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FROM THE EDITOR

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Lars H. Lindholm
Editor, Hypertension News

Dear ISH member,

Greetings from Barcelona where about 2,700 delegates have just finished the latest annual meeting of the European Society of Hypertension (ESH). It is my pleasure to report on four issues which I hope will be of interest to our readers.

First, and most importantly, the ISH Beijing 2018 Committee met and finalised the "first final" draft of the Beijing programme, now available for our members on the web, click here. In this issue of *Hypertension News*, you will find a report by Professor Thomas Unger on how the meeting has

Editor's report continued overleaf

Honorary Doctorate awarded to John Chalmers by Lund University, Sweden

At the time of its 350th anniversary in 2018, Lund University, Sweden awarded Professor John Chalmers, Sydney an honorary doctorate in Medicine. John Chalmers has outstanding qualifications in cardiovascular research with more than 800 original papers. His studies of the effects of treatment to reducing the onset of stroke has had a major impact on our current recommendations for the care of hypertensive patients with or without diabetes mellitus. John Chalmers has also supervised five doctoral students from Lund University at the George Institute for Global Health in Sydney. These programmes have taken place in the context of the National Research School in General Practice in Sweden, funded by the Swedish Research Council together with all medical faculties in the country.

John Chalmers, wearing his doctor's hat and carrying two major awards. Around his neck: Companion of the Order of Australia, the highest civic award in Australia; on his breast pocket: Officer of the French National Order of merit, presented to him by President Nicolas Sarkozy

IN THIS ISSUE

been planned (see page 6) and whom you may meet in Beijing as a speaker during the plenary sessions. ISH has received 1,525 abstracts so far, with the late-breakers still to come. Deadline for submission is 29 June 2018. At the end of May, about 900 delegates had registered, which is according to plan. As before, the accepted abstracts (oral as well as posters) will be published on line, but only for those who attend the meeting in Beijing.

Second, the Editorial Board of the Journal of Hypertension met and discussed who will replace Professor Alberto Zanchetti as Editor of the Journal. As many of you know, Professor Zanchetti recently died and is greatly missed by many of us (see page 20). Professor Giuseppe Mancia - previously the Deputy Editor - has kindly agreed to serve as Editor of the journal, with the Secretariat in Milan, until the end of 2021, and the Board thanked him for doing so. The process of finding a new Editor after 2021 will start next year with advertising, letter of interest, interviews etc.

Third, the Publisher of the Journal of Hypertension has previously agreed to give a 15% discount, equal to a saving of USD 495-615, on the open access rate when at least one of the authors is a *paying* member of our Society and/or the ESH. This offer will now be extended for one year and the Publisher is considering increasing the percentage to 20 or 25%, if all goes well.

Fourth, the 2018 version of the European guidelines on hypertension were presented and discussed during a couple of hours in an overcrowded auditorium (seating 1 700) at the meeting in Barcelona. The presentations were also "streamed" and put on the ESH web-site. In this issue of Hypertension News, you will find two short comments written by Professors Morris Brown (see page 15) and Bo Carlberg (see page 18) on these well balanced and rather conservative guidelines, who - with modern technology - could follow the presentations from home and see the slides in England and Sweden, respectively (!) The ESC/ESH guidelines will be released in full on 25 August.

Have a good read!

Lars H. Lindholm
lars.h.lindholm@umu.se

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Neil Poulter

President 2016 - 2018

This is my last report with only 3 months (once this article goes to press) to run of my 2-year term as President.

I write this as May Measurement Month 2018 (MMM18) is in full swing with a target of improving on the 2017 data – in terms of quality and quantity. Meanwhile the MMM 2017 results were published in The Lancet Global Health. **Click here to read this paper.**

Plans for the Hypertension Beijing 2018 (ISH) meeting are progressing well and we are looking forward to receiving further abstracts to be included in the late-breaker sessions. Abstracts will be accepted from 15 – 29 June, **click here to submit your abstract.**

In early May, ISH joined with the European Association for the Study of Obesity (EASO) to hold a one-day meeting in London on 'Clinical Care of Obesity and Hypertension'. The meeting was well attended by over 50 people with an interesting scientific programme. We hope that this will be the first in a series of annual meetings to be held around Europe.

I have had the pleasure of being involved with the CREOLE trial, designed to evaluate the most effective 2-drug combination for BP control among black patients from Sub-Saharan Africa. An investigator meeting was held in April and the trial includes the last patient, 'last visit' this month. The results of this unique trial should be presented later this year at one or more of the major meetings and we hope that a similar trial will be set up in India during 2018 and a third trial of the same type is also needed in the Far East.

The European Society of Hypertension (ESH) congress just took place in Barcelona and the European Society of Cardiology (ESC) will take place in Munich at the end of August. Joint sessions with the hosts have and will take place at these respective events.

Meanwhile, the whole world of hypertension was shocked and saddened by the untimely death of Alberto Zanchetti, one of the founding fathers of ISH. We encourage you to read a tribute to Professor Zanchetti by John Chalmers in this issue of Hypertension News **(see page 20).**

ISH was invited to submit a commentary about the most recent US (ACC/AHA) guidelines for publication in *Hypertension*. This will be published imminently and raises a few questions about whether such a guideline is suitable at the global level. In general, ISH joined several other commentators in expressing concern over the new definition of hypertension – to our mind an unnecessary distraction with no obvious advantages.

The Vice-President, Alta Schutte is, I know, planning ahead for her 2-year Presidency and I have every confidence that she will at least maintain the momentum on several fronts which the societies activities have shown in the last 2 years.

I hope very much that ISH will continue to play a truly global role in promoting and encouraging the advancement in research and knowledge required to optimise the prevalence detection and management of raised blood pressure.

As the only global society for individual members, I'm delighted to say that ISH has made real strides in that direction since 2016 and I have every belief it will continue to do so after 2018.

Neil Poulter

secretariat@ish-world.com

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Maciej Tomaszweski

ISH Secretary
University of Manchester, UK

ISH has been kindly invited by Professor Dame Anna F. Dominiczak, the Editor-in-Chief of *Hypertension*, to contribute our views on the recent American guidelines on the management of hypertension. I am delighted to confirm that Professor Neil Poulter, ISH President, has led on this contribution on behalf of the ISH Executive Committee, Scientific Council and our membership. The contribution will be shortly published in *Hypertension* and I encourage all readers of *Hypertension News* to look out for our article in *Hypertension* soon.

The Society was pleased to host a joint session with the European Society of Hypertension (ESH) at the recent ESH meeting in Barcelona in June 2018. The session 'Challenges in hypertension diagnosis and treatment' featured several prominent ISH and ESH speakers.

The ISH booth at ESH 2018 in Barcelona

An exciting programme for new investigators, mentors and mentees is awaiting those who will attend our ISH Beijing 2018 meeting. Professor Fadi Charchar and Dr Ruan Kruger, on behalf of the Mentorship and Training Committee as well as New Investigator Committee, have organised a breakfast mentorship session, several oral and poster sessions and a Mentorship and New Investigator Pre-meeting Symposium. The latter will take place on 20th September at the Bird's Nest Olympic venue. **Please click here for more information or to register for this exciting event if you have not done so.**

Continued overleaf

The ISH Awards Committee have just released a call for ISH awards. Click here to find out more. We are looking forward to receiving your nominations for the following awards:

- ISH Franz Volhard Award and Lectureship for Outstanding Research
- ISH Developing World Award
- ISH Paul Korner Award, **supported by the High Blood Pressure Research Foundation**
- ISH Robert Tigerstedt Lifetime Achievement Award
- ISH Distinguished Fellow Award
- ISH Honorary Fellow Award
- ISH Award of Excellence for Research in Cardiovascular Health and Disease in Women
- ISH Mid-Career Award for Women Researchers
- ISH Honour for Senior Women Researchers

We will announce the winners of these prizes during ISH 2018 Scientific Meeting in Beijing.

Professor Alta Schutte and the ISH Membership Committee have confirmed that 600 members have paid their dues this year. We are continuously chasing the unpaid dues from the current ISH members - if you have not done so already, please pay before the end of June to retain your membership status. Please email Charlotte at membership@ish-world.com

Please check out the recent updates on ISH 2018 Scientific Meeting in Beijing at http://www.ish2018.org

Maciej Tomaszewski
maciej.tomaszewski@manchester.ac.uk

Join us for Hypertension 2018 in Beijing

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Hypertension Beijing 2018 gets into gear!

Thomas Unger

Chair, ISH Beijing 2018 Committee

The International Society of Hypertension (ISH) will hold its 27th Scientific Meeting on September 20-23, 2018 in Beijing, China, in collaboration with the Chinese Hypertension League (CHL) and the Asian Pacific Society of Hypertension (APSH).

With **plenary lectures** by internationally renowned experts in hypertension and related diseases, **around 80 parallel oral sessions**, including 'meet the expert' sessions, debates on hot topics, award ceremonies, and industry symposia, Hypertension Beijing 2018 will host an exciting three-day scientific programme.

More than 1,500 abstracts have already been submitted to be presented in free oral and poster sessions, and even more will come in as late breakers. With **more than 150 invited lectures**, the scientific programme will cover all disciplines of prevention and treatment of hypertension, hypertension-related diseases and their risk factors.

The **Plenary Lectures** will give an overview of some of the burning issues in hypertension-related cardiovascular and metabolic diseases:

On the first day, **David G. Harrison**, Vanderbilt University, Nashville, USA, will inform about "The immunology of hypertension", followed by **Nilesh Samani**, University of Leicester, UK, with "Understanding the genetic basis of coronary artery disease: progress, clinical translation and challenges".

On the next day, the plenary session will be opened by **Daniel Levy**, NIH, Bethesda ML, USA, with a lecture on "New recommendations for the classification and treatment of hypertension", followed by **Peter Cameliet**, Catholic University of Leuven, Belgium, with "Angiogenesis revisited: role and (therapeutic) implications of endothelial metabolism". Finally, **Victor J. Dzau**, National Academy of Medicine, Washington DC, USA, will explore "The future of hypertension".

On the third day, the plenary session will be reserved for the ISH: After the traditional **Presidential Lecture**, given by the president of ISH, Neil Poulter, Imperial College, London, UK, and the **Franz Volhard Lecture**, named after the eminent German nephrologist Franz Volhard, and presented by this year's awardee, the ISH 2018 awards will be presented.

Further to the above mentioned keynote addresses and award lectures, the scientific programme will explore and discuss virtually all aspects of hypertension and related diseases based on three pillars: **Basic Science, Clinical Science, and Population Science**.

From the very beginning of the society, support and presentation of **Basic Hypertension Research** has

always been a hallmark of its activities. The presentations on the discovery of atrial natriuretic factor by Adolfo de Bold in Interlaken, of endothelin by Masachi Yanagisawa in Kyoto, or the first comprehensive discussion of angiotensin receptors in Glasgow, these were unforgotten highlights of previous ISH congresses, just to name a few. This time, a broad spectrum of new basic results will be presented with emphasis on recent exciting data on salt handling in the skin, microbiota in the gut, immunological processes, vascular biology and vascular dementia, and all the "omics" such as genomics, proteomics and metabolomics. The renin-angiotensin system, still a rich source of new experimental and clinical results, will be given two sessions, one on the (pro-)renin receptor and signaling mechanisms, the other one on the "Protective Arm" of the RAS, an exciting new aspect of the system.

The **Clinical Sessions** will cover a wide spectrum of hypertension-related clinical factors and conditions as well as therapeutic approaches. Clinical cardiovascular trials, hypertension-related kidney- and heart disease, atrial fibrillation and stroke will be in the focus as well as secondary forms of hypertension with strong emphasis on primary aldosteronism, a condition which has received increasing interest in recent years. Further clinical topics will be discussed in sessions dedicated to obstructive sleep apnea, to metabolic aspects of hypertension, to life-span issues from pregnancy to old age, and to 'e-health'. More practical clinical sessions include ambulatory blood pressure monitoring, adherence problems, and the management of resistant hypertension.

This brings us to therapeutic issues. Since the congress takes place in China, traditional and non-pharmacological measures of treatment will have a special place besides drug development and pharmacotherapeutics. Here, we expect an exciting debate on inhibitors of the RAS: ACE inhibitors versus ARBs.

The clinical part will be rounded up by the popular case discussion in a clinical-pathological setting, as has been done with great success in the past, and by two joint sessions, one of the two sister societies, ISH and ESH, the other of the Chinese, Japanese and Korean Hypertension Societies (CHL, JSH, KSH).

Coming to **Population and Public Health**: Due to its global extension including more and more countries of low and middle income, these topics have increasingly gained importance on the agenda of the ISH. This fact will be widely acknowledged with several sessions including the management of hypertension in the population as well as May Measurement Month (MMM), a global ISH initiative. Specific population-related problems in Africa, Asia, Eastern Europe, and Latin America will also receive special attention in dedicated sessions. Furthermore, a particular session will be devoted to RESOLVE, an international highly recognized, non-profit initiative devoted, among others, to healthy people and communities.

The never-ending question of salt intake in the population will be dealt with in a dedicated session with the (traditional) pro- and con debate, and, of course, there will be a lot of discussion on recent hypertension guidelines, a topic, which has fueled vivid debates around the world since the recent publication of the US-American hypertension guidelines.

As a special gift to the programme this year, one of the internationally leading clinical journals, **The Lancet**, will be represented with a session named 'The Lancet Commission on Hypertension Group'.

Complementary to the many parallel oral sessions, **Breakfast Workshops** such as 'Meet the Experts', this time on renal hypertension, extra-renal salt handling and hypertension registers, will be offered as well as two joint breakfast sessions of the European Council for Cardiovascular Research (ECCR) and the High Blood Pressure Research Council of Australia (HBPRCA). Additionally, the **Asian Pacific Society of Hypertension (APSH)**, co-organisers of the congress, will run several dedicated sessions.

Two further topics have recently gained lively interest and have seen increasing activities: **'Women in Hypertension'** and **'New Hypertension Investigators'**. These two important fields will be especially recognised with a session **'Women in Hypertension'** dealing with particular aspects and problems of females in a hypertension research career, and a breakfast session on hypertension in females. The **'Austin Doyle Award'** session for young investigators (supported by Servier Australia) will select the awardee(s) from a shortlist of top-ranked abstracts which will be presented during this session. In addition, the **'ISH New Investigator Awards'** for oral presentations and posters as well as the **'New Investigator Oral Presentation'** session are directed to attract young researchers around the world to the field of hypertension. This is accompanied by a special breakfast workshop **'ISH Mentorship Scholar Award / Mentorship and Training Committee session'**.

Finally, let's not forget the posters: Every day, there will be a **Moderated Poster Session** in the early afternoon based on the submitted abstracts, and there will be several **Industry-sponsored Symposia** on different hypertension-related topics.

Altogether: ISH Beijing 2018 is a highly topical, comprehensive hypertension congress of global orientation and importance, organised by the ISH, the truly international hypertension society, together with regional partners around the world and hosted by our colleagues and friends of the Local Organising Committee of the Chinese Hypertension League, represented by Professor Zhaosu Wu (Congress President) and Professors Jiguang Wang (Executive President) and Yuquing Zhang (Secretary General).

Don't miss this exciting event: come and join in!

Thomas Unger
t.unger@maastrichtuniversity.nl

Tian'anmen Square, the Forbidden City & Hutong

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MMM18: An Update

Neil Poulter

A simple measure to save lives
maymeasure.com

The first publication of the May Measurement Month 2017 (MMM17) was recently published[1] in The Lancet Global Health. The journal kindly agreed to fast-track the 2017 results, so they were published before MMM18 was over[2].

Before summarising the MMM results, the issue of authorship of this first MMM results paper merits discussion. Ideally, we would like to see every volunteer at every site in every country recognised for their efforts. Sadly, that would involve listing thousands of names. In the end, in addition to the central coordinating team whose names appeared on the front page of the article, over 100 Investigators would appear on PubMed in association with the article. We fully appreciate that more people deserve recognition and hope that that recognition will be realised as regional and national publications follow on to describe the MMM17 campaign. We are currently in negotiations with journal editors to consider a supplement which might contain national publications from all/any national leaders who wish to do so.

Rationale and Objectives

MMM was designed to raise awareness of the importance of blood pressure (BP) measurement around the world. This was on the background of raised BP - i.e. not hypertension - being the biggest contributor to the global burden of disease and to global mortality[3,4]. Since reporting a BP-associated global mortality of about 9.4 million deaths per year as of 2015[4], this figure has risen to 10.5 million by 2016! Critically, awareness of their condition is reportedly only about 50% among those with hypertension[5] and so MMM was set up to address this problem.

How should awareness be evaluated in a cross-sectional survey such as MMM? We targeted the number of countries involved, the number of people screened and the number of screenees detected with BPs possibly requiring intervention or more intervention (≥ 140 mmHg systolic and/or ≥90 mmHg diastolic). Finally, we wanted to know in how many countries did MMM constitute the largest BP screening ever to have taken place in the individual countries involved.

Results

The brief outcomes in relation to each of these targets were:

· Number of Countries: 100 (If you count UK as England, Northern Ireland, Scotland and Wales)

· Number of adults screened and included in analyses: >1.2 Million

· Number of screenees with untreated BP in the hypertensive range: >150,000

· Number of screenees with treated BP but uncontrolled (≥140mmHg or ≥90mmHg): >100,000

· Number of countries where MMM was the largest screen: 34 of 46 surveyed (74%)

We believe that constitutes strong evidence that our primary aim was achieved!

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DOi:

The secondary aims of the project included looking at associations between each of the three BP measurements ideally recorded on each screenee and between BPs recorded with various environmental, lifestyle and demographic variables.

This unique database allowed us to evaluate the size of differences between the three BPs taken in series and the effect in making a diagnosis of hypertension based on any one reading versus the mean of the first and second or second and third readings. In short, the mean of two and three looks sensible if only one set of readings is to be used to diagnose hypertension!

We confirmed the usual relationship between systolic and diastolic BP with increasing age, lower BPs in pregnancy, and higher BPs with alcohol intake (>1 unit/week) and increasing BMI. Other findings included higher BPs among those with a history of stroke, those with diabetes, and those on treatment for raised BP. Perhaps less well established findings were of significantly higher BPs among smokers, lower BPs among those with a history of a previous myocardial infarction, and BPs were lower when measured on the right arm and higher on a Saturday with the lowest BPs being on a Tuesday!

Limitations

The greatest weakness of the 2017 campaign was the inadequacy of the bespoke MMM App. That was reflected by the fact that only 8% of the data were entered via the *2017 App*. The residual 92% were entered – most commonly by hand and then, only variably faithfully in relation to the original questionnaire. Consequently, too many data were lost and/or uninterpretable and we were unable to investigate some variables with confidence. The *2018 App* is far superior and should allow much more robust investigation of all variables recorded including additional ones such as the impact of 'room' temperature and altitude on BP levels.

Criticisms also include that the data generated were not representative of the countries from which they arose. Consequently, the national prevalence of hypertension in any country cannot be evaluated. However, the campaign was, by design, targeted at those who 'ideally' had not had their BPs measured in the previous year and hence MMM was not designed to estimate national prevalence rates nor to compare prevalences across countries.

We were also unable to provide drug treatment or follow-up for those found to have BPs in the hypertensive range (treated or otherwise). The ethical, cost and logistical implications of being able to do so would be enormous and beyond the scope of MMM as it stands. Other concerns include the cost of the project. Having been dependant on volunteer staff and the generosity of investigators worldwide, along with the donation from OMRON of 20,000 BP measuring devices, the cost to ISH worked out at below one US$ per 'case' of raised BP (untreated or treated). Health economic analyses are not required to show that this is clearly 'cost-effective'.

Prospects

Looking to the future as a charity with limited income, however, the International Society of Hypertension (ISH) will have to seek external financial support if it wishes to fund MMM beyond 2019. A more complex design, including some components of treatment (beyond advice) and follow-up is beyond the means of ISH. Meanwhile we await the publication of many papers from around the world with more granular data from MMM17 and by September 2018 we hope to have the global results of MMM18 ready for presentation and publication at the next ISH biennial meeting in Beijing in September 2018.

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Neil Poulter
ISH President
manager@maymeasure.com

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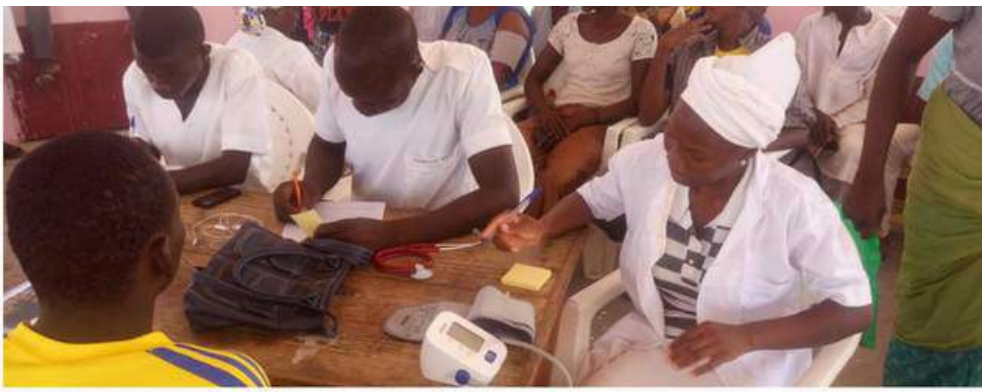
MMM18 in pictures

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Dark chocolate to treat peripheral artery diseases?

Thomas Kahan

Karolinska Institutet, Department of Clinical Sciences Danderyd Hospital, Division of Cardiovascular Medicine, Department of Cardiology, Danderyd University Hospital Corporation

Stockholm, Sweden

Endothelial dysfunction, impaired generation of nitric oxide, oxidative stress, reduced glucose oxidation and accumulation of toxic metabolites are likely to contribute importantly to the reduced blood flow to peripheral skeletal muscle characteristic of intermittent claudication and other forms of peripheral arterial diseases[1]. Nitric oxide is a vasodilatatory molecule rapidly degraded by reactive oxygen species. Cocoa is rich on polyphenols and causes arterial vasodilatation by reducing oxidative stress and thus increasing the generation of nitric oxide. Dark chocolate is rich in cocoa and dark chocolate has been shown to induce arterial vasodilatation, which has been suggested to be mediated by an enhanced availability of nitric oxide[2].

Loffredo and co-workers set out to examine the acute effects of chocolate ingestion on endothelial function, assessed by forearm post-ischemic flow mediated vasodilatation, and on walking performance in patients with intermittent claudication. They randomized 20 patients with stable peripheral artery disease to single blind treatment with 40g of dark chocolate (containing at least 85% cocoa) or milk chocolate, and measured maximum walking distance and time by treadmill (3.5 km/h and 12% inclination), flow mediated vasodilatation, and various markers of oxidative stress before and 2 h after the ingestion of chocolate in a crossover design, with one week in between the two examinations[3]. Mean age was 69 years, one third were women, most patients were hypertensive and former smokers, and one third had diabetes. Primary outcomes were walking distance and flow mediated vasodilatation.

Dark chocolate increased maximum walking distance and time (from 111±64 to 122±61 m, and from 124±61 to 142±62 s, respectively; both P <0.001) while no change was observed by milk chocolate (from 116±72 to 109±65 m, and from 124±60 to 125±64 s respectively; both $P \leq 0.01$ *vs* dark chocolate). Similarly, dark chocolate improved flow mediated vasodilatation (indicating improved endothelial function) more than milk chocolate (P <0.01). Compared to milk chocolate, dark chocolate increased circulating polyphenols and reduced biomarkers of oxidative stress more (all P <0.001). Furthermore, in a multivariable analysis the magnitude of change in oxidative stress after chocolate was independently related to the increase in walking distance (P <0.05).

This study shows that dark chocolate can acutely (within 2 h) improve endothelial function and walking performance in patients with intermittent claudication. Milk chocolate had no such effects,

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suggesting that this beneficial effect may be a result of an enhanced availability of nitric oxide due to down-regulation of NOX2 mediated oxidative stress by polyphenols in dark chocolate. There are some limitations with this study. The study population was small and there was no placebo control. The authors only investigated acute effects following one single dose of chocolate. However, the results are supported by findings in fatty liver steatosis, where oxidative stress plays a pivotal role in inducing endothelial dysfunction and disease progression[4]. In those patients, the same authors reported that dark chocolate given for 14 days improved forearm flow mediated vasodilatation, increased circulating polyphenols and reduced biomarkers of oxidative stress more than milk chocolate. Whether long-term administration of dark chocolate may have beneficial effects on walking performance and symptoms in patients with peripheral arterial disease require further study.

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Thomas Kahan
thomas.kahan@sll.se

New Investigator Member Spotlights 2018

Blessing Osemengbe Ahiante

April Spotlight

Nazar M Azahar

May Spotlight

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The New European Guidelines on Hypertension, presented at the ESH meeting in Barcelona, 9 June 2018

Lars H. Lindholm

At the recent meeting of the European Society of Hypertension (ESH) in Barcelona, the new (2018) hypertension guidelines were presented by a large group of present and former members of the ESH Council. The auditorium - which seats 1,700 – was packed. Since there was 'standing room only' the organisers had arranged for the presentations and slides to be shown in another auditorium as well. Taking photos of the slides was not forbidden, and many in the audience did so. The presentations and slides were also 'live-streamed' and could easily be followed on the ESH website (www.eshonline.org). Needless to say, people could also take screen shots of the slides from the comfort of their homes, and I am convinced that many did so.

Since the presentations and slides were put in the 'public domain' and since there is a considerable interest to discuss them, we have asked two ISH members for comments (see overleaf). They didn't attend the meeting in Barcelona but could follow the presentations online. In this issue of Hypertension News, we have, however, not included any of the many slides and tables which were shown.

To me, these new recommendations are balanced, more realistic, and more conservative than the recent American ones, which some of us have had some concerns about[1]; e.g. hypertension is once again defined as blood pressure of 140/90 mm Hg and above. Finally, and to my delight, the European guidelines have downgraded the beta-blockers as first treatment of hypertension in most patients[2]. The full presentation of these new guidelines, which have been extensively reviewed, will appear on 25 August at the meeting of the European Society of Cardiology (ESC). The guidelines will be simultaneously published by ESC and ESH. We are eagerly looking forward to reading them!

Lars H. Lindholm

lars.h.lindholm@umu.se

European Guidelines continued overleaf

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Comments on the 2018 ESC/ESH Guidelines for the management of arterial hypertension

Morris J. Brown

London, UK

Quick history

The treatment of hypertension is one of Medicine's success stories. Partly because Hypertension is the commonest non-communicable, treatable cause of serious morbidity, partly reflecting clever science and clinical investigation, we have more genuine choice of effective, well-tolerated drugs, and more long-term data proving their efficacy and tolerability, than elsewhere in Medicine. Most of these drugs, off patent, are so cheap, whilst complications of Hypertension are so devastating and expensive, that hypertension treatment is not only cost-effective but cost-saving, and deserves credit for substantial reductions in cardiovascular events, antedating widespread use of statins.

New drugs for hypertension, and the heyday of morbidity-mortality studies, are long past. These studies, and their prospective meta-analysis, provided unconditional negative answers to the big questions of the 1990s: were 'older drugs' failing to prevent CHD by causing adverse metabolic problems; were calcium blockers killing patients; did RAS blockers confer 'benefits beyond blood pressure control'.[1]

Recent challenges

The similar outcomes for the major classes switched focus from comparisons of morbidity-mortality to how best to lower blood pressure (BP); to optimal BP thresholds and targets; and to how BP be best measured. The last is important. But how ironic that a condition which is its measurement, on whose sole basis drugs are registered without proof of long-term efficacy and safety, still cannot agree what should be measured. The tragicomedy of this dilemma is illustrated by SPRINT. This brilliant trial was the highpoint of the last decade, asking how far BP should be reduced. But its translation into guidelines and practice has been bedevilled by use of an unfamiliar measurement device which, sin of sins, removed the placebo effect of treatment. When meta-analysis of RCTs shows the average difference in BP that has translated into long-term benefit (<10 mmHg) to be smaller than the average difference between devices, it is difficult to determine thresholds and targets.

So a 2018 guideline has a challenge to re-kindle enthusiasm, and do justice to its year of preparation by Bryan Williams, Giuseppe Mancia, and colleagues. One justification for quinquennial renewal is that guidelines are imperfect, compromise readings of incomplete data and arguments. There is no single route to consensus, so *vive la difference* among methodologies. These vary between the extremes of bottom-up, expert-scarce, stakeholder-rich, guidelines of NICE, UK, and top-down, expert-driven guidelines of ESC/ESH, delivered as 10 tableaux to an adulatory audience, with 2 symbolic minutes for discussion.

Continued overleaf

What's new

Bryan and Giuseppe highlighted six recommendations:

· **wider use of home BP monitoring to confirm diagnosis**

· **single pill combination treatment, started as initial therapy in most patients**

· **simplified treatment algorithms, comprising A+{C or D}**

· **new target BP ranges (aim for 140/90, then proceed to 130/80, but no lower than 120/70)**

· **detection of poor adherence**

and listed 26 gaps in evidence, needing further studies.

Have they succeeded in giving Hypertension its 2020 vision? To some, it is a puzzle how international guidelines can differ so much from each other. But given the variation in methodology, and acknowledgement that gaps (questions) outnumber recommendations (answers) by >4:1, the agreement is more striking than the discords. Similarly, my impressions are not criticisms, but musings of a triallist unfettered by the collective responsibility of a large committee.

What's excellent, what's good

Solution for resistant hypertension

Among the highlights, I expect the treatment algorithm to have greatest impact. As the English Channel widens, it is reassuring to interpret what's new as a rapprochement of UK and Continental approaches. The UK has long sought to limit the number of first-choice options at each stage of treatment, reflecting both the evidence for long-term benefit (sub-optimal for beta-blockade) and a rational connection between the physiological target of each drug class, and the pathway(s) at fault in the individual patient. It is a law of physics that pressure = force/area, suggesting two fundamental routes to Hypertension and its reversal. That subsets of patients are identifiable, with overwhelmingly superior response to one drug class than another, was substantiated by the British and Irish Hypertension Society (BIHS)'s PATHWAY-2 study, in which spironolactone vanquished conventional antihypertensive therapy as add-on for resistant hypertension. Roland Schmieder paid generous tribute to our PATHWAY programme for validating spironolactone as unconditional first choice in this condition – probably because resistant hypertension is what befalls the 99% of patients with primary aldosteronism who are never diagnosed.[2]

Single pill combinations

However, in moving from the six-sided diamond of ESH to the language of A+C+D, the 2018 guideline leapfrogs the stratified approach of current UK guidance to an emphasis on single pill combinations. This change illustrates the tightrope which guidelines tread between grand visions that lead doctors across a threshold, and details essential to implementation. Two tripwires may catch the unwary. In the large BIHS trials of initial combination therapy, PATHWAY-1 and ACCELERATE, inclusion required an untreated SBP>150 or DBP>90, and side effects were lower on combination than monotherapy. Excessive hypotension in milder patients could reverse symptom-benefit ratio. The second practicality is cost. Treatment with individual A, C or D costs a euro a month. There are no generic combinations of A+C; those of ACEi + diuretic cost 2-4 times the individual drugs, and use insufficient diuretic; only one ARB+diuretic is cost-neutral. It is hard to recommend triple combination pills without endorsing particular brands costing 8 times as much as component drugs. Treatment of hypertension could cease to be cost-saving. Within the 16-week phases of PATHWAY-1, ARB and diuretic achieved identical average BP readings, home or clinic, whether taken as one or two pills.[3]

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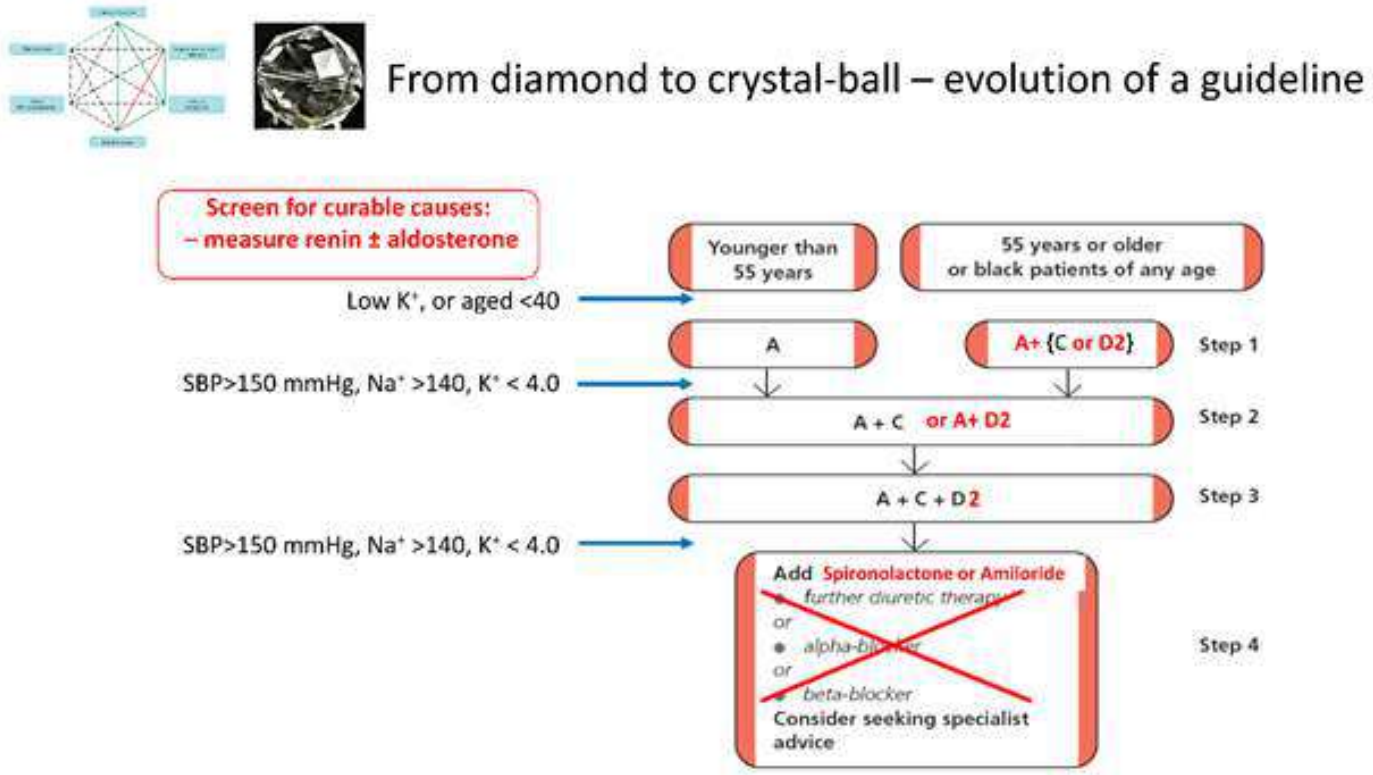

Figure 1

Initial combination therapy abolishes temptation to find each patient's best drug. Such lumping simplifies practice, but splitting helps patients to surpass average. A constituency not favoured by the guideline is the young, with no mention of using lifetime rather than absolute risk to enfranchise earlier treatment, or of the long-term benefit of recognising secondary hypertension. For a 30-year old with BP of 145/95 mmHg, it seems suboptimal either to start combination therapy or to wait for absolute risk to trigger treatment. A 25-euro measurement of plasma renin can lead to curable causes of hypertension, or predict optimal monotherapy.

A closing recommendation was for head-to-head comparison of thiazide and non-thiazide diuretics, but a more important question may be whether K+-sparing diuretic should supplement or substitute both of these at an earlier stage than resistant hypertension. Observations in registries point to a U-shaped curve relating CV outcomes to plasma K+. PATHWAY-3 showed half-dose HCTZ-amiloride to lower BP by 4 mmHg more than either diuretic alone, with respectively neutral and beneficial effect on plasma K+ and glucose.[4]

Legend to Figure

The new guideline (adapted).

On the right, recommendations mirror presentation by ESC/ESH except that [i] initial monotherapy remains the rule, not the exception, in younger patients, and [ii] K+-neutral combination of diuretics is preferred to K+-lowering sub-classes. Recommendations in red represent changes from NICE 2011.

On the left, 3 stages in the treatment algorithm are suggested as optimal for renin screening. A low value in a young patient may prompt initial therapy with diuretic, and/or investigations for primary aldosteronism.

(A= ACE inhibitor or Angiotensin receptor blocker; C=Calcium Blocker; D2=Diuretic combination)

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The Future

Imagery of the new guideline now enters Purdah until presentation at ESC. Respecting this embargo, I fill the vacuum with a crystal-ball depiction (Figure) of an ideal guideline, amalgamating ESH/ESC with a prediction of NICE 2018. The original AB/CD rule underpinning NICE was in part stimulus to research (eventually the PATHWAY programme), and in part belief that any memorable rule is better than no rule, encouraging escalation rather than inertia.[5] ESH/ESC's 'one pill, many drugs' is a clever evolution, if cheap formulations of optimal dose-combinations ensue. But the long-term vision for chronic, non-communicable disease should, through prevention and cure, be to maximise numbers on 'no pill, no drugs'.

Morris J Brown

morris.brown@qmul.ac.uk

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Bo Carlberg,

Umeå , Sweden

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Diagnosis of hypertension

At the session in Barcelona, Professor Krzysztof Narkiewicz from Gdansk made the first presentation and declared that ***"maybe you expected an earthquake but we decided to keep the classification and definition of hypertension from 2013"***. Hence, hypertension is still defined as an office blood pressure (BP) of 140/90 mmHg or above. The definitions of grade 1-3 hypertension are also unchanged, and so are the definitions of normal ambulatory BP and normal home BP. Hence, the new European guidelines do *not* follow the 2017 ACC/AHA definition of hypertension (BP 130/80 mm Hg or above) which is wise!

When to treat

In the new European guidelines, immediate pharmacological treatment is recommended to all people with a BP of 160/100 mmHg or higher. In those with grade 1 hypertension (140-159/90-99 mm Hg) with low to moderate risk, the effects of life-style intervention should be evaluated before drug treatment as in previous guidelines. In patients with coronary artery disease, treatment may be considered when BP is in the 'high normal' range i.e. 130-139/85-89 mm Hg. In patients with a systolic BP (SBP) of 150 mmHg and above, anti-hypertensive therapy is recommended to start with a two-drug

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combination, unless the patient is frail or elderly.

The new guidelines give us rather complicated recommendations on when drug treatment should be started and how intensive the treatment should be. For most patients, we have three different BPs to keep in mind for each group of patients: (1) There is one BP threshold for initiating treatment and (2) another for the BP goal. In addition, there is (3) one BP level we should not go below.

I think that in these new guidelines, the BP target is often quite narrow, in relation to the normal BP variability. For example, in a large population with hypertension, without complicating organ damage aged 18-65 years, you should start treatment if BP is 140/90 mm Hg or above and aim at a SBP of 130 mmHg or lower, but not below 120 mmHg. In addition, the diastolic target for this group of patients is 70-79 mmHg. Thus, the BP target is 120-129/70-79 mmHg. Needless to say, it may not be easy to tune in the BP within such a narrow range. A further problem is that you do not know what your patient's achieved blood pressure will be one month after the latest change in therapy. With similar evidence available, it would have been easier to have only one target: e.g. if BP is above xxx mmHg, start or intensify therapy; if BP is below xxx mmHg do not intensify therapy. Both, of course, to be modified if there are side effects.

In Barcelona, Professor Mancia from Milan told us that the results of the SPRINT trial had not had any major impact on the European guidelines, which is reassuring (!) However, in these new European guidelines the treatment targets are, in fact, lower for many groups of patients than in they were in earlier guidelines and this can be debated. E.g. the new treatment goal for patients above 80 is now a BP of 130-139/70-79 mmHg. Also, for patients with diabetes the new BP target of 120-130 mmHg is lower than the latest recommendation from American Diabetes Association (ADA)[1]. Finally, to me, the low BP target and the benefit of treatment may be questioned in low risk patients[2].

How to treat

In the European hypertension guidelines from 2013 beta-blockers were kept as first-line therapy, whereas in most other recommendations they were not. Now, this has finally changed. ARBs, ACE-inhibitors, diuretics and calcium channel blockers are now recommended as first line drugs, in most patients. Beta-blockers are only recommended if there are special indications for them e.g. heart failure, post-MI etc.

Device based therapy

Finally, the new European guidelines give a clear message on the use of device-based therapies. They are not recommended - apart from in clinical studies - until further evidence regarding their safety and efficacy is s available. This is a clear and scientifically sound statement which, I am sure, will stimulate further technical developments and clinical trials.

I look forward to reading the full text of these new and comprehensive European recommendations and the evidence behind them in late August.

Bo Carlberg
bo.carlberg@umu.se

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Alberto Zanchetti
27.07.1926 - 25.03.2018

John Chalmers

Alberto Zanchetti was a remarkable man, with huge intelligence and capacity, so many talents, so much warmth and humanity. An immediately likeable and loveable man! Professor Zanchetti died unexpectedly, after a short illness, while fully engaged in life and science until that final illness. But he had reached the age of 91 in excellent health and with full 'joie de vivre'.

Born in Parma, he graduated in Medicine there before moving to Pisa to work under Professor Moruzzi, the world famous neurophysiologist, and made major contributions before leaving to join Professor Cesare Bartorelli, Chief of the Institute of Internal Medicine in Sienna. Here he made his mark on the role of thiazide diuretics in the treatment of hypertension and then followed Bartorelli to Milan where his career bloomed and over time he rose to become the Director of the Centro di Fisiologia Clinica e Ipertensione, Ospedale Maggiore, Universita di Milano, and then some 20 years later, the Scientific Director of the Instituto Auxologico Italiano, Milano and Emeritus Professor of Internal Medicine at the University of Milan. One of his major legacies lies in all the students he mentored over many years.

Alberto Zanchetti was a most accomplished scientist and a shining beacon in our field of hypertension and cardiovascular diseases. He astounded us time and time again at scientific meetings by his encyclopaedic knowledge, encompassing the whole field of cardiovascular medicine, and it often seemed, all fields beyond. And almost as often, by his evident pleasure in talking about these topics! And he and his colleagues continued to produce fine science, with a stream of illuminating meta-analyses in the past few years.

But Alberto was so much more than just the scientist. He was the complete renaissance man, with a passion for, and a deep appreciation of the arts, of music, of history and particularly of the classics. He amazed us with the breadth and depth of his knowledge and understanding of fields outside of our usual endeavours. And in his heyday, he delighted in making sure that our Milan meetings, both ISH & ESH, exposed us to the best music, be it opera at La Scala, or Bach at Santa Maria delle Grazie, and to the finest paintings and sculptures before the meeting dinners, at a splendid art gallery or museum.

One of Alberto Zanchetti's greatest contributions has been as an interpreter, critic and distiller of science and of the latest trends in our field of hypertension and cardiovascular diseases. He always had a rare capacity to extract the essential message of the latest paper or presentation, and that has been one of his core strengths as Editor-in-Chief of the Journal of Hypertension, a

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task he has accomplished with great distinction for around 20 years. It has also been a key for his contributions to so many guidelines, first of the WHO-ISH and later of the ESH/ESC. Another of his great contributions was his role in the birth and development of the ISH and later of the ESH.

As would be expected, Professor Zanchetti won many awards and honours, including the Marzotto Prize for Culture and Science in 1961, the Award for International Achievement of the AHA in 1977, the Franz Volhard Lecture and Award of the ISH in 1986, the Henri Denolin Lecture of the European Society of Cardiology in 1991 and the Riva-Rocci Award of the Italian Society of Hypertension in 1997, and he rose to be President of the ISH, of the ESH and of the European Society of Clinical Investigation. He was in much demand by societies around the world as keynote speaker and he was often honoured with Honorary Membership or Fellowship of National Societies of Hypertension as well as Honorary Doctorates of prestigious universities.

But all those achievements and attributes pale into insignificance beside the human qualities that made Alberto Zanchetti such a well-loved man in our field. It was these human qualities that made him stand out and sought after by all! He was equally warm and approachable with the young and shy research student, the experienced clinician or researcher, the industry representative in the exhibition hall and with our spouses and families. He was in so many ways "pater familias" for the world of hypertension, certainly for those in the ISH and ESH. His passing leaves a very big hole but thinking of Alberto brings to mind many happy and inspiring memories. Vale Alberto Zanchetti.

John Chalmers
chalmers@georgeinstitute.org.au

Nordic lights, Arjeplog, Sweden. Photo: Christer Andersson.

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Left to right: Agustin Ramirez, Brandi M. Wynne, Cesar A. Romero

Argentine Society of Hypertension (SAHA) meeting, Buenos Aires

Cesar A. Romero & Brandi M. Wynne

Annually, the basic science, translational and clinical investigators of the Argentinian Society of Hypertension (SAHA) comes together for its scientific meeting. This year, on April 12th-14th 2018, the SAHA meeting took place in Buenos Aires. This year's meeting was organized by Dr Pablo Rodriguez (Organizing Committee President) and Dr Paula Cuffaro (Scientific Committee President), and was a great success. This year SAHA brought together more than 1900 people; this includes physicians as well as research investigators from basic and clinical areas related to the cardiovascular and hypertension field. Internationally recognized speakers from both Europe and the USA, as well as national leaders in hypertension gave lectures and symposium, all discussing the latest advances in hypertension research.

The Argentine society meeting is the central hypertension meeting in Latin America, thus attendees from Uruguay, Chile and Brazil also attended and presented their original work. ISH representatives, Agustin Ramirez (Argentina, Council Member), Brandi Wynne (USA, New Investigator Committee) and Cesar Romero (USA, New Investigator Committee) attended the meeting. SAHA and ISH jointly hosted a Young Investigator's Symposium on April 12th, which was well-attended and moderated by Dr Ramirez (ISH) and Dr Irenne Ennis (SAHA). Dr Wynne discussed the importance of a mentorship in young investigators, as well as details to think about when finding and developing the mentoring relationship. Dr Wynne also introduced the available ISH initiatives, emphasizing the ISH Mentorship Scheme offered for young investigator. This was followed by Dr Romero (ISH) who presented data about selecting topics in hypertension research, the importance of correctly defining scientific questions, and correctly designing the research to obtain meaningful answers. The last speaker was Dr Alejandro Diaz (SAHA member and ISH Research Fellow), who discussed best practices for showing quality data. The symposium was attended by young investigators and physicians starting and/or further developing their interests in hypertension research. The session ended with a fruitful open panel discussion, allowing for questions and comments from and between attendees. On Friday 13th, a special conference was held to inaugurate the young investigator section of the SAHA, namely "Jovenes Investigadores de la SAHA". This section aimed to incorporate young physicians, researchers and students to the SAHA, having the ISH-NIC as a role model.

The SAHA president Dr Judith Zilberman gave a warm welcome to the new investigators and discussed the benefits and opportunities that SAHA has created to support hypertension research in Argentina, focusing on young investigators. Dr Romero (ISH) was invited to present in more detail the ISH-NIC initiatives available to young investigators, and invited people to join the ISH. Additionally, Dr Brandi Wynne (ISH) gave a lecture on Friday evening about the interplay between inflammation, salt and hypertension. The Argentine meeting of hypertension was a great opportunity to reinforce the friendship and collaboration between the ISH and the SAHA, and we look forward to future collaborative events and research.

Cesar A. Romero
cromerocba@hotmail.com
Brandi M. Wynne
brandi.m.wynne@emory.edu

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The Shanghai Institute of Hypertension, Shanghai, China

Qi-Fang Huang & Ji-Guang Wang
The Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China


Ji-Guang Wang

The Shanghai Institute of Hypertension was established in 1958 under the auspices of the municipal government of Shanghai. The Institute is dedicated to clinical, basic, population and translational research in hypertension. Inside the Institute, there are several research platforms, such as the Shanghai Key Laboratory of Hypertension, Cellular and Molecular Biology Laboratory, Centre for Epidemiological Studies and Clinical Trials, Centre for Vascular Evaluations, and Centre for Community Control of Hypertension. The clinical wing of the institution is the Departments of Hypertension in Ruijin Hospital and Ruijin North Hospital. The Institute offers postgraduate programs for master's and doctoral degrees in cardiovascular medicine in Shanghai Jiao Tong University School of Medicine.

Over the years, especially in the past decade, the Institute had published a series of scientific papers in international literature. We performed genome-wide association studies in the Chinese population using various techniques with our own biological bank of more than 20,000 hypertensive patients and normotensive controls. Using the early technique of microsatellite markers, a susceptibility locus for hypertension was mapped to the chromosome region 2q14-q23[1]. In subsequent association and functional studies, a rare variant Arg188Gln of the kynureninase gene (*KYNU*) located in this region was found to be associated with hypertension, and the KYNU protein with the mutation (Gln) showed less catalytic efficiency than the wild type enzyme[2]. We also performed a genome-wide association study on the basis of SNPs, and participated in the Pan-Asia collaboration of genome wide association studies. This collaborative project confirmed seven loci that had been previously reported to be associated with systolic and/or diastolic blood pressure in populations of European descent. In addition, this project identified several new genetic variants (ST7L-CAPZA1, FIGN-GRB14, ENPEP, NPR3 and TBX3) associated with hypertension[3].

In our population- and patients-cohort studies, we reported a special form of masked hypertension, termed as "isolated nocturnal hypertension" and characterized by elevated night-time blood pressure and normal daytime blood pressure. This form of hypertension, though mild in the level of

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blood pressure, does confer cardiovascular risk[4]. In our China Ambulatory and Home BP Registry study initiated in 2009, participants underwent clinic, home, and 24-h ambulatory BP measurements. We investigated the accuracy of home blood pressure monitoring in the diagnosis of white-coat and masked hypertension in comparison with ambulatory blood pressure monitoring. We found home BP monitoring has high specificity, but low sensitivity in the diagnosis of white-coat and masked hypertension, and may therefore behave as a complementary to, but not a replacement of, ambulatory BP monitoring[5]. In our elderly population study, by recording pulse waves at the left and right ankles by pneumoplethysmography and calculating the percentage of upstroke time per cardiac cycle, we found that upstroke time per cardiac cycle at baseline had an overall sensitivity and specificity of 86% and 80%, respectively, for the diagnosis of peripheral arterial disease (upstroke time per cardiac cycle, ≥21.7%) in comparison with computed tomographic angiography and significantly ($P<0.0001$) predicted total and cardiovascular mortality[6].

Our fundamental research focused on the role of inflammation, an immune response in vascular remodeling in hypertension, and on vascular adventitia. Our recent research has shown that adventitia and perivascular tissue are a complex and heterogeneous compartment of the vessel wall, and a dynamic mixture of several interactive cell types. We have found that fibroblasts secrete osteopontin (OPN) to induce macrophage chemotaxis and cause neointima formation[7]. We have also found that perivascular adipose tissue (PVAT)–derived complement 3 (C3) induces differentiation of fibroblasts to myofibroblasts, which contribute to vascular adventitial remodeling processes[8]. We have confirmed that deficiency of complement C3a and C5a receptors prevents angiotensin II-induced hypertension via regulatory T cells (Tregs). Tregs deletion blocks the protective effects of C3a and C5a receptor deficiency (DKO) against blood pressure elevation, suggesting complementing Tregs could be a novel strategy for the treatment of hypertension[9]. Moreover, PVAT-derived PDGF-D contributes to aortic aneurysm formation via activating adventitial inflammation[10]. We found that brown adipose tissue (BAT)-derived fibroblast growth factor 21 (FGF21) upon adenosine A2A receptor (A2AR) activation, plays an important endocrine role in hypertensive cardiac remodeling. Recombinant FGF21 administration improves iBAT-depletion-induced dramatic cardiac remodeling in hypertensive mice. Brown adipocyte-specific FGF21KO blocks the effects of A2AR agonism in attenuating hypertensive cardiac remodeling. These provide the first line of evidence for a direct crosstalk between BAT activity and cardiac protection in hypertension[11]. These studies suggest that inflammation and immunity-mediated adipose dysfunction may play an important role in hypertension-related target organ damage.

Hypertension affects approximately a quarter to a third of adult population. Hypertension control therefore requires joint efforts of the community, including patients themselves and their community and family physicians. The institute recently started a collaborative project in a community in Shanghai to do research on the management of hypertension. We established a web- and wireless-based system for the measurement, transmission, storage and analysis of blood pressure. This automated system might improve blood pressure control in this community, in the future hopefully will expand to the whole city of Shanghai or even other Chinese provinces, and in the long run will help reduce the risk of cardiovascular complications of hypertension.

Ji-Guang Wang
jiguangwang@aim.com

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Please get in touch with the author for further references

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8 Waldegrave Road, Teddington, Middlesex

TW11 8HT

UK

Tel (UK): +44 20 8977 7997
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