations in NCC play a causal role in calcineurin-inhibitor-mediated hypertension [2].

In this study (currently available ahead of print in the American Journal of Physiology- Renal Physiology), Rojas-Vega and colleagues sought to determine whether levels of NCC are increased in transplant recipients that develop hypertension [3]. To gain insights into NCC expression and activation, the authors examined NCC protein levels and phosphorylation levels in exosomes isolated from urine samples. Exosomes are small (40-100 nm) cell-derived vesicles that are released into the extracellular space and can be found in all biological fluids. They retain many of the properties of the cells from which they originate and because of this are emerging as potential diagnostic tools that may provide insights into the physiological status of a tissue or biological system.

The authors examined adult kidney transplant recipients receiving tacrolimus as part of immunosuppressive therapy and explored the relationship between urinary exosome NCC levels/activity and the development of hypertension. The authors observed that NCC levels in urinary exosomes were approximately 1.7-fold higher in male patients that developed hypertension than those that remained normotensive. Similarly, phosphorylation of NCC (a measure of channel activation) were increased approximately 1.5-fold compared with male patients that remained normotensive.

While the results that the authors present are interesting and consistent with animal studies, there are a number of limitations to consider. First, the relatively small number of patients limited the scope of the analysis. In particular, due to the low incidence of hypertension in female recipients (3 of 17), the authors were not able examine NCC changes in female transplant recipients.

In addition, a correlation between exosomal NCC levels and levels in the distal tubule is not assessed here and would be difficult to establish with the experimental design used. It is worth noting that correlation between exosomal and tissue NCC levels has been established in animal studies [4], however it will be critical to establish this relationship for exosomes to have true diagnostic potential. Finally, as the authors acknowledge it is

difficult to establish a causal relationship between tacrolimus and the development of hypertension; particularly as a population of patients that did not receive tacrolimus was not available for study (all patients at their institute receive tacrolimus as part of their immunosuppressive regimen).

Nevertheless the major strength of this study is its novel approach to non-invasive assessment of molecular changes in the transplant population. The authors have demonstrated feasibility in assessing urinary exosome protein levels and this may ultimately serve as a surrogate measure of molecular changes in the kidney. While it will be important to establish strong correlations between exosome and tissue protein levels, this approach has broad applicability and could lead to further studies aimed at obtaining molecular insights that would normally require biopsy.

- Dylan Burger

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Institute Focus

Enrico Agabiti Rosei

Hypertension Excellence Center
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Excellence in research, teaching and clinical practice in the field of hypertension has a long lasting tradition in Italy. We established our activity in Brescia in the mid-seventies, after moving from the University of Perugia. The University in Brescia was founded in 1982, when it became independent after having been part, at least as a Medical School, of the University of Milan for many years. The former Director of the Clinica Medica of the University of Brescia, where the clinical, educational and research activities in hypertension are based, was Professor Giulio Muiesan, who passed away at the beginning of 1990, and from that date till the present time the Director has been Prof. Enrico Agabiti Rosei.

The clinical work of the University Institute of Clinica Medica and its Hypertension Excellence Center (HEC) is performed within the Spedali Civili of Brescia. This is a public hospital (1,500 beds) with a long and glorious history starting from the end of the fifteen century and now one of the largest in the country. It has been ranked in one of the top 5 positions for quantity and quality of health activities over the last few years.

Clinical activities

The University Centre for the Study of Hypertension and Cardiovascular Risk factors (Hypertension Excellence Centre, HEC) is within the large Division of Clinica Medica (100 beds, including sections of Endocrine and Metabolic diseases, Emergency Medicine, Respiratory Medicine) in the Hospital Department of Medicine, chaired by E. Agabiti Rosei. It has access to all the general resources of a large hospital, including all the medical and surgical competences and modern imaging and laboratory facilities.

In particular, HEC is dedicated to the prevention, diagnosis and treatment of hypertension and cardiovascular disease. It includes a laboratory for noninvasive cardiovascular assessment (Prof. ML Muiesan/Prof. M Salvetti), a Laboratory for vascular structural and functional evaluation (Prof. D Rizzoni), a Laboratory of Molecular Medicine (Prof. M Castellano). Investigations supported by these laboratories permit the precise evaluation of early cardiovascular alterations in hypertension, the diagnosis of secondary forms of hypertension, the monitoring of several hemodynamic signals, the assessment of genetic mutations responsible for many diseases related to hypertension.

The Centre is recognized as a referral clinical centre for evaluation and treatment of resistant hypertension and secondary hypertension (particularly pheochromocytoma and Conn's syndrome), as well as rare vascular diseases.

Research activity

Research work has been quite productive, with a constant scientific output over the last 4 decades, and results have been published in the most important scientific journals dedicated to cardiovascular and metabolic medicine. A translational approach has been usually applied, from bench to bedside, from basic and experimental studies to human pathophysiological and clinical investigations.

A research topic of major interest has been the evolution of clinical and preclinical cardiovascular structural and functional alterations in hypertension and in metabolic diseases, including:

i) Structural and functional abnormalities in hypertensive heart disease, also in relation to the effect of anti-hypertensive treatment. Among the results obtained are the first demonstrations of the prognostic value of regression of left ventricular hypertrophy (LVH), of changes of LV geometry and of inappropriate LV mass.

ii) Clinical and prognostic significance of carotid intima-media thickness and plaques, also during treatment.

Special interest has been dedicated to new technological approaches such as 3D echocardiography, videodensitometry, radiofrequency, strain rate for early detection of structural and functional abnormalities.

iii) Study of microvascular structure and function of small resistance arteries, using wire- and pressure-micromyography techniques, in primary and secondary hypertension as well as in diabetes and obesity, before and during treatment. Studies have been also performed in animal models of hypertension. Among the main results obtained is the first demonstration of the prognostic significance of media to lumen ratio of small resistance arteries, the detection of severe alterations of the microcirculation in diabetes and in obesity, even in absence of hypertension, and the effect of treatment. The results of this research work deserved several awards, including a prize for the best paper published in "Hypertension".

Recently, interest has been focused on noninvasive approaches to the evaluation of microvascular structure, including capillaroscopy, videomicroscopy and techniques for the evaluation of the morphology of retinal arterioles (scanning laser-doppler flowmetry, adaptive optics, with quantification of wall to lumen ratio), all extremely promising for a more precise stratification of cardiovascular risk in hypertensive patients.

Recently, research in this field has focused on the role of perivascular fat in the release of anticontractile factors in humans and in animal models. Interrelations between mechanical properties of large arteries and microvascular alterations before and during treatment have been recently demonstrated, giving strong support to the concept of the fundamental importance of the cross-talk between large and small arteries.

iiii) Since 1988 members of HEC and the Laboratory of Molecular Medicine have been engaged in research activities on the molecular biology and genetic epidemiology of hypertension. They have investigated molecular mechanisms and genetic bases of primary and secondary hypertension, including those underlying the development of target organ damage. This line of research has critically examined the role of common genetic polymorphism and more recently focused on the search of rare mutation responsible for mendelian forms of hypertension. The Laboratory of Molecular Medicine has developed a diagnostic procedure of next generation sequencing for the systematic screening of pheochromocytoma patients and participates in several collaborative projects investigating genetic forms of hypertension, including the Pheochromocytoma/ Paraganglioma Working Group of the European Network for Adrenal Tumors (ENS@T).

The Centre has participated in the European Community Project "Ingenious Hypercare", integrating Genomics, Clinical Research, and Care in Hypertension, financed by the sixth Framework Programme, and is also part of the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group and of the CADISP Group (Genetics of Stroke Cervical Artery Dissection and Ischemic Stroke Patients).

Prof E Agabiti Rosei has initiated and is responsible for an ongoing epidemiological study in an area of East Lombardia (VOBARNO Study). This was started more than 20 years ago with the aim of assessing the evolution of organ damage (ultrasound assessment), blood pressure (ABPM) and cardiovascular events as related to CV risk factors and genetics in a middle aged/elderly population. Scientific relations have been established with several European and American Institutions, based on the exchange of researchers and collaborative studies, i.e. University of Manchester, UK, Mc Gill University, Montreal, Canada, University of Paris Descartes, Paris, France, University of Maastricht, The Netherlands.

International and National Learned Societies

The Hypertension Excellence Center of the Brescia University Hospital has participated in several multicenter trials conducted in Italy and in Europe (HOT, ELSA, SYST-EUR, VALUE, ONTARGET, RACE, MORE, SHOT, SCOPE, ARAPACIS, REPOSI).

Members of the Hypertension Excellence Center are active members of the Italian Society of Hypertension (SIIA) and of ESH.

Enrico Agabiti Rosei has been President of the Italian Society of

Institute Focus

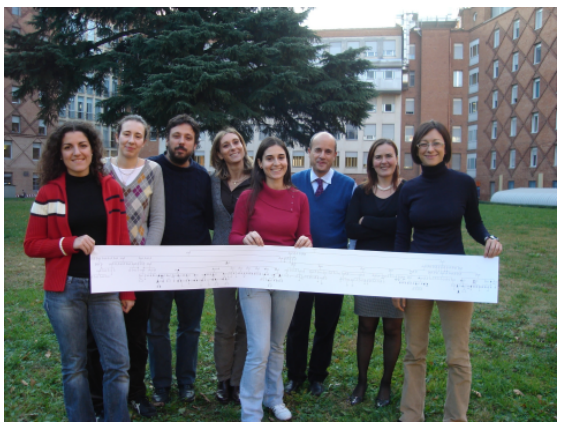
Hypertension and, after being a member of the Scientific Council of the ESH, became the current President of the European Society of Hypertension in June. He has been chairman of the European Society of Cardiology Working Group (ESC WG) on the Heart and Hypertension and is the chairman of the ESH WG on Heart, Arrhythmias and Thrombosis. He has also been a Member of the Science Council of the ESC and of the Executive Committee of the European Council for Cardiovascular Research. He is a Member of the Scientific Council of the Italian Society of Hypertension (ex officio), of the Italian Society of Internal Medicine (SIMI) and of the Italian Society of CardioNephrology.

M Castellano and ML Muiesan have been members of the Council of the Italian Society of Hypertension, D Rizzoni is a member of the nucleus of the ESC Working Group on Peripheral Circulation and of the Executive Committee of the European Council for Cardiovascular Research. M Castellano, M Giacchè, L Mori and A Panarotto are involved in the European Network for the Study of Adrenal Tumors and the International Familial Pheochromocytoma Consortium Research Group. A Paini and ML Muiesan are members of the Artery Society Council.
All Members of the Brescia Excellence Centre have been involved in the organization of symposia, teaching courses, seminars and lectures. Every two years since 1991 a Satellite Symposium of the Scientific meeting of the ESH has been organized in Brescia (13 editions in total).

Teaching activity

The Director and all those who are responsible for the Research Laboratories are also part of the academic staff, as Professors at the University of Brescia. Therefore, HEC is actively involved through its members in a number of educational activities at different levels, including college students of Medical School and other health activities (dietitians, sports and physical activities sciences, etc), postgraduate students of several residency programs, physicians and other health professionals. Such activities include lessons, seminars, interactive courses, meetings at local level or endorsed by national and international cardiovascular Societies, an Italian inter-university Master Course in "Arterial Hypertension and Cardiovascular Prevention", an International PhD Program in Arterial Hypertension and Vascular Biology. In addition, the Center organizes several meetings each year which are open to the general population. These are attended by hundreds of participants and cardiovascular risk factors are individually assessed and appropriate counselling is offered.

- Enrico Agabiti Rosei



Neil Poulter - New President-Elect of ISH

Professor Neil R. Poulter *(pictured right)* was made President-Elect of the ISH at the recent Council meeting in Milan. He will be President from September 2016 to October 2018. Neil Poulter is the current chairman of Preventive Cardiovascular Medicine at Imperial College London, UK and the Co-Director of the Imperial Clinical Trials Unit.

He has lived and worked in Africa, the Caribbean and Australia and has coordinated many multinational studies. Hence, he is a truly global researcher who has published about 400 papers, mostly on high blood pressure issues. Neil Poulter intends to focus on the promotion of two key areas:

Firstly, enhanced **implementation** of what we already know about how to improve blood pressure control globally.

Secondly, how to fill the gaps in our knowledge concerning what **combination of drugs are optimal** for blood pressure lowering and cardiovascular disease prevention in each of the world's major ethnic groups.

Neil Poulter is a learned and respected colleague and a good friend of many of us. He has a very high integrity, good common sense, and a lovely sense of humour. I believe, he will make a very good President of ISH.

- Lars H Lindholm

"Working together for better BP control and CVD reduction"

Hypertension Seoul 2016

The 26th Scientific Meeting of the International Society of Hypertension
in collaboration with the 12th Congress of the Asian Pacific Society of Hypertension (APSH)
the 25th Annual Scientific Meeting of the Korean Society of Hypertension (KSH)

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Awards

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Key dates

Abstract Submission Deadline	February 29, 2016
Notification of Acceptance	April 30, 2016
Early Bird Registration Deadline	May 31, 2016

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Hypertension in Pregnancy

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1. The hypertensive syndromes of pregnancy

A blood pressure of 140/90 mm Hg or more is found in about 20% of all pregnancies. Because of the increasing tendency amongst women to start a family later in their reproductive years and the rising prevalence of obesity, hypertension is becoming more common.

1a. Pre-existing hypertension

If raised blood pressure is confirmed before 20 weeks gestation the patient is assumed to have pre-existing hypertension even if no pre-pregnancy blood pressure readings are available. Depending on age, hypertension is seen in up to 15% of pregnancies. Five percent of these will be due to secondary, usually renal hypertension. The remainder are classified as having essential hypertension. The poor outlook in women with chronic hypertension in pregnancy has generally been under-recognised; their peri-natal mortality is around 40/1000 births, about four times that all pregnancies (1).

1b. Hypertension after 20 weeks gestation

About 10% of women whose blood pressures were normal in early pregnancy develop a sustained rise after 20 weeks gestation. Of these, up to half will have pre-eclampsia; the remainder are classified as having gestational/pregnancy-induced hypertension. There is increasing evidence that gestational hypertension is not an innocent condition and may represent an early or mild form of pre-eclampsia.

1c. Pre-eclampsia/eclampsia

The criteria for the diagnosis of pre-eclampsia have been amended recently to reflect the clinical presentation of the disease. Dipstix proteinuria is not a reliable investigation which may not be confirmed on rechecking or may be due to contamination, urinary tract infection or underlying renal disease. Proteinuria should be quantified with a spot urinary protein to creatinine ratio (PCR). A level of 30 mg/mmol or above is abnormal. Recently revised criteria for the clinical diagnosis of pre-eclampsia comprises new onset hypertension with new onset proteinuria and/or a rise in serum creatinine to 90 µmol/L or more and/or a rise in serum aspartate aminotransferase to twice the upper range of normal and/or a fall in platelet count to less than 100,000/dL (2)

In cases of severe pre-eclampsia/eclampsia patients usually have varying symptoms and signs including headaches, right upper quadrant pain, hyper-reflexia, clonus, altered mental state, persistent visual scotoma, blindness or stroke. There may also be evidence of disseminated intravascular coagulation, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), utero-placental dysfunction and intrauterine growth retardation.

1d. Pre-eclampsia/eclampsia complicating pre-existing hypertension

Around 25% of women with pre-existing hypertension develop super-added pre-eclampsia. There is no convincing evidence that antihypertensive therapy at any stage of pregnancy prevents the development of pre-eclampsia.

1e. Post-partum pre-eclampsia

A previously rare under-recognised hypertensive complication of pregnancy is post partum *de novo* hypertension which may be accompanied with proteinuria, thrombocytopenia and raised serum aspartate levels (4). The mechanism of post-partum hypertension is uncertain but clearly cannot be due to placental ischaemia.

2. Treatments

2a. Aspirin

There is reliable trial evidence that aspirin 75 mg daily is of value in high-risk pregnancies, reducing pre-eclampsia rates by up to 17%. Thus aspirin should be prescribed to women with a history of hypertension in previous pregnancies, those with pre-existing hypertension as well as women who have experienced early onset (<34 weeks gestation) pre-eclampsia in a previous pregnancy. Aspirin is also recommended for women with pre-existing type 1 or 2 diabetes mellitus.

2b. Thresholds for antihypertensive drug therapy

There is no consensus on the threshold for prescribing antihypertensive drugs in pregnancy or the targets to which pressure should be reduced. It is probably prudent to consider treatment if the clinic blood pressure persistently remains above 160/90 mm Hg. There are few randomised placebo controlled trials of antihypertensive drugs in pregnancy. Those available suggest methyldopa and labetalol are equally ineffective at preventing pre-eclampsia, placental abruption or small for gestational age babies. Whilst there is no evidence that blood pressure reduction benefits the fetus, the mother may benefit in terms of prevention of severe hypertension (5).

2c. Choice of antihypertensive drugs

All antihypertensive drugs and particularly the beta-blockers are associated with some reduction in birth weight. Both methyldopa and labetalol are used in all stages of pregnancy. Both drugs are effective and safe but there has been some reluctance to prescribe methyldopa because of the theoretical risk of postnatal depression. There is limited information on the calcium channel blockers in

pregnancy and they may aggravate the tendency to develop ankle swelling. Nifedipine is a reasonable choice of therapy in women whose blood pressure remains above 160/90 mm Hg despite the use of methyldopa with labetalol. Calcium channel blockers may also be suitable first line drugs in women of African origin.

Angiotensin converting enzyme inhibitors are absolutely contraindicated in pregnancy as there are several reports of an increased frequency of severe developmental anomalies. It is prudent to prescribe and use alternative drugs where necessary in women who are planning a pregnancy. However if this is not possible, such as in type 1 diabetes, both ACE inhibitors and angiotensin receptor blockers must be stopped as soon as pregnancy in confirmed. Thiazide diuretics are rarely used now because of the theoretical risk of further reducing central intravascular volume in women with pre-eclampsia. The alpha blockers are rarely used in pregnancy and are best avoided as they can cause urinary stress or urge incontinence.

2d. Blood pressure targets

The target blood pressure in pregnancy remains uncertain but there is now evidence that lowering the diastolic blood pressure to 85 mmHg or less confers no extra benefit when compared to a target of 100 mmHg. (Fig 1) Women who are treated more aggressively do achieve lower blood pressures and fewer episodes of severe hypertension, but there were no differences in pregnancy outcomes including super-added pre-eclampsia. All women who have a blood pressure consistently above 160/90-100 mm Hg should be given antihypertensive therapy.

Excessive or sudden blood pressure reduction should be avoided. One of the aims of treating hypertension in pregnancy is to avoid pre-term delivery, particularly before 37 weeks gestation. The only "cure" for pre-eclampsia is to deliver the baby but induction of labour before 37 weeks is associated with an increased risk of adverse fetal outcomes. A risk/benefit analysis must be undertaken when deciding on delivery before 37 weeks gestation.

2e. Severe pre-eclampsia/eclampsia

The management of severe pre-eclampsia or eclampsia is the responsibility of obstetricians working in maternal high dependency settings so this topic is not covered in detail here. Randomised controlled trials have clearly shown that magnesium sulphate should be given in cases of severe pre-eclampsia and eclampsia to prevent and treat seizures. Methyldopa, labetalol and nifedipine should be continued by mouth. Intravenous labetalol infusions or hydralazine by slow intravenous injection may be necessary if the blood pressure remains high. Induction of labour before 37 weeks may be indicated if there is evidence of foetal compromise or high maternal risk.

3. Follow-up

3a. Immediate follow-up

Post-partum hypertension should be managed along similar lines as hypertension in pregnancy. Usually however the blood pressure settles to normal without drugs over 2 to 6 weeks. If the pressure remains above 140/90 mm Hg after 6 weeks then it is probable the patient has chronic hypertension and requires further investigation. Women who developed pre-eclampsia are at increased risk of developing it again in future pregnancies and should be advised to seek early medical care. They should be informed of other risk factors including obesity, grand multiparity, and future pregnancies by a new partner.

3b. Long-term follow up

There is increasing evidence that women with a history of eclampsia, pre-eclampsia as well as gestational hypertension are at greater risk of developing essential hypertension and its complications of heart attack or stroke in later life (6). The mechanisms of this increased risk are uncertain but women should be advised to have their blood pressure checked at least five yearly for the rest of their life. They should also avoid becoming overweight or obese and to keep their salt intake below 6 g daily.

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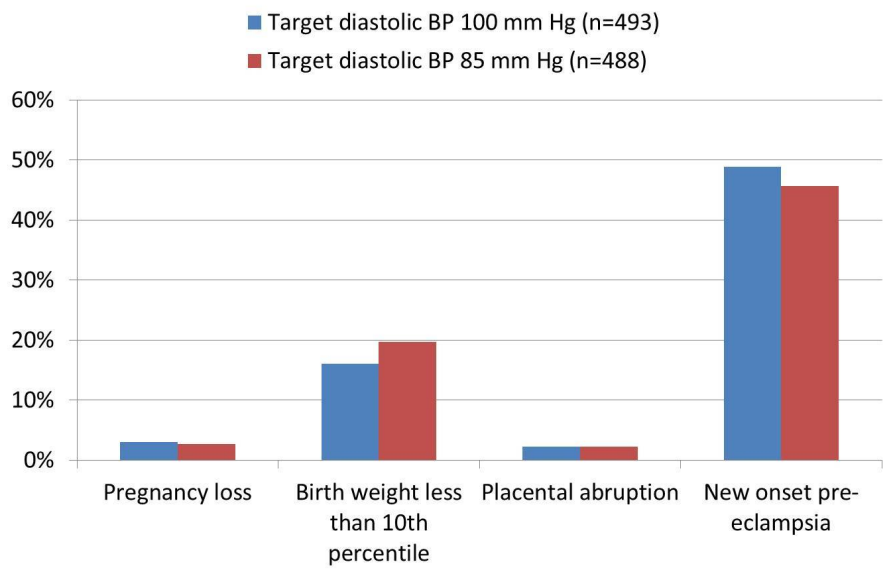

Figure 1. Results of the Control of Hypertension in Pregnancy Study (CHIPS), Ref 5. No significant differences were found in pregnancy outcomes with tight control of blood pressure compared with less tight control

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Statins and Myalgia: Fact or Fiction?

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Up to 40% of patients with hypertension take a statin[1] and the proportion will increase. Contemporary guidelines have lowered the threshold for statin use in primary prevention (7.5% risk of a cardiovascular event over 10 years in the USA,[2] 10% risk according to NICE guidelines in the UK).[3] Applying these thresholds, most middle aged and elderly hypertensives will qualify for statin use. Countering the more widespread uptake of statin use in primary prevention advocated by these guidelines are claims, popularised by the lay press and uncritically published in some medical journals,[4,5] that statin use is accompanied by an unacceptable incidence of side effects that adversely compromise lifestyle and which challenge whether the small absolute benefits in some lower risk groups are worth the intolerance of the statin. So what are the facts? Before discussing the data it is important to distinguish between severe muscle related events (myopathy and rhabdomyolysis) and less severe muscle aches and pains (myalgia) - the former being associated with marked elevation in creatine kinase levels, in contrast with the latter, which is not. All statins can cause myopathy, but the incidence is low - about 0.1%. This compares with an incidence of about 0.04% on placebo. Rhabdomyolysis is much rarer .[6] Preclinical studies show that statins decrease mitochondrial function, attenuate energy production and alter muscle protein degradation thereby providing a mechanistic explanation for a potential link between statin use and muscle symptoms. Moreover, an increased frequency of rare pathogenic variants in muscle disease-associated genes has been reported to be associated with a substantial increase (up to 20 fold) in subjects with severe myopathy.[7,8] Pharmacokinetic interactions of statins with inhibitors of cytochrome P450 isoenzymes will also increase the risk of myopathy.

There is, however, no evidence that these molecular mechanisms are responsible for the more generalised aches and pains, without evidence of creatine kinase elevation, reported in clinical practice.

The critical debate arises from the discrepancy between the outcomes reported from randomised, double blind, placebo-controlled trials and observational data on less severe muscle symptoms (myalgia) in everyday clinical practice.

Let us first consider the trials. Most trials report severe adverse drug reactions and withdrawals from drug treatment where, with the exceptions noted above for myopathy, there is no difference in safety outcomes for statin treatment and placebo. Few trials have, however, adjudicated non-serious AEs. Two trials have systematically reported muscle symptoms. In the Heart Protection Study[9] muscle symptoms were recorded after direct questioning at each visit. 6% of patients in both the simvastatin group and the placebo group reported muscle aches or pains at each visit and 33% of patients in each treatment group reported similar symptoms at least once during the study. In JUPITER[10] the incidence was somewhat lower but similar in both statin and placebo treated arms of the trial .

Certain criticisms of the trials have been raised. First - few trials have reported and adjudicated AEs. This is not required by regulatory bodies. The number of such events - more than 300,000 in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), is large and few trialists have subjected them to systematic evaluation. Second - in some trials apparently statin intolerant patients were excluded following a pilot run-in on statin. Third - that trial sponsors could have influenced the reporting of the results of trials and downplayed the side effect profiles of the drugs.

Observational studies contrast dramatically with the outcomes of controlled trials. 10-20% or more of patients taking a statin have been reported to complain of muscle related side effects - pain or weakness (myalgia).[7] The causal association of these symptoms with statin use has not, however, been established. Regrettably certain authors.[4,5] have deliberately misrepresented the claims of Zhang and colleagues[11] that statins were causally related to side effects in 20% of cases. Zhang *et al* reported on discontinuation of statins in routine clinical practice in a large cohort of over 100,000 patients. Statin *related* events were documented in 17.4% of patients, but more than 90% of those who were rechallenged with statin were taking a statin 12 months after the related event. Zhang and colleagues concluded that many of the statin- related events had other causes and this is consistent with the view that non pharmacological mechanisms are responsible for the intolerance.

In a separate study reported recently,[12] rechallenge of patients previously withdrawn from a statin because of myalgia, was associated with the return of identical symptoms in both statin and placebo treated patients. A further study[13] recruited over 300 patients intolerant of at least 2 statins due to muscle symptoms. They were randomly allocated, double blind, to either a PCSK9 monoclonal antibody, alirocumab, or ezemibe or atorvastatin. Equal numbers (about 20%) from each group withdrew due to muscle related side effects, and about 80% in each group reported no side effects of any kind leading to discontinuation during follow up. The evidence for a causal link between statin use and myalgia is thus extremely difficult to establish in the vast majority of patients.

The BMJ, which published the unsubstantiated claims of Abrahamson *et al.*[4] and Malhotra,[5] that the association was causal, was persuaded by an independent review body to retract these implications. Nevertheless, the damage had already been done and, along with extensive media reports on side effects of statins, public confidence in the drugs was compromised with the result that patients discontinued their statins or were unwilling for them to be prescribed. Regrettably this has impacted on those recommended statins not only for primary prevention, but also for those who had already experienced a cardiovascular event in whom, of course, the risk of a future event is much higher and the absolute risk reduction with statins much greater.

There are few areas of medicine where there seems to be such a discrepancy between the results of controlled trials and the observations from clinical practice and, whilst there are many differences between the populations under investigation and the manner in which the information is recorded, one of the key differences is whether or not patients knew they were taking a statin.

In order to shed further light on this extraordinary controversy we intend to take advantage of the unusual experience of the ASCOT study in which patients were initially randomised to one of two blood pressure lowering strategies (ASCOT-BPLA)[14] and then by way of factorial design re-randomised to a statin, atorvastatin, or placebo (ASCOT-LLA).[15] ASCOT-LLA was a double blind trial that was stopped prematurely after 3.3 years of follow-up due to a highly significant risk reduction in the primary end point of non-fatal myocardial infarction and fatal cardiovascular disease. Patients were then offered open label atorvastatin and continued in the blood pressure arm of the trial for a further 2.2 years when the trial was terminated. Approximately two thirds of patients who were formerly assigned atorvastatin or placebo took the statin for the remainder of the trial.

In addition to the recording of SAEs and withdrawals from treatment, non-serious AEs were documented at each visit throughout the trial. A database of more than 300,000 AEs has been cleaned by observers ignorant of medication assignment and will be interrogated for evidence of muscle related symptoms and other AEs putatively associated with statin treatment. The patient population and the methodology applied to establish whether or not there is an association between statin use and the development of a particular AE will be derived for those on blinded and unblinded treatment in an identical way. The results of our analyses, which should be available later this year, will hopefully shed further light on the current ongoing controversy.

In the meantime, the high incidence of statin related symptoms demands a practical and pragmatic approach to their management. The European Atherosclerosis Society proposes the following:-[7] withdraw statin followed by one or more re-challenges after a washout. (This helps to establish causality). Try alternative statin, a statin at lowest dose, intermittent dosing of highly effective statin (alternate days or twice weekly), or the use of non-statin lipid lowering drugs.

It was beyond the brief of this commentary to consider other putative AEs associated with statin treatment. For most, if not all, reports from observational studies are at variance with those obtained from double blind controlled clinical trials, in which there is no evidence, for example, of excess of erectile dysfunction, worsening memory or dementia with statins. These observations will be further explored in ASCOT. The exception is the development of new-onset diabetes for which there was a 9% excess compared with placebo in a meta-analysis of randomised trials.[16] This was related to dose and potency of the statin and was confined to those who had at least one risk factor for diabetes. One new case per 1000 years of statin treatment. Over a 4-year period statins prevent 9 new vascular events for each case of new-onset diabetes. Powerful evidence that the risk benefit ratio is strongly in favour of statin use.

The debate and controversy will no doubt continue. The reporting of bad science and its popularisation by the lay press is a hindrance to optimal practice. The MMR scandal is a typical example. As clinicians we have a responsibility to educate our patients and hopefully new findings will add to the weight of evidence in support of the efficacy, safety and tolerability of statins.

- Peter Sever

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Pulmonary hypertension 2015

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Pulmonary hypertension (PH), defined as a resting mean pulmonary artery pressure greater than 25mmHg, can accompany many diseases but can also present as an isolated entity. The international community continues to recognize 5 major subgroups. Group 1, referred to as pulmonary arterial hypertension (PAH), includes PH associated with connective tissue disease and congenital heart disease as well as hereditary and idiopathic PAH. It is characterized by marked structural remodeling of pulmonary arterioles. Group 2 is PH secondary to left heart disease and Group 3 secondary to various causes of hypoxaemia. Group 4 is PH as a result of chronic proximal or distal pulmonary vascular thrombosis (chronic thromboembolic pulmonary hypertension, CTEPH). Group 5 is a miscellaneous group that includes haematological and metabolic disorders.

PAH is a rare disease, with an estimated prevalence ranging from 10 to 52 cases per million. Recent data from various registries indicate that the demographics of idiopathic PAH patients have changed. Typically, as recorded in the US National Institutes of Health registry in the 1980s, PAH was diagnosed in young adults, mean age around 36 years. More recent registry data show a shift towards older patients, with a mean age of presentation around 55 years. CTEPH is also uncommon, but also under diagnosed. Its estimated prevalence after acute pulmonary embolism is less than 10% (probably nearer 3%) and estimated incidence around 24 cases per million population per year. PH associated with left heart disease and chronic obstructive pulmonary disease (COPD) is more common because both heart disease and COPD are common.

In all presentations prognosis is determined by the response of the right ventricle to the increased pressure load. Primary treatment is directed at any underlying disease and patients with chronic thromboembolic disease should be considered for surgery, thromboendarterectomy, by a specialist centre. Specific drugs targeted at reducing pulmonary artery pressure are licenced for PAH. Until recently these came from 3 pharmacological classes – prostanoids (epoprostinol, treprostinil), endothelin receptor antagonists (bosentan, ambrisentan, macitentan) and phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil). A new class, soluble guanylate cyclase stimulators, exemplified by riociguat has recently been approved. It is also licensed for inoperable CTEPH, if surgery

has been ruled out by an experienced surgeon. An alternative option for CTEPH offered in some centres is balloon pulmonary angioplasty of accessible occlusions but experience with this technique is still relatively early.

While successful surgery is curative for CTEPH, instances of cure in PAH remain unusual, and limited to calcium antagonist responders (around 6% of PAH) and cases of PH associated with systemic lupus erythematosis and HIV. The targeted drug therapies improve functional capacity in PAH and there is some evidence for improved longevity, but prognosis remains poor; 5-year survival around 65% even in the best centres. Reliance on historical data for survival comparisons has to be interpreted with care as the demographics of the PAH is changing. The older age of diagnosis means patients present with concomitant disease. There is no good evidence that targeted therapies address the structural remodeling of pulmonary arterioles in PAH. This is difficult to review as tissue biopsies are not an option. But it is important for evaluation of the next generation of targeted treatments aimed at reverse remodeling. The possibility that molecular imaging, a tool used in oncology, might help is actively being explored.

There is no shortage of new drug targets in PAH. These have come from a better understanding of the genetics of PAH (e.g. bone morphogenetic protein receptors mutations) and a steady rise in interest in the pathology (e.g. aberrant cell proliferation, inflammation, metabolic phenotype). A major challenge will be the efficient selection of promising drugs to take forward in pivotal clinical trials. Established clinical trial endpoints are 'patient hungry' and there are not enough patients to permit many studies to be conducted in parallel. More creative clinical study designs are needed to enable go-no-go decisions to be made. Implantable devices that provide continuous reporting of cardiopulmonary haemodynamics may one day provide a solution, allowing patients to switch rapidly from one drug to another according to response, but the technology has not been evaluated in PH.

The disappointment with renal nerve ablation for systemic hypertension has not deterred interest in sympathetic nerve ablation for pulmonary hypertension. A small case series from China has prompted wider interest. A better understanding of the underlying mechanism is required and it should not be considered a treatment at this time. Similarly, infusion of progenitor cells, with or without genetic modification, is still an experimental procedure with a lot of further research needed.

PH has benefited from greater awareness is recent years and the outlook for the patient has improved. Research into PH is enjoying a golden era but while we await a major breakthrough, there is still much to be done to ensure that patients are diagnosed early and managed expertly.

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Biochemical testing for non-adherence to antihypertensive medications

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Hypertension is one of the most important modifiable risk factors of cardiovascular disease. However, despite the availability of potent and tolerable therapies, blood pressure targets are achieved in only around two-thirds of patients.[1] Non-adherence is one of the key reasons for this apparent resistance to treatment and translates directly into poor cardiovascular outcomes.[2]

Detection of drugs or their metabolites in bodily fluids to assess non-adherence

High performance liquid chromatography – mass spectrometry (HPLC-MS/MS) is widely used in forensic science laboratories to detect presence of medications in bodily fluids. [3] We have translated this method into a diagnostic tool to objectively measure non–adherence to antihypertensive medications in the clinic. Our test requires only a small volume (5-10mL) of urine. The spot sample is usually collected in the morning and can be kept in the refrigerator before being sent to the laboratory within 24-48 hours. Once the sample is in the laboratory, it is kept frozen until analysis. Samples are analysed in batches. It requires approximately 30-40 minutes to analyse each sample. The first step in laboratory analysis is cleaning and concentration of the sample. An aliquot is then loaded on the HPLC-MS/MS. A biochemical compound is then identified by its unique mass to charge ratios signature. The results are technically validated against our in house library and finally clinically interpreted by one of the consultants.

The evidence

We have demonstrated that 25% of patients attending the specialist hypertension centre are non-adherent to their anti-hypertensive therapy.[4] The rates of non-adherence were particularly high amongst those referred for renal denervation. A recent cost modelling study has concluded that the use of the test in cases with resistant hypertension is cost effective.[5] Our Department now receives samples for urine analysis from across the UK.

Clinical experience

We utilise this test routinely in managing most new referrals in our Hypertension Clinic. We conduct the urine analysis on the day of the patient's visit to the clinic, thus preventing patients from modifying their adherence behaviour. The results are used not only as a diagnostic cue but more importantly as an opener to conversation about non-adherence to treatment. The causes for non-adherence are complex and varied and a tailored multi-pronged approach has been advocated.[6] If forgetfulness is a reason, we provide a dosette box. Where dosing complexity is a factor, we try to simplify the pharmacotherapy and utilise drug combinations where possible. If side effects are stated as the reason for non-adherence, a rationale change in medications is undertaken. Other causes for non-adherence such as depression can be identified and where required psychological support provided. These approaches have been previously described but the major utility of the test is its objectiveness that allows a constructive conversation with patients. We find that the test is also a powerful educational tool for patients who question the rationale of the need to take medications when they feel well and are asymptomatic. The results demonstrate to them that the lack of medications in their body is linked to their high blood pressure and therefore the medications are required to control their hypertension. We also highlight non-adherence in their problem list and reiterate this in each communication with the patient's General Practitioner.

Limitations of the method

Currently there is limited availability of the test as the equipment costs around £200,000 and requires high levels of technical expertise and a large amount of time to set up the method. We are the only centre in the UK to offer the service at national level. Further outcome studies are required to assess the utility and correlation of detecting non-adherence at a single time point with long-term outcomes.

Conclusion

In our view, this test has changed our clinical practice, is well accepted by patients and is an important step forward in addressing the problem of non-adherence. We firmly believe that the test could be as effective as the discovery of a potent new anti-hypertensive medication.

CASE STUDY

First Visit

A 42-year old female known to be hypertensive for 8yrs was referred for management of her "resistant hypertension" by her GP. On examination there was nil of note except for a raised BMI of 37.8kg/m^2. Her BP was 160/90 mmHg by 24hr ABPM, aldosterone/ renin ratio and urine catecholamine screens were normal. She mentioned her BP had always been difficult to control but denied non-adherence. The results of her initial HPLC-MS/MS-based urine analysis are shown in this box (see right).

PRESCRIBED DRUG	RESULT
LOSARTAN	NOT DETECTED
AMLODIPINE	NOT DETECTED
INDAPAMIDE	NOT DETECTED
DOXAZOSIN	NOT DETECTED
BISOPROLOL	NOT DETECTED

Second Visit

The results of HPLC-MS/MS-based urine analysis were discussed with the patient. She agreed she may be 'forgetting her medications'. Subsequently antihypertensive therapy was started afresh with Losartan and the rest of the antihypertensive medications were taken off her prescription list.

Third Visit (6 months)

Her average BP was 129/79 mmHg on 7-day Home BP monitoring. The results of biochemical screening for non-adherence are shown below:

PRESCRIBED DRUG	RESULT
LOSARTAN	DETECTED

Figure: Highlights of the urine antihypertensive drug screen analysed by HPLC-MS/MS at the University Hospitals of Leicester NHS Trust

Figure: Highlights of the urine antihypertensive drug screen analysed by HPLC-MS/MS at the University Hospitals of Leicester NHS Trust

Sample

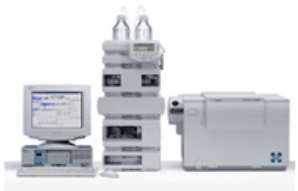
- Spot urine sample ~10 mL
- Stable and can be transported by post

Method

- Robust, accurate and relatively cheap
- 40 drugs/metabolites tested
- Analysis by HPLC-MS/MS
- Results interpreted by 2 consultants
- >1000 samples analysed at UHL from across the UK
- On going collaboration with multiple researchers

Clinical aspects

- Correlates with blood pressure
- Patients do not refuse test or feel policed
- Results leads to constructive discussion with patient
- Helps construct a tailored approach to improve adherence
- Experts who have used the test say that it has changed their practice



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Report of the first ISH/APSH Summer School in Asia and Australasia

Organized by the Chinese Hypertension League

Report by Trefor Morgan

The first Summer School of the Asian Pacific Society of Hypertension (APSH)/ISH in the Asia Pacific region was held at the Beijing Eastern Garden International Conference Co., Ltd near Eastern lake, the site of the water events (rowing, kayaking etc.) of the Olympic Games in 2008. The venue was extraordinarily suitable for this event and was of a high quality.

The Summer School was opened at 9AM on Monday August 3, 2015 in a ceremony attended by the following distinguished guests and all the school participants:

Prof. Lisheng Liu, Former President of World Hypertension League
Prof. Guangling Li, Vice-director, Dept. of Disease Control, National Commission of Health and Family Planning
Prof. Zhaoxing Li, Chairman of Chinese Association of Public Diplomacy and Former Foreign Minister of China
Prof. Yuanhong Ding, Former Chinese Ambassador to United Nations, Switzerland and Belgium, and Head of Chinese Delegation to European Union
Prof. Trefor Morgan, Secretary of APSH
Prof. Ernesto Schiffrin, Former President of ISH
Prof. Giuseppe Mancia, Former President of ESH
Prof. Yong Huo, President of Chinese Society of Cardiology
Prof. Xiaoying Li, President of Chinese Society of Gerontology
Prof. Xinhua Zhang, Secretary General of World Hypertension League

The school ran over 5 days. The activities on each day consisted of discussion of a major topic in the morning. This was composed of talks by the faculty on major points amplified by presentations on specific points by the scholars. The afternoon sessions consisted of update sessions presented by the faculty on topics of major importance followed by research presentations by either the scholars or faculty.

There were a total of 31 scholars. One scholar from Pakistan was unable to obtain their Visa in time and was unable to attend. The participants were from Bangladesh 2, China 12, India 2, Indonesia 3, Japan 1, Malaysia 4, Nepal 2, Philippines 2, Singapore 2, Thailand 1.

The coordinator and organizer of the Sumer School was Professor Zhaosu Wu, President of Chinese Hypertension League (CHL). The Dean of the School was Professor Trefor Morgan, Secretary General of APSH.

The International Faculty members were:

Giuseppe Mancia Milan, Italy
Ernesto Schiffrin Montreal, Canada

The regional faculty members nominated by sponsoring societies were:

Prof. Mark Nelson Australia
Prof. Yuqing Zhang China
Prof. Jiguang Wang China
Dr Arieska Ann Soenarta Indonesia
Prof. Rashid Rahman Malaysia
Prof. Subramanian Srinivas Singapore
Prof. Pankaj Handa Singapore

The ISH New Investigator Committee was represented by Dr Sofie Brouwers from Belgium and Professor Fadi Charchar from Australia. Professor Michael O'Rourke from Australia was in Beijing at a separate conference and attended and spoke on his work on one day of the Summer School.

In addition to the educational and scientific activity, social programs were arranged during the after-school hours consisting of attendance at a Chinese Opera and a visit to the centre of Beijing for sightseeing and shopping.

All in all it was a full week of activity.

Themes of the Summer School covered in the Morning.
-Epidemiology and Prevention of Raised Blood Pressure
-Guidelines. Similarities and Differences. How to implement
-Blood Pressure Measurement. When, Where and How?
-Secondary Hypertension-- Investigation and Management
-Hypertension Management in Special Subgroups

Update Lectures by Faculty Members.
Sympathetic Nervous System and Hypertension - Giuseppe Mancia
Hyperaldosteronism - Ernesto Schiffrin
Resistant Hypertension - Rashid Rahman
Hypertension in acute stroke - Jiguang Wang
Sleep BP and cardiovascular disease - Trefor Morgan

Pictures below - left: Prof. Trefor Morgan (Dean) / Right: Prof. Zhaosu Wu (Coordinator/Organizer)

Evaluation

This Summer School was the first of its kind in the Asia Pacific region. The contents of the curriculum appeared to be appropriate to the participants. Update lectures by faculty members were of high quality, followed by panel discussions which were well received. Apart from introductory theme lectures by the faculty, every scholar was assigned and gave a presentation(s) on specific topics, followed by whole-class

discussions, which were very interactive and informative. Some scholars reported that this training course was the best they have ever attended and what they learnt will be very useful for their future career in combating hypertension and related diseases. As such, this Summer School will have important impact in the development of hypertension control programs in their own countries and furthermore in the Asia Pacific region. We are pleased that the first Summer School attained the main goal set by APSH and ISH -- to develop skills and expertise of emerging senior health workers from the Asia Pacific region in prevention, detection, diagnosis and clinical management of hypertension.

It is planned to hold a second Summer School in 2017. The duration and format has yet to be decided, but it was felt that there should be a greater opportunity for social interaction at this event.

Acknowledgements

The Summer School organizers are very grateful for the support and guidance from ISH, particularly Prof. Rhian M Touyz, ISH President. The Summer School organizers are also grateful for the generous support from Novartis Pharmaceutical and Merck & Co.,Inc.

Report of the first ISH/APSH Summer School in Asia and Australasia

Organized by the Chinese Hypertension League

Report by Sofie Brouwers and Fadi Charchar
on behalf of the ISH New Investigator Committee

As Professor Morgan mentioned in his report, we were delighted to attend the Summer School as representatives of the ISH New Investigator Committee (NIC). The School was an excellent opportunity to meet and recruit new investigator colleagues from the Asia Pacific region. We both presented talks on our respective areas of interest. Fadi in the area of genomics and Sofie on the role of different drug classes in antihypertensive treatment. The response of the participants to our presentations was great and both talks stimulated much discussion. The event itself was very well organized with a well-balanced expert faculty from many countries. It was evident that the greatest contributions of the faculty were their openness to share their challenges in the field of hypertension research and their expert advice that comes from their *par excellence* CVs.

Mealtimes (always an adventure in China - especially when the staff do not speak English) and coffee breaks encouraged informal discussion amongst the scholars and faculty members. Discussion sessions were outstandingly managed and lead to academic stimulation of the group as a whole. It seemed that ideas were incubating for future projects and collaborations across fields and nationalities. Many of the social activities were fantastic. However, there was a big sigh of relief when the Karaoke night was cancelled for a shopping trip to Beijing.

In total, we were able to enthuse 31 participants to join the Society and become involved with the ISH New Investigator Network; established to serve as a platform for interaction between students and new investigators and allow new avenues for communication, collaboration and education. We enjoyed interacting and learning from our colleagues in the region. We feel that this is particularly important in light of the upcoming two ISH Biennial Scientific Meetings in Asia (Seoul - 2016 and Beijing - 2018). There was a lot of interest in the ISH Mentorship Scheme from participants. This is an exciting scheme where the ISH NIC introduce new investigator Society members to more experienced investigators from the rich membership of the ISH. One particular Society initiative that also created interest at the Summer School was the new Women in Hypertension Scheme spearheaded by ISH President Professor Touyz.

Most importantly of all we believe that we met a very motivated group of colleagues with high potential. This fruitful meeting allowed us to establish many new contacts with future collaborators and we believe that such activities are the best way to ensure more active involvement of new investigators in the Asia Pacific region with the ISH. We would particularly like to thank our new friends from the Summer School for helping with translation and for making the School an event to remember.

ESH 2015 -Meeting Reports

On June 12-15, the European Society of Hypertension (ESH) organised their annual meeting; this time in Milan, Italy. The meeting was, as always, very well run under the professional leadership of Professor Giuseppe Mancia and his group. We have asked a few of our younger investigators to select some of the presentations and below, please find their contributions. Moreover, we are delighted to include a report on the meeting written by Professors Giuseppe Mancia and Anna Dominiczak. The organisers of the ESH meeting are to be congratulated on a job well done!

- Lars H. Lindholm
Editor

Join the ESH at their next meeting in Paris, 10-13 June 2016 **www.esh2016.org**

Anna Dominiczak

(left) ESH, Immediate past president

Giuseppe Mancia

(right) Chairman, 2015 meeting

The 25th Meeting of the European Society of Hypertension (ESH) was held in Milan from 12th to 15th June 2015. The meeting received about 1,900 abstracts from all European but also from non-European countries, with about 100 countries represented in total. Based on the score provided by 4 European Reviewers, 350 abstracts were selected for oral presentation whereas more than 1,400 were accepted as posters. The programme included a large number of structured events, subdivided into investigator-generated Topical Workshops (n=14), Sessions co-organized with other scientific Societies (n=7), Lectures (n=19), Debates (n=3), Breakfast Workshops (n=16), Working Group Sessions (n=8) and Sessions discussing within the appropriate format clinical cases, therapeutic trial data and practical aspects ("How-to") of instrumental examinations for the detection of organ damage in untreated and treated patients.

As per tradition, the programme included 3 large Teaching Seminars (one per day) focused on diagnostic and therapeutic problems posed by clinical practice at general practitioner as well as at a more specialized management level. There were also industry-sponsored events (n=19) which were run within the main meeting and investigator-generated satellites on specific topics that were held both in Italy (n=4) and in other European countries (n=5). This allowed most, if not all aspects of basic and clinical hypertension research, as well as practical issues of current interest and controversy, to be addressed and suitably discussed between experts and with the audience. The meeting enjoyed the presence of many young investigators whose participation was facilitated by a high number of accommodation grants and free registrations offered by ESH. As with past meetings, the contribution to research and progression of knowledge in hypertension was recognized by the attribution of ESH awards to a number of prestigious scientists in a widely attended plenary session on the second day of the meeting.

Although the event typology was somewhat different from the past (more mini-symposia and less extended satellites) the number of industry-sponsored events held at the 2015 ESH meeting was similar or higher than at previous meetings, which should reassure the hypertension world of the continuing interest of industry in the diagnosis and treatment of a condition which is still the first cause of death worldwide. However, although remaining by far the largest continental hypertension scientific event worldwide, the number of participants at the 2015 Milan meeting (n=3,506) was several hundred less than at the meetings held in the recently in Athens (with the International Society of Hypertension), Milan and London. This may be due, in part, to the decline of research on new antihypertensive drugs or treatment strategies by pharmaceutical or device companies. On the other hand, because spontaneous research and scientific interest on hypertension are still very high (as shown by the consistently high number of abstracts received), it mainly reflects the current difficult economic situation, which can make travel problematic, particularly from countries with limited economic resources. In this context, however, a highly positive element was that the 2015 ESH meeting enjoyed a record attendance of participants at the scientific sessions. Throughout the meeting, virtually all lecture rooms were full even beyond their seating capacity. The last day, a well-known critical time at all meetings, was also characterized by a large attendance at all sessions. Hence, participants attending this hypertension meeting represented a highly committed group of scientists and physicians.

ESH 2015 -Meeting Reports

Ruan Kruger, ISH New Investigator Committee
Media Working Group member
North-West University, Potchefstroom, South Africa

Recent findings in Epidemiology – ESH 2015 meeting (Milan, Italy)

Epidemiology research presented at the 2015 ESH meeting in Milan, Italy has again captured attention with interesting findings from various groups in the world including Belgium, Germany, United Kingdom, South Africa, China, Japan, Poland, Switzerland, Russia and Italy. We often hear that coffee is not always healthy, but Guessous et al. from Switzerland found a negative association of pulse pressure with caffeine, paraxanthine, and theophylline excretions. They suggested that caffeine and its metabolites lower blood pressure probably by modifying arterial stiffness – *this is good news.* Talking about *news*, Torlasco and colleagues from Italy obtained information on the prevalence and awareness of hypertension and other cardiovascular risk factors in individuals participating in the 2014 "World Hypertension Day" in Italy. Their findings showed a high hypertension prevalence, accompanied by an unsatisfactory awareness of its complications. They strongly encouraged more rigorous efforts to improve hypertension control and increase patients' awareness of the risks associated to this condition.

Discussions on home versus ambulatory blood pressure monitoring have been under the radar for some time now and a collaboration between China and Belgium has explored the discrepancy between methods. Li et al. posed the question on whether preference should be given to home or ambulatory blood pressure. She suggested to reliably diagnose hypertension and starting treatment, office blood pressure should be followed by ambulatory blood pressure monitoring. Using home instead of ambulatory blood pressure misses the high-risk diagnosis of masked or sustained hypertension in over 25% of patients. Another study from Belgium aimed to create a web-based application that allows easy assessment for different methodological approaches of a given measured value of arterial stiffness. This is because arterial stiffness has been demonstrated to predict and be related to cardiovascular disease, but the use of different devices and methods, however, still hampers the widespread clinical use of these reference values. Londono et al., reported that this easy and intuitive web-based interface provide the percentile references associated with a given measurement of arterial.

Piotrowicz et al. from Poland studied the observations from the subclinical worsening of cognition and mood assessed with screening tools and found a relation with poorer BP control. This lends support to the widespread use of the Comprehensive Geriatric Assessment even in apparently self-dependent oldest patients with hypertension.

From old to young. A German group studied 7-year old children in a nine month exercise intervention program and observed beneficial effects not only on motor performance, but moreover on hemodynamic parameters including blood pressure and pulse wave velocity.

Children participating in the exercise intervention showed a reduced age-related increase in hemodynamic parameters, but also a significant decrease in the assessed variables. Ketelhut et al., suggested it is mandatory to increase regular physical activity in early childhood to positively influence cardiovascular risk profile and motor skills.

ESH 2015 -Meeting Reports

Sofie Brouwers, ISH New Investigator Committee Networking and Mentorship Working Group member
Vrije Universiteit Brussel, Brussels, Belgium

Can the polypill tackle the huge challenge of adherence? – ESH 2015 meeting (Milan, Italy)

Non-communicable diseases, with cardiovascular diseases (CVD) at the top of the list, have become the most common cause of death worldwide, leaving the communicable diseases (HIV, polio, tuberculosis) behind. Today we face insufficient risk factor control in high-risk subjects and inadequate secondary prevention. Systematic approaches are warranted to improve primary prevention and to overcome the insufficient use of secondary prevention medications worldwide, especially in low-income countries (1). To combine the basic and effective cardiovascular drugs, the polypill strategy was suggested almost a decade ago, initially as a broad 'vaccination' approach in primary prevention. The term polypill was introduced by Wald and Law (2) as a preventive strategy to treat all individuals above 55 years of age and everyone with existing cardiovascular disease. Based on this initial idea with 6 active components, a more selective use of a polypill composed of a combination of medications that are known to effectively treat CVD (aspirin, an ACE-inhibitor and a statin) was proposed in primary prevention in individuals with a high cardiovascular risk. This idea was primarily elaborated for developing countries and is now also being depicted as a promising strategy for developed countries, where efforts for cardiovascular prevention are not reaching their goals and the medical expenses are immense. Although an improvement in the control of cardiovascular risk factors is seen, the control rate remains largely insufficient while the burden of disease keeps growing. Besides raising awareness and improving life style interventions, in particular the lack of treatment adherence is a huge challenge in patients with cardiovascular disease. The complexity of the drug regimen, the number of drugs and the type of drug influence the nonadherence. The drugs available at present have surely proven efficacy, but their impact is substantially lowered by the problem of nonadherence. Haynes precisely described the problem: *"Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments."* (3).

In secondary prevention, the accessibility and affordability of a polypill might improve treatment in developing countries, whilst in developed countries the polypill can increase treatment adherence, lowering cardiovascular events and health care costs (4). The 'simple' worldwide introduction of the polypill might make the difference in tackling the growing epidemic of cardiovascular diseases by improving cost-effectiveness and increasing adherence. We impatiently await the results of large trials indicating whether the polypill will be able to fulfill these high expectations.

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ISH Biennial Scientific Meetings – looking back and moving forward

As we plan the next ISH meeting in Seoul, we think of the many successful meetings of the past and of the exciting times ahead. Over the years attendance has varied (see table), for many complex reasons, but we are confident that our future meetings will continue to be well attended with participants from across the world.

While sponsorship from the pharmaceutical industry has changed over the recent past, there is now new interest from new partners, such as biotech companies, device companies, non-health-related companies etc. Working with local organising committees and the outstanding assistance of Helen Horsfield at our Secretariat in London, we certainly look forward to a well-attended meeting in Seoul and seeing you there (Seoul, 24-29 September 2016). The ISH prides itself on the quality of the science at its meetings. So don't miss out on the opportunity to present your work, learn about new ground breaking cardiovascular research, share ideas and develop collaborations with scientists from other parts of the world at this meeting. There will be numerous travel grants to apply for and reduced registration fees for ISH members, delegates under 35 and those from developing countries.

Please help us make the Seoul hypertension meeting a great success through your contributions and participation.

Venue	Year	Attendees
Mexico City	1982	1 500
Interlaken 1984		1 750
Heidelberg	1986	1 500
Kyoto	1988	1 400
Montreal	1990	3 000
Madrid	1992	5 000+
Melbourne	1994	4 500+
Glasgow	1996	6 100
Amsterdam	1998	6 000
Chicago	2000	4 000+
Prague (with ESH)	2002	6 700
Sao Paulo	2004	2 700
Fukuoka	2006	4 100
Berlin (with ESH)	2008	8 600
Vancouver	2010	2 200
Sydney	2012	1 500
Athens (with ESH)	2014	4 900
Seoul	2016	?
Beijing	2018	?
Glasgow	2020	?

- Lars H. Lindholm
Editor

Short report on recent collaborative efforts on prevention and control of hypertension by the World Hypertension League (WHL)

Mark Niebylski
CEO, The World Hypertension League

Plans are underway to expand on the success of the World Hypertension Day (17 May) this year, to get a higher awareness of high blood pressure in the different populations of the world. This will be done by coordinating the efforts of different WHL organisations and sharing resources e.g. fact sheets and slide sets. On World Hypertension day, WHL launched a Regional Sub-Saharan Africa Office with Dr. Daniel Lemogoum, Cameroon as director, as an addition to the other regional offices in Latin America and Asia.

A fact sheet on hypertension for Sub-Saharan Africa was also developed by WHL in cooperation with ISH (www.whleague.org/index.php/j-stuff/web-links).

Moreover, a Sub-Saharan Africa hypertension Infographic for professionals, providers, and hypertension societies has been made available (www.whleague.org/images/HTN_Infographic_Professionals_2015.pdf).

We envisage that there will be more opportunities for collaboration in the future building on our partnerships with the ISH and the World Health Organization (WHO). The WHL plans to host its Council meeting at the 2016 ISH Biennial Scientific Meeting in Seoul which promises to be a perfect venue to meet and discuss future collaboration.

- Mark Niebylski

Council's Corner: Hypertension Issues - a personal view

Markus Schlaich
Royal Perth Hospital Unit Faculty of Medicine, Dentistry & Health Sciences, The University of Western Australia Level

Device-based approaches for hypertension treatment – do we really need them?

Hypertension treatment is a classic domain of lifestyle interventions and pharmacotherapy. Achieving a normal body weight, adhering to a balanced diet, reducing salt intake, moderation of alcohol consumption and regular exercise are just some of the interventions for which overwhelming evidence exists to demonstrate their safety and effectiveness in lowering elevated blood pressure. These interventions are typically low cost and have many additional health benefits. All it really takes is some effort to get started and endurance to keep going. This does not sound hard, but ask a few middle-aged obese hypertensive patients with pre-diabetes who are trying to juggle their demanding job, children's activities and social commitments and answer their question: "Doctor, when should I do this?"

The advances in antihypertensive pharmacotherapy over the last few decades have been substantial and we are very fortunate to have a number of drug classes that are safe, effective, and generally well tolerated. In the era of evidence-based medicine a reduction in hard endpoints is an important criterion and again, several antihypertensive drugs classes tick that box. The introduction of single pill combinations helped to reduce the pill burden and represents another important development in antihypertensive pharmacotherapy. I do agree with many of my colleagues that in the vast majority of patients with hypertension we should be able to control blood pressure with a combination of both lifestyle modification and pharmacotherapy. Yet, reality is that non-adherence to both is very common, even more so over time, and that up to 50% of patients diagnosed with hypertension are not controlled and remain at elevated cardiovascular (CV) risk. While every effort should be taken by health professionals to advise patients on the benefits of these therapies, we also have to respect what I refer to as a "patient's choice", that is the unwillingness to modify their lifestyle and/or take antihypertensive or other drugs for that matter typically for the rest of their lives. In addition, there are patients who are intolerant of some antihypertensive drugs, cannot afford them all, or have difficulties accessing health services. For these patients we have to explore alternative therapies and device-based approaches may be part of the solution. Recent developments in this area are commonly based on sound pathophysiologic considerations and have provided promising and sometimes conflicting results in human studies. Baroreflex activation therapy, renal sympathetic nerve ablation, and central arteriovenous anastomosis are important milestones in this area, but much more research is required to prove long term safety and efficacy in lowering blood pressure and ultimately in reducing CV events. Identification of the ideal candidate for any of these approaches is another challenge. As with most therapeutic interventions, one size does not fit all and we have to learn a great deal about each of these device-based approaches. While I am convinced that lifestyle modification and pharmacotherapy will remain the standard of antihypertensive therapy, I do believe that we are entering a new era that is driven by our understanding of pathophysiologic principles and advances in biomedical technology.

Let us keep an open mind and embrace the technical progress while building on well established and solid foundations.

- Markus Schlaich

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If you haven't yet paid your membership fee for 2015 and are interested in retaining your links to the Society, we would be delighted to receive your payment.

Please contact the Secretariat for more information.
Email membership@ish-world.com

Please help us to recruit new members

If you have a colleague who would like to become a member of ISH please ask them to complete the online application form that can be found in the Membership section of the Society's website:

www.ish-world.com

Applications are considered by the Membership Committee every 8-12 weeks.

Please contact membership@ish-world.com with any questions.

ISH Secretariat Contact Details

The ISH Secretariat moved from Hampton Medical Conferences to The Conference Collective on 1st April 2014.

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