In the new US Hypertension Practice Guidelines – presented two weeks ago at the annual meeting of the American Heart Association (AHA) in Anaheim, CA – hypertension is defined as a blood pressure (BP) of 130/80 mm Hg and above (mean of two or more recordings at two or more visits). Those with 120–129 mm Hg in systolic BP and below 80 mm Hg in diastolic BP have “Elevated BP”. Treatment should start with non-pharmacological intervention followed, if needed (BP 140/90 mm Hg and above for the general population, 130/80 mm Hg and above for high-risk patients), by combined drug treatment. Primary drugs are: Thiazide or thiazide-type diuretics, ACE-inhibitors, ARBs, and both types of Calcium-channel-blockers. Beta-blockers are not first-line drugs, unless the patient has ischaemic heart disease or heart failure. The new target blood pressure is BP below 130/80 mm Hg for most patients; systolic BP below 130 mm Hg for those aged 65+.

An estimated 46% of US adults have hypertension when the new practice guidelines are applied to the 2011–2014 National Health and Nutrition Examination Survey (NHANES) population (n=9 623); 76% in the age group 65–74 and 82% in those aged 75+ (ref.). These figures are considerably higher than when the JNC-7 guidelines were applied to the same population (ref.). The estimated percentages of US adults recommended antihypertensive medication are: 36% (all), 74% (65–74 y.), and 82% (75+ y.). Interestingly, two of these treatment figures are only slightly higher than when the JNC-7 guidelines were used (ref.). A comprehensive discussion of the new guidelines, written by Ernesto Schiffrin, Canada, can be found on page 5.

At the same time as the new US guidelines were released, Bo Carlberg (former member of the Hypertension News team) and his young co-worker Mattias Brunström, Sweden, published a comprehensive meta-analysis in JAMA Internal Medicine of 64 unique BP trials comprising more than 300 000 patients. Primary preventive BP lowering

Continued on next page...
was associated with reduced risk of death and cardiovascular disease only if baseline systolic BP was 140 mm Hg or higher. At lower levels of baseline BP, treatment was not associated with any significant benefit in primary prevention, unless the patients suffered from coronary heart disease.

A discussion of this elegant meta-analysis written by Thomas Kahan can be found on page 8.

The new US guidelines are comprehensive (122 printed pages), well written, easy to read, and interesting. The treatment goals (see above) are prudent and would have been more draconic, had the project group used the SPRINT target (systolic BP below 120 mm Hg).

Moreover, the project group should be commended for applying them to a large study population to get estimates of the prevalence of hypertension as well as the percentage of patients in need of treatment in the US (ref.). One may ask, however, if the recommendations are realistic, when about 80% of people aged 65+ get a diagnosis of hypertension and almost all of them are to be treated. Time will tell, if these recommendations are accepted by American practitioners, hypertension and other specialists as well as by the population.

Finally, the new US recommendations are likely to influence coming European and other guidelines, where the results of the meta-analysis, discussed above, and other new trials will be taken into account. Until then, let us follow the outcome in the US with interest – it is indeed “America First” now!

- Lars Lindholm

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Join us at the ISH meeting in Beijing in 2018!

SAVE THE DATE
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27th Scientific Meeting of the International Society of Hypertension, 20-23 September 2018, Beijing, China

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For more information and an overview of registration fees, please visit www.ish2018.org.
February 16th-18th to review ISH activities in the previous year and plan those for the following year.

From a scientific viewpoint, I am delighted to report that the ‘CREOLE’ trial which is running in 6 sub-Saharan countries and is designed to evaluate the optimal 2-drug combination of antihypertensive agents in terms of BP-lowering in black patients, has almost completed recruitment. This trial should be ready to report in time for the Beijing meeting and will generate unique data as to which combination of 2-drugs (A+C or A+D or C+D) lowers 24 hour BP levels most effectively in black hypertensive patients.

From an administration viewpoint, we are in the process of re-arranging the five ISH Regional Advisory Groups (RAGs) to hopefully generate more equitable distribution of ISH activity around the world.

We will update you on this matter once the revised RAGs have been ratified by the council.

May I remind current members to renew their ISH memberships for 2018 in response to the renewal notices that many will receive in the next few weeks.

Finally, on behalf of the Executive Committee of ISH, may I wish all members of ISH and readers of Hypertension News a very Happy Christmas.

Another busy 3 months for ISH brings my first year as President to an end.

We have closed the May Measurement Month (MMM) database (as of November 26th) so that final data cleaning should allow key analyses to be completed before Christmas. That will be followed by an investigator meeting in mid-January, when results will be presented to investigators from all over the world and the campaign for MMM 2018 will be fine-tuned.

Since my last report, Professor Alta Schutte was appointed as President-Elect (many congratulations) and meetings and arrangements for the 2018 ISH meeting in Beijing are progressing well under the leadership of Professor Thomas Unger.

The Society is closely involved in the development of a series of BP treatment algorithms which will be incorporated into the Global Hearts Initiative – led by World Heart Federation (WHF), World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC). The same algorithms will also be used in the RESOLVE programme – which is targeting improved BP control as one of the three targets designed to save 100 million lives! The Society has also joined the Global Coalition for Circulatory Health which is coordinated by WHF and WHO.

In March 2017, the Council, plus other officers of the Society, met in Dubai to replace the ‘usual’ Council meeting - which normally takes place during the summer at the annual ESH meeting. Such was the success of our March 2017 meeting in Dubai, that we plan to regroup in Dorking (England) from

REFERENCES

- Neil Poulter
A huge global public screening campaign led by the International Society of Hypertension (ISH) to highlight the importance of measuring blood pressure.

Launched in May 2017, the goal was to screen as many people as possible aged over 18 years who ideally had not had their BPs measured for at least 12 months prior. Neil Poulter, ISH President, said “Raised blood pressure is the biggest single contributing risk factor for global death and the worldwide burden of disease, and May Measurement Month has already begun to lay strong foundations for significantly increasing public understanding”

Following the screening, objectives of the programme were to a) provide participants diet and lifestyle treatment advice to participants with blood pressure in the hypertensive range (>140mmHg systolic and/or >90mmHg diastolic), and b) to use the data on untreated hypertension to motivate governments to improve local screening facilities and policies - thereby reducing the global burden of disease associated with hypertension.

Overall implementation and management of the 2017 campaign was conducted by an ISH Project Team based at the Conference Collective in London, UK, with local screening activities in each country coordinated by at least one dedicated volunteer Country Leader, who in turn managed regional and site level volunteer efforts. Thanks to these incredible volunteers, over 100 countries took part in the campaign and we are on track to achieve blood pressure measurements from over 1 million participants - making this one of the biggest public screening exercises the world has ever seen.

We expect to receive all data by the beginning of December which will allow the analysis to be completed by the end of 2017. We hope the analysis will include (but not be limited to):

- The prevalence of previously undiagnosed hypertension at a national, regional, global and ethnic level among volunteers.
- Age and sex stratified levels of systolic (S) BP and diastolic (D) BP generated at a national, regional, ethnic and global level.
- The association between the same BP parameters, time of day and day of week, and where available, room temperature and altitude.
- The association between the same BP parameters and previous CV disease, diabetes, smoking and alcohol intake and, where available, anthropometric variables.

Now we’re looking ahead to May 2018 and to reaching even more countries and more people around the world and to improving the quality of data for our scientific analysis. If we are to achieve this, then once again, we need the generous help of volunteers from all over the world to make this happen. So if you’d like to help us create history and improve world health, please get in touch.

email: manager@maymeasure.com
A Simple Measure to save Life - be part of it
#checkyourpressureMAY MEASUREMENT MONTH

- MMM Project Team
I am delighted to confirm that the ISH Executive has ratified the membership of the Awards Committee. The following members of the ISH have been invited (and accepted) to serve on the Committee: Professor Neil Poulter (Chair), Professor Alta Schutte (Vice President and President-Elect), Professor Maciej Tomaszewski (Secretary), Dr Ruan Kruger (New Investigator Committee representative), Professor Nadia Khan (Council member), Professor Sadayoshi Ito (Council member), Professor Tony Heagerty (Past President) and Professor John Chalmers (Past President).

Together with the recently established Awards Committee, the ISH has 14 separate Management groups/Committees; this includes the Board of Management of Journal of Hypertension and the Editorial Board of ISH Hypertension News. A total of 80 ISH members serve on these committees in different capacities. These members come from 38 different countries across 6 continents, which means that almost 10% of our members are involved in leadership roles in the Society.

ISH Beijing 2018 Meeting

ISH Beijing 2018 Committee members met the Local Organising Committee in Shanghai on 21st September 2017. The meeting was attended by the ISH President, myself, Professor Masatsugu Horiuchi (ISH Treasurer), Professor Thomas Unger (Chair of the Committee), Professor Ji-Guang Wang (Beijing 2018 Liaison Officer) and Professor Lars Lindholm (Past President). We have made very good progress with the framework of the programme and identification of speakers for our 27th Scientific Meeting (Hypertension Beijing 2018).

New Investigator Programme, Singapore

The New Investigator Committee (led by Dr Ruan Kruger) and Mentorship and Training Committee (led by Professor Fadi Charchar) contributed an exciting and intellectually stimulating scientific and social programme during the Asia Pacific Society of Hypertension Meeting in Singapore (6-8 October 2017). Over 70 participants from nearly 20 countries attended these ISH events; Professor Mark Caulfield from William Harvey Research Institute, London, UK gave the symposium keynote lecture. Please view the ISH Facebook page and page 29 of this newsletter issue for more information on the ISH Singapore events.
Mentorship and Training Committee

The Mentorship and Training Committee recently circulated a call to membership in search of suitable mentors for a new group of ISH mentees. This call received an overwhelmingly positive response - 130 ISH members confirmed their readiness to support and act as ISH mentors. Professor Charchar and his Committee are extremely grateful for such a wonderful response to their appeal - they will be in touch with the selected few who best match the training requirements of the mentees.

NIC/AHA TAC Collaboration

The New Investigator Committee (NIC) partnered again with the Trainee Advocacy Committee (TAC) of the American Heart Association (AHA) Council on Hypertension during the annual Scientific Sessions of the Council in San Francisco (14-17 September 2017). The tradition of this collaboration dates back to 2014. As in previous years, the ISH New Investigator Committee (represented by Drs Oneeb Mian, Cesar Romero, Brandi Wynne, Dylan Burger and Richard Wainford) was delighted to co-sponsor awards for the best science presented by the new generation of researchers.

Welcome - New ISH Committee Members!

We welcome Professor Enrico Agabiti Rosei as the new representative of the European Society of Hypertension (ESH) on the ISH Council. Professor Agabiti Rosei is replacing Professor Josep Redon. We are very grateful to Professor Redon for the years of his service on the ISH Council.

I am delighted to confirm that Dr Susie Mihailidou from Sydney, Australia will join the Communications Committee to promote the visibility of the Society’s publications in social media.

2018 Membership Renewals

The ISH annual membership fees for 2018 will slightly increase – from USD 175 to USD 185 for ISH Professional Members and from USD 215 to USD 225 for Joint ISH-ESH Members. We encourage you to pay your 2018 dues by the end of the year.

Look out for your 2018 Membership Renewal notices in your emails!

Let me take this opportunity to wish all the readers of Hypertension News a wonderful festive season and the most prosperous 2018!

- Maciej Tomaszewski
This is a somewhat provocative manuscript published in Diabetes Care just last month.

Preeclampsia is a common cause of maternal and infant morbidity and mortality in pregnancy\(^1\). Its prevalence is higher in women with type 1 diabetes and is associated with increased risk of renal disease later in life\(^2\).

In this study by Kelly and colleagues, the authors examined markers of subclinical renal injury and the relationship with development of preeclampsia in normoalbuminuric women with type 1 diabetes\(^3\). The authors focused on two biomarkers of tubular injury: Kidney Injury Molecule -1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) as well as estimated GFR as determined by CKD-epi.

Interestingly, urinary NGAL, was significantly increased at first visit (~12 weeks) in women with diabetes who developed preeclampsia when compared with those women who did not. By contrast, neither plasma NGAL or urinary KIM-1 were associated with preeclampsia. In addition, eGFR was increased at first visit in women who developed preeclampsia compared with those who did not.

The difference in eGFR is perhaps not surprising as it is reflective of glomerular hyperfiltration and glomerular stress. Given the well-established microalbuminuria in preeclampsia this has long been appreciated as a glomerular disease. As such, association of early hyperfiltration (beyond what is typically seen in normal pregnancy) with subsequent development of preeclampsia is perhaps not surprising. Nevertheless changes in GFR may have value in risk assessment in early pregnancy.

Perhaps more surprising is the elevation in NGAL in those who developed preeclampsia. NGAL is better known as a marker of damaged epithelial cells, largely in ischemic and nephrotic injury. Based on their observations, the authors propose a prediction model for development of preeclampsia which incorporates urinary NGAL and observed an improved predictive value compared to models based on only clinical factors. Tubular injury is not typically considered a hallmark of preeclampsia so changes to urinary NGAL and utility in prediction of preeclampsia are surprising. It is notable that no changes were seen in a separate tubular injury marker KIM-1.

A number of caveats must also be considered. First, the study focused exclusively on women with diabetes and findings may not extend to healthy individuals or to other conditions. Second, the number of patients studied was low. Third, there were some baseline differences between women with type 1 diabetes who developed preeclampsia and those who did...
not. Finally, the discrepancy between KIM-1 and NGAL results is curious, although in the manuscript the authors suggest that KIM-1 has weaker prognostic value than NGAL. All limitations are acknowledged by the authors and they correctly advocate for large international collaborations to validate early studies such as this.

Nevertheless, the present study does highlight a potential role for subclinical renal injury in predisposing women with type 1 diabetes to preeclampsia. In addition, this early work sets the stage for larger investigations to determine whether incorporation of NGAL into current models can improve risk prediction for preeclampsia.

- Dylan Burger & Akram Abolbaghie

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Hot Off the Press

Thomas Kahan

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Blood pressure lowering and outcome according to baseline blood pressure

Many guideline recommendations for hypertensive patients favour a target for treatment in most patients to a systolic blood pressure of less than 140 mm Hg. Furthermore, systematic reviews and meta-analyses suggest that more intensive treatment is beneficial compared to less intensive treatment [1,2]. There is less agreement on how far systolic blood pressure should be reduced. While results from recent reviews and meta-analyses [3-5] suggest that a target systolic blood pressure of approximately 130 mm Hg in high-risk cardiovascular patients may be optimal, the benefit for hypertensive patients in primary prevention and with less risk remains more uncertain.

Recently, Brunström and Carlberg [6] performed a study that may help to increase our understanding on these issues. The authors performed a systematic review and meta-analysis on the association of blood pressure lowering with cardiovascular morbidity and mortality across different baseline systolic blood pressure levels to assess the optimal cut-off for treatment of hypertension. The authors included trials with 1000 or more patient years of follow-up that compared antihypertensive drug treatment versus placebo, or compared one drug treatment with different target blood pressure values. Studies comparing different drug classes were not included, and excluding studies in patients with heart failure or left ventricular dysfunction and in patients with a recent myocardial infarction. Brunström and Carlberg eventually included 74 trials with 306 273 participants (40 % women, mean age 64 years). The majority, 51 studies including 192 795 patients (47 % women, mean age 63 years), were considered primary preventive, while the remaining trials were considered secondary preventive, mostly in coronary heart disease or stroke patients.

Continued on next page...
Mean baseline systolic blood pressure in the primary preventive studies was 154 mm Hg. Patients were followed up for a mean of 4.0 years and the mean difference between active treatment and control was 7 mm Hg. Treatment to lower blood pressure reduced the risk for all-cause mortality by 7% (95% confidence intervals 0 to 13%) with a baseline systolic blood pressure of 160 mm Hg or above, by 13% (0 to 25%) with a baseline pressure of 140-159 mm Hg, and did not reduce all-cause mortality (2%, -4 to 10%) with a baseline systolic blood pressure below 160 mm Hg. Similar results were obtained for major cardiovascular endpoints (MACE), coronary heart disease, and stroke, while heart failure was reduced only at basal systolic blood pressures of 160 mm Hg or above, and for values below 140 mm Hg.

There were 12 trials in coronary heart disease patients including 77,562 participants. Baseline systolic blood pressure was lower in these studies (138 mm Hg) than in the primary preventive trials. Patients were followed up for a mean of 4.5 years, and the mean systolic blood pressure difference between active treatment and control was 4 mm Hg. Thus, no analyses stratified by baseline systolic blood pressure were performed. Overall, treatment to lower blood pressure reduced the risk for MACE (by 10%, 3 to 16%), coronary heart disease (by 12%, 0 to 23%), stroke (by 17%, 4 to 27%), and heart failure (by 17%, 4 to 28%), with no significant effects on all-cause mortality (by 2%, -7 to 11%) or cardiovascular mortality (by 5%, -9 to 16%). The six trials in stroke patients including 33,102 participants had a baseline systolic blood pressure of 146 mm Hg and mean follow up was 2.9 years. The mean systolic blood pressure difference between active treatment and control was 6 mm Hg. There was a trend for a reduced risk for cardiovascular mortality, MACE, and stroke in these analyses. Of note, there were fewer patients and a shorter follow up period, as compared to the other patient groups.

Conclusions derived from meta-analyses are critically dependant on the selection of studies included, the quality of studies eventually included, the statistical methods applied and the methods of standardization of the results, and the availability of individual patient data. These issues may contribute to the slightly different conclusions shown in the study by Brunström and Carlberg, as compared to other recent publications. Nevertheless, these results confirm the benefit of antihypertensive treatment in primary prevention of patients with a baseline systolic blood pressure of 140 mm Hg or above. Furthermore, the mean age of the participants in the studies considered primary preventive was 63 years, suggesting that these results are likely valid also in older (65 years or above) patients. However, the current results did not show a benefit of antihypertensive treatment in primary prevention with a baseline systolic blood pressure below 140 mm Hg. Second, the current results in patients with coronary heart disease, where baseline systolic blood pressure was 138 mm Hg, provide circumstantial evidence for a benefit of antihypertensive treatment for patients with a baseline systolic blood pressure below 140 mm Hg.

In conclusion, while a target for treatment in most hypertensive patients may be a systolic blood pressure of less than 140 mm Hg, the current analysis support previous results to suggest that target systolic blood pressure of 125-135/70-75 mm Hg in high risk cardiovascular patients may be warranted [7].

- Thomas Kahan

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The International Society of Hypertension (ISH) will hold its 27th Scientific Meeting “Hypertension Beijing 2018” at Beijing International Congress Center, on September 20-23, 2018. The ISH congress is organized in conjunction with the Chinese Hypertension League (CHL) and the Asian-Pacific Society of Hypertension (APSH).

The ISH was established in 1966, more than fifty years ago. From the very beginning it has been devoted to promoting and encouraging scientific research and knowledge about the epidemiology, the pathophysiology and the sequelae of arterial hypertension including acute and chronic heart and kidney disease and stroke. Besides the therapeutic aspects, prevention and management of hypertension and hypertension-related diseases have gained more and more attention and weight within the activities of the society in recent years.

While the ISH had its original foundations in Europe, the Society soon spread to the American continent and to Australia and Japan and, subsequently, to all seven continents of our world. Thus, the ISH has become the only scientific hypertension society which is globally present and operating.

According to the words of the current ISH president, Neil Poulter, professor at Imperial College, London, UK, the ISH “…is the world’s premier Society dedicated to research into the causes of hypertension and the best treatment for raised blood pressure. The ISH recognizes that to counter the hypertension epidemic it takes the brightest minds, the best research and effective education and implementation. This goal underpins the activities and strategic alliances of the ISH.”

Strategic alliances are mandatory to guarantee success in today’s globalized, interconnected world. The ISH engages in partnerships with many if not all national and international hypertension societies and institutions that represent blood pressure interests. Most prominent among those are the World Hypertension League (WHL), the International Society of Nephrology, the World Health Organization (WHO), and in addition, recognized international journals like The Lancet and the Journal of Hypertension. Regional Advisory Groups of the ISH have been formed to assist in teaching activities in developing and still economically disadvantaged countries worldwide. All of these will be represented at the upcoming congress in Beijing.

Research into high blood pressure and related diseases has always been a major focus within the activities of the ISH. I remember an ISH congress in Interlaken, Switzerland in 1984. I was to give the first oral presentation in the main program, and I was very proud of this honor and also of belonging to ISH, this prestigious club. But this was, of course, not the main point - that ISH congress was one of the

Continued on next page...
first occasions where Adolfo de Bold from Canada presented his findings on a natriuretic principle stored in vesicles in the atria of the heart, which was later to become Atrial Natriuretic Peptide (ANP).

Stimulated by this seminal discovery, we rushed home to our laboratory in Heidelberg, Germany, and we were able to publish the first paper on ANP measurement by HPLC in the blood of rats following volume stimulation in “Nature”. Without the ISH congress, this would probably not have happened, at least not so fast.

Four years later, in 1988, Masashi Yanagisawa, a young scientist then working in Tsukuba, Japan, gave one of his first presentations about the gene and peptide sequence of endothelin at the ISH congress in Kyoto, kicking off a worldwide long-lasting "epidemic" of research into the peptide family of endothelins, their receptors and functions with all the basic and clinical aspects emanating from this initial description.

These are just two examples of how ISH congresses have attracted and stimulated researchers’ minds, giving rise to important scientific progress in hypertension and beyond.

Research, translation and implementation together with a good grain of education have been the major features of the bi-annual ISH congresses around the world for more than fifty years, and they still are. Young researchers, and especially female scientists, are particularly welcome at the congress and receive special attention through, among other things, fellowships and stipends. They will carry the flag of hypertension-related issues into the future.

The ISH congress "Hypertension Beijing 2018” will feature keynotes by eminent international scientific leaders along with sessions on virtually all aspects of hypertension. These include epidemiology and population science related to high blood pressure in developed and in developing countries around the world, including initiatives such as “May Measurement Month (MMM)”, which started this year and will be followed up in subsequent years to raise awareness of the “silent killer” and identify hypertensive individuals. Hypertension research, basic and clinical, will be presented and discussed further from atrial fibrillation to traditional Chinese medicine, from genetics to vascular biology, from endocrine hypertension to new devices in hypertension treatment and so on. Specific regional issues in Africa, Asia, East Europe, India, Oceania and The Americas will be given room as well as gender-specific and age-related aspects of hypertension.

Come and join us at “Hypertension Beijing 2018”! Be inspired by high quality scientific presentations, by discussions and interactions with colleagues from around the world. I’m certain that our Chinese hosts will give all of us participants a warm welcome, letting us enjoy the typical Asian hospitality in their homeland China, the famous “Middle Country”.

- Thomas Unger

Click here to get inspired for your trip to Beijing!
Fourteen years after the previous comprehensive US guideline on management of hypertension (JNC7), and 4 years after the controversial guideline of the 2014 Report from the Panel Members appointed to the Eighth Joint National Committee (JNC8 panel member report), the American Heart Association and the American College of Cardiology have come out with an extensive and novel guideline for management of high blood pressure which was presented at the AHA Scientific Sessions on November 13, 2017 in Anaheim, CA, USA. It was simultaneously published online in the Journal of the American College of Cardiology and in Hypertension, journal of AHA, on the same date.¹

Importantly, the recommendations in the guideline are accompanied by Class of Recommendation and Level of Evidence applied to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care.

A major novelty of the Guideline is that for the first time it modifies the classical definition of hypertension that used to be blood pressure (BP) ≥140/90 mm Hg. It proposes a category of Elevated blood pressure at a systolic BP (SBP) of 120 to 129 mm Hg. Subjects in this category need to undergo lifestyle changes to prevent progression of their condition to hypertension. The new guideline defines hypertension as BP ≥130/80 mm Hg. At or above this level of BP, when confirmed on a second occasion, individuals need treatment, which can include lifestyle modification or in cases of more elevated BP and greater cardiovascular risk in addition the use of antihypertensive medications. The change in the definition of hypertension means that 46% of US adults are identified as having high BP, compared with 32% under the previous definition according to US National Health and Nutrition Examination Survey (NHANES) 2011-14.² The prevalence of hypertension was higher when defined by the present 2017 ACC/AHA guidelines compared to the JNC7 guidelines within all age, gender, race-ethnicity, and cardiovascular disease (CVD) risk groups.³

Hypertension is classified as stage 1 when BP is ≥130/80 but <140/90 mm Hg, confirmed at a second visit. It is stage 2 when BP is measured ≥140/90 mm Hg and confirmed on a second occasion.

Although the guideline does not specify whether BP should be measured with the auscultatory manual technique or with oscillometric devices, or the so-called automated office blood pressure (AOBP), which may all give different results depending on how they are carried out, it does insist on a standardized and accurate BP measurement technique. It also emphasizes the need to use out of office BP measurements, both ambulatory and home BP monitoring. The importance of diagnosing white coat hypertension and masked hypertension with out of office measurements is underlined. Recommendations are given for use of validated instruments and proper standardized technique to be used in not only in office but also home BP measurements. Since specific goals are given for thresholds and target BP, it would have been critical to indicate how the BP levels indicated, such as 130/80 mm Hg, are to be obtained: with manual, oscillometric or AOBP measurements, since differences between these may be important, with 10-20 mm Hg higher SBP in usual clinical measurements, if BP is not measured with unattended AOBP, which could result in overtreatment and harm. The controversy regarding the different techniques and lack of enough data on the exact difference in BP results may be a reason why the guideline committee did not aim for the SPRINT goal of SBP<120 mm Hg, and settled for a target SBP of <130 mm Hg for most patients aiming to balance potential under and overtreatment.
Another important novelty is that specific recommendations are given regarding evaluation of global cardiovascular risk to guide management not only based on BP values. Use of an atherosclerotic cardiovascular disease (ASCVD) “risk calculator” (http://www.cvriskcalculator.com) to determine the patient’s risk of heart disease or stroke over the next 10 years is recommended.

For Elevated blood pressure, lifestyle modification is recommended. In the case office BP is ≥120/80 mm Hg and marked hypertension is suspected, it is recommended that out of office BP be evaluated. If out of office BP ≥130/80 mm Hg, lifestyle modification should be continued and antihypertensive drugs initiated.

In those patients in stage 1 (BP at or above 130/80 but below 140/90 mm Hg) with no history of CVD or a cardiovascular risk over the next 10 years of less than 10% of suffering a cardiovascular event, lifestyle modification alone may be recommended and BP reassessed in 3-6 months. If still ≥130/80 mm Hg, antihypertensive drug therapy should be started. If on the other hand, the stage 1 patient has higher CV risk than 10% in 10 years, primary prevention of CVD requires introduction of antihypertensive drugs. Similarly, for the patient with known clinical CVD, diabetes mellitus, or chronic kidney disease (CKD), secondary prevention requires lifestyle changes and BP lowering medication (1 medication). Patients should be reassessed in 1 month for effectiveness of medication therapy. If goal is met after 1 month, BP should be reassessed in 3-6 months. If goal is not met after 1 month, different medication or titration should be considered. Monthly follow-up should be continued until control is achieved.

For stage 2 patients (with BP ≥140/90 mm Hg), healthy lifestyle changes and antihypertensive medication (2 medications of different classes) are recommended, either as separate agents or as fixed dose combination. Patients should be reassessed in 1 month for effectiveness, and if goal is met after 1 month, reassessed in 3-6 months. If goal is not met after 1 month, different medications or titration should be considered. Monthly follow-up should be pursued until control is achieved. If patients present with severe BP elevation >180/120 mm Hg, antihypertensive drug therapy should be initiated immediately.

Goals of treatment are BP <130/80 for most hypertensive patients, including diabetic, CKD and elderly patients (unless the latter are institutionalized or wheelchair bound, or present orthostatic hypotension, syncope or falls, in which cases individualized adjustment to less intensive treatment is reasonable). This is a major change relative to previous recommendations and other guidelines that recommend target BP <140/90 for diabetic and CKD patients. It should be noted that among the elderly who are recommended antihypertensive medication according to the 2017 ACC/AHA guideline thresholds but not those from the JNC7 guideline, BP was lower but they had a higher mean 10-year CVD risk. Recommendations for lifestyle modification include reducing salt and using the DASH diet and incorporating potassium-rich foods, suggestions for weight loss, smoking cessation, reducing alcohol intake and increasing physical activity.

Specific recommendations are given for choice of antihypertensive drugs, which include first line agents such as angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), diuretics and calcium channel blockers (CCB). Recommendations are given according to severity of BP and response to treatment, ethnicity and age, as well as presence of comorbidities (see below).

Patients suffering from hypertensive urgencies (systolic BP >180 mm Hg and/or DBP >120 mm Hg) may be non-adherent to antihypertensive therapy. They also do not have new or worsening target organ damage. It is recommended in the guideline that antihypertensive drug therapy be restarted or intensified, and anxiety, that often plays a role, treated. In hypertensive emergencies (systolic BP >180 mm Hg + target organ damage and/or DBP >120 mm Hg + target organ damage), the guideline recommends that the patient be admitted to an intensive care unit for monitoring of BP and intravenous administration of appropriate antihypertensive agents if there is worsening target organ damage.

The guideline provides suggestions for screening of secondary forms of hypertension such as primary aldosteronism, renal artery stenosis, pheochromocytoma/paraganglioma, etc., and referral to specialist care.

With respect to management of adults with comorbidities and special patient groups, guidance is provided for stable coronary heart disease, heart failure, CKD or renal transplantation, peripheral vascular disease, diabetes mellitus or metabolic syndrome, and atrial fibrillation, among others. In stable coronary heart disease, beta blockers such as metoprolol and bisoprolol are suggested, to which renin-angiotensin blockers should be added, and if needed, dihydropyridine CCBs, and in addition, diuretics and mineralocorticoid receptor antagonists to control blood pressure. If there is persistent angina, CCBs can be added to beta blockers. Guideline directed beta blockers may be pursued beyond 3 years. In heart failure, use of diuretics to control volume followed by ACEI or ARB and beta blockers to control blood pressure to a goal of >130/80 mm Hg is recommended. ARBs may prevent recurrence of atrial fibrillation and should be considered in these patients. Recommendations are also given for aortic
hypertension uncontrolled on full doses of 3 different classes of first line agents that can be used as combination therapy, or requiring a fourth agent for control of blood pressure, it is recommended first to ensure that the patient is adherent to treatment and is taking as prescribed ≥3 antihypertensive medications at optimal doses, including a diuretic. Pseudoresistance should be excluded by ensuring accurate office BP measurements, assessing nonadherence with the prescribed regimen, and obtaining home, work, or ambulatory BP readings to exclude the white coat effect. Contributing lifestyle factors need to be identified, such as alcohol intake, and interfering substances such as NSAIDs, amphetamines, decongestants, etc., discontinued. Secondary causes of hypertension such as primary aldosteronism, CKD and renal artery stenosis, pheochromocytoma and obstructive sleep apnea should be ruled out. Once this is ensured, diuretic therapy should be maximized, a mineralocorticoid receptor antagonist added, and if needed, other agents with different mechanisms of actions, including loop diuretics in patients with CKD or those receiving potent vasodilators like minoxidil. Eventually if BP remains uncontrolled after 6 months of treatment, the patient should be referred to an appropriate specialist for known or suspected secondary causes of hypertension.

Strategies to improve adherence and control of BP, to promote lifestyle modification and improving quality of care for low resource populations are addressed. As well, structured, team-based care interventions for hypertension control are recommended. Strategies based on health information technology and use of telehealth to improve hypertension control are suggested. Use of performance measures and other quality improvement strategies at the level of patients, providers, and systems is suggested to facilitate hypertension control. Finally, it is recommended that all hypertensive patients should have “clear, detailed, and evidence-based plans of care allowing achievement of treatment and self-management goals, encouraging effective management of comorbidities, with timely follow-up with the healthcare team, and adhering to CVD guideline directed management and therapy.”

The 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults is comprehensive, innovative, in part evidence-based but with significant expert opinion-based recommendations. It introduces the category of Elevated blood pressure, a new definition of hypertension and new thresholds and goals of treatment. The guideline insists on the accurate and standardized measurement of blood pressure and the use of out of the office BP measurement. However, as pointed out, it does not address the problem of differences in BP measurement with different approaches (auscultatory vs. oscillometric, vs. AOBP) and devices in the office. It stresses the importance of global CVD risk assessment for...

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decision-making relative to treatment. Lifestyle modification and choice of antihypertensive agents are detailed, secondary hypertension screening and comorbidities are addressed, urgencies and emergencies as well as resistant hypertension are considered. Adherence, communication technology and health services and community involvement are also discussed and recommendations are made regarding their application to improve BP control.

I believe that one of the main consequences of the dissemination and implementation of this new guideline will be the intensification of therapy for most hypertensive patients, hopefully without unintended consequences, and leading to improved CV outcomes.

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COMMENT ON PREVIOUS ISSUE ARTICLE  
With over a billion people with raised blood pressure, how do we set our priorities straight? Alta Schutte and Peter M Nilsson

In the previous issue of ISH Hypertension News, Drs. Alta Schutte and Peter Nilsson (1) address a problem that is overlooked by clinicians and scientists, including those active in cardiovascular prevention. Namely, that although large scale epidemiological studies show hypertension to be the first cause of death and burden of disease worldwide (2,3), the adverse effect of this condition for public health and people’s survival is underestimated.

As Schutte and Nilsson emphasize, one of the reasons is that epidemiological studies do not (and cannot) take into account masked hypertension, i.e. a condition in which office blood pressure (BP) is normal whereas home and (or) ambulatory BP are elevated (4). The resulting underestimation of the hypertension-related cardiovascular risk is by no means trivial because 1) in samples representative of the entire population, masked hypertension has been detected in about 1 out of 7 individuals with a normal office BP, which means that, globally, a huge number of people are affected and 2) the adverse consequences of this condition for vital organ function and structure as well as for the risk of a clinical event are substantially greater than in normotensive people, approaching in some studies those of individuals with an in- and out–of–office BP elevation (4,5).

Recalculation of the risk of death and disease attributable to hypertension should of course also take into account that in a large fraction of hypertensive patients (probably 30-40% globally, and up to 50% in the elderly) out-of-office BP normality, i.e. white coat hypertension, makes the risk less than that calculated

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on the basis of office BP values, although still significantly greater than that of normotensive subjects (6). As argued by Schutte and Nilsson, however, the balance remains largely dominated by masked hypertension with probably a net substantial increase of the hypertension-attributable risk compared with currently reported figures.

What should be done to allow masked hypertension to diagnostically emerge? Schutte and Nilsson correctly note that population-wide out-of-office BP monitoring is impractical or even unthinkable in many countries, and place a greater hope in single or combined clinical or demographic conditions that have been shown to be markers of an ambulatory or home BP elevation. There is no question that, based on published data, this may be a helpful approach, and that probably already today at least the most reliable of these markers (e.g. high normal office BP and silent organ damage) should be used for this purpose. Personally, however, I also have confidence in the future development of simple, cheap and reasonably accurate devices that may allow BP to be assessed away from the clinic environment, offering information on its abnormalities.

Technical improvement aside, it is also important to remember that crucial information on clinical aspects of white coat and masked hypertension is not available. Very limited evidence exists on whether antihypertensive treatment is beneficial in white coat hypertension, and no study has ever addressed whether, and to what extent, masked hypertension is favourably affected by antihypertensive drugs. It would be paradoxical to achieve an improvement in identification of this condition in the general population without knowing whether and to what extent its increased risk can be favourably modified by treatment.

- Giuseppe Mancia

REFERENCES


People with normal or even optimal blood pressure should not be overlooked if they have high out-of-office blood pressure, i.e. self-measured home and/or 24-h ambulatory monitored values [1]. Out-of-office blood pressure is a more reliable prognosticator than the blood pressure conventionally measured in an outpatient clinic or a health checkup center. In particular, self-measured home blood pressure using a validated automated device has the advantage of assessing blood pressure in a relatively standardized and relaxed environment at home, providing results that is highly reproducible and reliable for predicting cardiovascular complications [1]. With the greater number of measurements able to be taken at home, such continuous records of daily self-measurement enable us to capture a large amount of blood pressure information on long-term seasonal and annual changes [2-4]. We recently reported that the highest and lowest home blood pressures were observed in mid-to-late January and mid-to-late July, respectively, among hypertensive patients on antihypertensive pharmacotherapy, with our findings suggesting that home blood pressure should be carefully monitored in order to mitigate cardiovascular risk [2]. Furthermore, home blood pressure measurements require an active commitment by the patients themselves in medical care and health management, thereby resulting in a marked improvement in the adherence to medication.

The risk of cardiovascular complications in patients with masked hypertension, as Schutte and Nilsson indicated in the previous issue of Hypertension News, should be again emphasized. Individuals with optimal, normal, or even high-normal conventional blood pressure are assumed to be associated with minimum or mildly increased cardiovascular risk [5,6]; however, among those with masked hypertension based on self-measured home blood pressure, their value was 2.3-fold higher than in those with true optimal conventional blood pressure without masked hypertension [7]. Confirmatory findings have been reported based on ambulatory blood pressure information [8,9]. Out-of-office blood pressure considerably refines the risk stratification at levels of conventional blood pressure in which one is assumed to have a relatively low risk of cardiovascular complications, particularly for those with masked hypertension. The recently published American Heart Association Guidelines recommend home blood pressure monitoring as a screening tool for masked uncontrolled hypertension in adults being treated for hypertension, and ambulatory blood pressure monitoring as a confirmation of the diagnosis of masked uncontrolled hypertension before considering intensifying antihypertensive drug treatment [10].

In contrast to masked hypertension, the prognostic significance of white-coat hypertension is still under debate [11,12]. One critical issue is the definition of white-coat hypertension which differs among studies, making the risk of white-coat hypertension difficult to pin down [12]. Based on the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) data, the frequencies of white-coat hypertension range from 6.3%-12.5% depending

Kei Asayama, Yutaka Imai & Takayoshi Ohkubo

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on the ambulatory monitoring intervals, i.e. daytime, nighttime, or 24-h [13]. The multivariable-adjusted hazard ratios (HRs) for white-coat hypertension vs. normotension declined from 1.38 (95% confidence interval [CI], 1.03–1.87) based on daytime information to 1.16 (CI, 0.82–1.64) based on a combination of 24-h plus daytime and nighttime, which was similar to that of normotensive participants [13]. Furthermore, the out-of-office blood pressure in the general population was investigated in Ohasama, Japan; the stroke risk in residents with normotension and in those with complete white-coat hypertension (i.e. office hypertension but normal blood pressure both self-measured at home and in 24-h ambulatory settings), did not markedly differ (HR, 1.38; CI, 0.82–2.32); however, in residents with partial white-coat hypertension, either home or ambulatory normotension with office hypertension indicated that they were at significant risk of stroke (HR, 2.16; CI, 1.36–3.43) [14]. Although the prevalence of complete white-coat hypertension was 9.4%, 17.3% of the Ohasama population could be categorized as having white-coat hypertension (i.e. partial white-coat hypertension) when the home or ambulatory blood pressure was monitored [14]. White-coat hypertension has been reported to be a transitional condition to hypertension outside medical settings [15]. The definition of white-coat hypertension under the current guidelines is not considered to be sufficiently precise. To identify truly low-risk white-coat hypertension, patients with hypertension in the office setting should be carefully monitored and followed-up with multiple out-of-office blood pressure measurements in various settings.

Expert committees further recommend the measurement of out-of-office blood pressure to confirm the diagnosis of hypertension and evaluate the effect of antihypertensive treatment [5,6]. According to the multi-center Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP), the risk increases across tertiles of systolic home blood pressure both at baseline and during follow-up without evidence of a J- or U-curve [16]. Notably, the mean blood pressure in the lowest tertile was 138.2 mm Hg at baseline and 116.8 mm Hg under treatment with antihypertensive drugs, and the mean blood pressure in the middle tertile, which was 123.4–133.5 mm Hg, was associated with a significantly higher risk of a major adverse cardiovascular event than the lowest tertile based on on-treatment systolic home blood pressure [17]. Though not proven by a randomized controlled trial, the long-term management of hypertension in an individual should be based on home blood pressure self-measurement. Given that affordable and validated automated blood pressure measurement devices are readily available, and that the advantages of using self-measured home blood pressure information are well recognized, it is time to heed the call-to-action articles published by Pickering and colleagues advocated 10 years ago [18] to use home blood pressure measurements.

- Kei Asayama, Yutaka Imai & Takayoshi Ohkubo

See references overleaf - page 19

The 'Our Fellows Work' section on the ISH website has been created to increase the visibility of the scientific work and findings of new investigators and trainees globally.

*Click here to read or watch the latest Our Fellows Work interviews.*
REFERENCES:
In our paper published in ISH Hypertension News in the September 2017 issue, we highlighted the immense global burden of hypertension with a specific emphasis on conditions such as masked hypertension and white-coat hypertension that cannot be accounted for when reporting global prevalence estimates. In his response, Professor Giuseppe Mancia reiterated the challenges to better diagnose especially masked hypertension more effectively. Aligned with many working in this field he expressed his confidence in the development of affordable and accurate new devices to be used in the future in out-of-office settings. As Mancia emphasizes, on page 14, as yet there is very limited evidence on the beneficial effects of antihypertensive treatment on either masked or white-coat hypertension. In another response to our paper by Drs. Kei Asayama, Yutaka Imai and Takayoshi Ohkubo, they suggest widespread use of home blood pressure devices to overcome the challenge in detecting masked and white-coat hypertension. They elegantly provided evidence regarding the usefulness of self-measured home blood pressure. Indeed, with an engaged patient home blood pressure monitoring can improve medical care and management, as well as adherence to medication. And as they argue, there is no doubt that if affordable and validated monitors are readily available for home use, it is likely that elevated out-of-office pressure can easily be detected by patients.

Perhaps we could make two further comments to this discussion. Firstly, with prehypertension recognized as a common feature in masked hypertensive patients, (1) the new Stage 1 Hypertension category (130-139/80-89 mmHg) introduced by the AHA/ACC 2017 Hypertension Guidelines (2) may result in the detection of more masked hypertensive patients in developed countries. However, as we argued in our original paper, the burden of hypertension has shifted to low and middle income countries (LMICs) (3) where there is an insurmountable task to even detect and treat clinic blood pressures exceeding 140/90 mmHg. The usability of these new guidelines in LMICs are therefore questionable. Secondly, clear evidence supports the usefulness of self-measured home blood pressure, and there is much scope to implement this method in developed countries. (4,5) When reflecting again on the situation in LMICs, the availability of validated clinic blood pressure devices continues to be a challenge, where home blood pressure monitoring is a distant reality. But together with Professor Mancia we are hopeful that affordable devices or tools for the detection of masked and white-coat hypertension will be developed for use in all countries.

REFERENCES
Management of resistant hypertension

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Table 1. Causes of resistant hypertension
1. Non-compliance
   Half of patients will admit it (13)
2. Better with drugs that have less adverse effects (14)
3. Consumption of substances that aggravate hypertension
   Salt, licorice, NSAID’s*, EtOH, BCP, decongestants
4. Consensus guidelines that assume all patients are the same
5. Diagnostic inertia
   * Except for sulindac (15)

Laragh first proposed that management of hypertension should be guided by measurement of plasma renin activity. (7) A randomized trial of this approach reported lower systolic pressures, a trend to improved blood pressure control, and a greater reduction of medication needed among patients with volume hypertension (with low plasma renin activity). (8)

However, there are two different kinds of low renin hypertension, and to distinguish them it is necessary to measure plasma aldosterone. Patients with primary aldosteronism (~ 20% of resistant hypertension) (9) have a low plasma renin activity and a high plasma aldosterone, and are best treated with aldosterone antagonists (spironolactone or eplerenone). High-dose amiloride can be used for men (who get gynecomastia and mastalgia from spironolactone) when eplerenone is not available or affordable. Patients with Liddle syndrome, a mutation of SCNN1B, the renal tubular epithelial sodium channel (ENaC), or one of several mutations that affect the function of ENaC, have salt and water retention suppressing both renin and aldosterone, so have low plasma renin activity and a low level of aldosterone (Liddle phenotype). The specific treatment for this condition is amiloride. (10)

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In a recent clinical trial in Africa, patients with uncontrolled hypertension were randomized to usual care (UC) vs. physiologically individualized therapy (PhysRx) based on plasma renin activity and plasma aldosterone levels. (3) As mentioned above, there was no benefit of this approach in the study site in Kenya, where amiloride was not available and there were other factors influencing poor control. (3) However, at the Nigerian site, where patients were randomized to UC vs. PhysRx and conditions were more similar to developed countries, there was a marked improvement in blood pressure control: systolic control was obtained in 15% of UC vs. 85% of PhysRx (P = 0.0001), diastolic control in 45% vs. 75% (P = 0.11) and control of both systolic and diastolic pressure in 15% vs. 75% (P < 0.0001), even though the renal function was worse at that site. The algorithm used in the study is shown in Table 2. We found a very high prevalence of nonsynonymous SNPs affecting both primary aldosteronism and the Liddle phenotype. (12) The most important difference in the medication change from baseline to the end of the study was that a much higher proportion of patients allocated to PhysRx received amiloride (19% on PhysRx vs. 2.8% on UC). (3) The Liddle phenotype is far more common than most physicians suppose.

In patients with resistant hypertension it is important to overcome diagnostic inertia. After excluding rare causes of hypertension, such as pheochromocytoma, licorice or adult coarctation of the aorta, most patients will have their blood pressure controlled using physiologically individualized therapy based on their plasma renin activity and aldosterone.

- J. David Spence

REFERENCES:

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Microbiota and Cardiovascular Risk: The Missing and Found Link

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Our body is inhabited by trillions of bacteria. The term microbiota refers to the myriad of microorganisms that coexists with their hosts. In mammals, they colonize mainly the gastrointestinal tract in mostly anaerobic and rich nutrient environment. The gut microbiota codevelops with the host in a complex interplay between host genome, nutrition, and life-style. The role of gut microbiota in the regulation of multiple host metabolic pathways arise from interactive host-microbiota metabolic, signaling, and immune-inflammatory axes which in turn connect the gut, liver, muscle, and brain [1].

Gut microbiota and host immune system interact from birth. The microbiota shapes the development of the host immune system, and this in turn shapes the composition of the microbiota. This crosstalk is transmitted through hundreds of signaling pathways and different classes of molecules. The effects extend beyond the immune system and act upon multiple organs such as the gut, liver, muscle and brain through host-microbe metabolic axes, exemplified by production of bile acids, choline, and short-chain fatty acids (SCFAs).
that are essential for host health [2]. The production of these metabolites by microbes contributes to the host metabolic phenotype and hence to disease risk. The profound influence of the gut microbiota on the host immune system is strongly associated with long-term health prospects. Although the composition of the core gut microbiota is essentially stable throughout adulthood, there are components that are biologically and metabolically flexible, responding by alteration in species composition to different factors such as environmental stresses or changes in diet. The final effects of these changes may influence health or disease risk [3].

**A second genome**

Recent studies estimate that the microbiota genome contains 100-fold more genes than the host genome [4]. The development of efficient methods for genome sequencing and bioinformatics analysis enables fast and accurate analysis of the microbiome. The integrated analysis of metagenomic data and metabolic processes provides deeper understanding of the metabolic impact of the metagenome. This integrated analysis shows that microbiome act as a second genome to the host modulating not only metabolic process but extending to host physiology in the most general sense. In addition, this second genome can be transferred between individuals with profound impacts on host phenotype. From this transplantable second genome, some causal mechanisms for metabolic disease have been characterized. For example, the transplanted microbiota from obese to lean mice promoted absorption of monosaccharides from the gut lumen, selectively suppressed the production of fasting-induced adipocyte factor (Fiaf) and induced de novo hepatic lipogenesis and deposition of triglycerides in adipocytes and the liver [5]. On the contrary, germ-free lean mice lacking gut microbiota were resistant to becoming obese on a fat-enriched diet. Phosphorylated adenosine monophosphate – activated protein kinase (AMPK) was increased in skeletal muscle and liver of these mice. These examples show that there is a well established link between gut microbiome and human metabolic processes.

**Gut microbiota and metabolic diseases**

Over decades, the prevalence of metabolic diseases has steadily increased in developed countries [6]. Poor diet and lack of exercise are behind this phenomenon. Given that gut microbiota is an important environmental factor involved in the regulation of body weight and energy homeostasis, its role in metabolic disease has been explored. Studies in monozygotic and dizygotic twin pairs concordant for leanness or obesity showed that the gut microbiome is shared between the twin pairs in a great proportion [7]. In addition, the intestinal microbiota can cause metabolic disease in mice in relation to their genetic background [8,9]. Although many studies analyzed the microbiota and microbiomes of obese and lean individuals, there is a lack of consensus about specific bacterial species associated to leanness or obesity. However, a central study demonstrated that the intestinal microbiota of obese individuals differed in microbial diversity compared with that of lean persons, with a lower prevalence of Bacteroidetes and a higher prevalence of Firmicutes [10]. Moreover, later studies suggest that gut bacterial richness, expressed as bacterial gene count and regardless of exact composition, associates to metabolic parameters and body weight stability over time. Individuals with a low bacterial richness show more overall adiposity, insulin resistance and dyslipidemia and a more pronounced inflammatory phenotype when compared with high bacterial richness individuals [11]. The obese individuals among the lower bacterial richness group also gain more weight over time. A small double-blinded randomized controlled trial in insulin-resistant males with metabolic syndrome showed that intestinal infusions of allogenic or autologous microbiota from lean donors increase insulin sensitivity of recipients after six weeks. This change was accompanied by a significant increase in intestinal microbial diversity [12].

The origin for dysbiosis and loss of bacterial richness seems to be a complex interplay between diet, inherited microbiota, antibiotic treatments and clinical history, among others. Gram-negative bacteria are more resistant to antibiotics than Gram-positive bacteria, thanks to their largely impermeable cell wall. High-fat diet also increases the proportion of Gram-negative to Gram-positive microbes in the gut by favoring their growth. Lипополисахариды (LPS), a component of the outer membranes of Gram-negative bacteria, generates low-grade chronic inflammation (metabolic endotoxemia) in mice. Metabolic endotoxemia results in insulin resistance [13].

**Gut microbiota, diet and atherosclerosis**

Causal links between microbiome and cardiovascular disease (CVD) often include host-microbiota co-metabolites involving dietary intake, gut microbiota and liver metabolism. The best studied example is the pro-atherogenic and prothrombotic plasma metabolite trimethylamine N-oxide (TMAO). TMAO is shown to be formed through a cross-organism pathway involving nutrient pre-cursors abundant in a red meat (choline,

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phosphatidylcholine and L-carnitine) and the sequential action of both gut microbiota, initially forming trimethylamine (TMA), and host liver converting TMA into TMAO. Numerous studies reveal an association between systemic TMAO levels and cardiovascular risk in both humans and animals [14]. The concentration of TMAO is elevated in patients with atherosclerosis and directly correlates with pathology. TMAO induces platelet hyper-reactivity increasing thrombosis potential. It also reduces reverse cholesterol transport and induces pro-inflammatory cytokines expression and leukocyte recruitment promoting cholesterol accumulation in the foam cells of atheroma [15]. Interestingly, plasma TMAO levels among patients presenting with acute coronary syndrome may predict both near and long-term adverse cardiovascular events [16]. In addition, patients with heart failure (HF) have high levels of TMAO, which also associates to poorer long-term survival regardless of underlying etiology [17]. Otherhost-microbiota co-metabolites involved in CVD include branched chain amino acids and short chain fatty acids. Although host-microbiota co-metabolism is at the core of cardiovascular health, other potential mechanisms may also be involved. Gut microbiota endotoxins, such as LPS, may translocate into the bloodstream and start an inflammatory cascade that eventually promotes atherosclerosis. Patients with symptomatic atherosclerosis, high cardiovascular risk or coronary artery disease (CAD) exhibit unique microbiome patterns with potential pro-inflammatory characteristics [18, 19, 20].

**Therapeutic possibilities**

Clinical and animal studies have demonstrated that the gut microbiota and their imbalance state, either because of the bacterial richness or because of specific bacterial composition, are associated with metabolic and cardiovascular disease. Modulation of gut microbiota composition and function through diet, antibiotics, prebiotics and probiotics may enable, in the long term, the capacity to alter host metabolism for health benefits. However, the understanding of the causal links between gut microbiota and CVD is limited. The evidence from animal studies may help in delineating specific therapeutic approaches. Researchers managed to prevent atherosclerosis in a mouse model by decreasing plasma TMAO levels [21]. Vancomycin reduced myocardial infarctions and increased post ischaemic mechanical function recovery in a Dahl S rat model of ischaemia/reperfusion injury of the heart [16]. This effect was associated with a change in the gut microbiota composition and a reduction of plasma leptin. The administration of the leptin-suppressing probiotic *Lactobacillus plantarum* 299v confirmed the role of leptin in this effect [22]. Interestingly, *L. plantarum* PH04 (another strain of this probiotic) also exhibit cholesterol-lowering capabilities in hypercholesterolemic mice. The administration of *L. plantarum* PH04 was associated with a 10-fold increase in fecal lactic acid bacteria [23].

However, the evidence from human studies is contradictory. A meta-analysis of clinical trials of antibiotic therapy in patients with CAD failed to demonstrate any benefit with regard to mortality or cardiovascular events. This result suggests that gut microbiota modification by antibiotics does not modify the evolution of CAD [24]. Probiotics seem to decrease low density lipoproteins (LDL)-cholesterol and improve the LDL/high density lipoproteins (HDL) ratio, as well as lower blood pressure, inflammatory mediators, blood glucose levels and body mass index [25]. However, clear definitions of exact strains and dosages of the probiotics that will bring about positive health effects are lacking. In addition, factors like immunity and genetics of the host may largely influence the efficacy of probiotics. There is a need for further studies to understand the mechanisms by which probiotics may beneficially affect the cardiovascular system and to rule out negative effects on health.

**Conclusion and future**

The growing evidence from animal and human studies shows that gut microbiota influence host health and disease. However, we need major advances in our mechanistic understanding of how gut microbiota convert dietary and endogenous molecules into metabolites and how it communicates with peripheral organs in the host. The recent discoveries open the possibility for numerous microbial pathways as potential pharmacological targets for the treatment of cardiometabolic diseases. Our understanding of the interactions among gut microbiota organization and function, host genome and environmental factors would provide more personalized and tailored therapeutic interventions.

- Daniel Monleón

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Obituary: Cinzia Tiberi

All those who have submitted papers to the Journal of Hypertension for the last twenty-two years, and all those who have been contacted to review papers for it, the majority – I think – of the readers of the Journal of Hypertension have had numerous chances of corresponding with Cinzia and know how heavily she has contributed to the spreading of knowledge on hypertension.

Since 1995 she was the thread connecting the members of the Editorial Office in Milan. She was the liaison between the Editor in Milan and the Publisher in London and she was the reference point for all those corresponding with the Journal. She knew how to combine effectiveness with kindness, firmness with friendliness, urgency with leisure. She had met most of the protagonists of hypertension research in person as she had been responsible for the organization of the scientific programme of all the European Meetings on Hypertension held in Milan since the first one in 1983, and attended all these meetings providing help, wisdom and a smile.

Cinzia was fluent in foreign languages, particularly English and Spanish, the latter learnt at high school and college in Lima, Peru, when her father was director of an Italian bank there. Back in Italy, she gained a university degree in foreign languages in Milan, and in 1981 joined the staff of the Centro di Fisiologia Clinica e Ipertensione to help us organize the 1981 Meeting of the International Society of Hypertension in Milan.

She soon became an invaluable collaborator and in 1995 took charge of running the Editorial Office of the Journal of Hypertension in Milan, a job she continued tirelessly until Spring 2016 when she started another struggle, this time against illness, with the same determination, trust and optimism that she had used in her work for hypertension. She did not deserve to lose this battle but unfortunately she eventually did, and passed away on the 17th of July 2017.

With Cinzia, all of us, the group of the Editorial Office in Milan, have lost more than just one of us, we have lost the best part of us. We worked with Cinzia for many years and there is no risk we will forget her and her help, but we would like the ISH members consulting their Journal papers from 1995 to 2016 to be aware of how much of that huge body of information and knowledge is the result of Cinzia’s silent but heartfelt work.

- Alberto Zanchetti
The Journal of Hypertension: Official scientific organ of the International Society of Hypertension (ISH) and the European Society of Hypertension (ESH)

For about three decades the Journal of Hypertension, published by Wolters Kluwer Health, has been the scientific organ of the International Society of Hypertension (ISH) and the European Society of Hypertension (ESH). The Editor-in-Chief and his associates of the Milan Editorial Office are delighted to work together with the Journal Board of Management, formed by representatives of the two Societies, and chaired by Lewis Landsberg, in order to provide the members (many being members of both Societies) and the scientific community with a forum for high quality scientific publications and for guidelines, consensus documents, position papers prepared by ISH or ESH Task Forces.

In the Peripheral Vascular Disease section of the Web of Science, the Journal of Hypertension is ranked 10th, and is second among journals devoted to hypertension. Only Hypertension and Journal of Hypertension receive an Article Influence Score > 1 and therefore are considered "influential". Articles published in the Journal are widely cited in medical literature. The 2013 ESH-ESC hypertension guidelines have received 2000 citations of the Journal of Hypertension publication and 1604 of the European Heart Journal publication. The most widely cited Journal of Hypertension article in 2016 has been the paper with ISH/ASH hypertension guidelines. Two of the original papers published in 2014 were placed in the top 1% of the academic field of Clinical Medicine because highly cited.

The number of papers submitted to the Journal has been steadily increasing through the years. More than 1200 papers were submitted during 2016, and the number of submissions in 2017 is likely to approach 1300. If this is flattering for the Journal prestige, it causes strong competition for publication. The numbers of pages available yearly being fixed at approximately 2500, the consequence is that only about 22% of the submitted original articles can be accepted for publication.

As could be expected, the origin of the submitted papers has changed in recent years. Contributions from Europe were 54% in 2006, they have been 40% in 2016, while submissions from Asia increased from 20% in 2006 to 32% in 2016. Submission from North America, Oceania, Latin America and Africa have remained stable. We are delighted that more than one third of papers published in the Journal have lead authors that are members of either ISH or ESH, which confirms the Journal is a widely preferred vehicle for the members’ scientific publications.

Critical appraisal of data and scientific debate are stimulated by some characteristic features of the Journal of Hypertension: it has been the first in the area to initiate publication of editorial commentaries accompanying a selected number of articles (54 were published in 2016), and a unique feature of the Journal is the publication at the end of each article of a short summary evaluation of the paper, prepared by the article reviewers.

As readers and contributors of the Journal know, there is a current trend in the scientific community in favour of open access publication, thus the burden of publication costs shifts from the readers to the authors. While this trend reflects the longing of a new society for increasingly easier access to information as well as the authors’ expectation of a larger number of citations, there are obvious risks in placing the financial health of a journal in the hands of authors since. This may weaken the selection barrier of the peer review system (as has occurred with too many among the flourishing cohort of open access journals).

Therefore, three years ago, when the Journal of Hypertension decided to offer authors the possibility of open access publication, care was taken to avoid the undue influence of an author’s choice for open access on the review process. It was decided that the choice of paying for open access publication should be done after the review process is terminated and the paper is accepted by the editors.

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Open access obviously places an economic burden on the authors and their grant money. The publisher, together with the ISH and ESH representatives within the Board of Management, thought that members of the two scientific societies who endorse the Journal of Hypertension deserved some recognition for the prestige of their support. This recognition consists of a 15% discount on the open access rates (equal to a saving of around US $495-615). Therefore, beginning in 2018 the Editorial Manager system will be set up so that manuscript authors are asked whether they are members of either ISH or ESH. When the corresponding author chooses Open Access the discount will be applied if at least one of the authors is a paying member.

It is hoped that this offer will further strengthen the ties between ISH/ESH and their official journal, and will help establish an increasingly open forum for basic and clinical research on hypertension.

- Alberto Zanchetti

**Council's Corner: Hypertension Issues - a personal view**

**Ruan Kruger**

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**Primary prevention - are we on the right track?**

At numerous scientific meetings we hear about secondary prevention and treatment of individuals with disease, with the majority of publications reporting on outcomes and efficacy of treatment. A striking image was presented on various occasions by the current International Society of Hypertension’s (ISH) President, Professor Neil Poulter, whereby the patient and the physician are separated by a wall. The arm of the patient is sticking through a hole in the wall and the doctor is measuring blood pressure and handing out three pills. This is a setting we are all familiar with, but how do we teach an old dog (the patient) some new tricks?

The nature of mankind is to become comfortable with habits and ignore the fact that we all age, and that at some point, our poor judgements and unhealthy choices will catch up with us. To answer the above-mentioned question, it is pretty much impossible to teach new “tricks” when adverse lifestyle behaviours are a part of who you always were. This said, we try our best to advocate healthy lifestyle choices, encourage physical activity and the avoidance of substance abuse, but are we testing our efficacy and success rate in promoting healthy living? It is inevitable that all living creatures’ lives end at some point, however a wise academic once said that “you can choose the level of comfort in which your life will end.” Of course, there are exceptions to this argument, but still we determine our own risk factors that promote the onset of cardiovascular disease development.

So what are we doing wrong? The focus is too much on secondary prevention, drug development and favourable business opportunities, and not on primary prevention strategies. A larger focus on population-based primary prevention and advocating a healthy lifestyle from the earliest possible age in schools, churches, colleges and the workplace would render a much smarter and healthier generation to curb the increasing trends of hypertension and related comorbidities. In the past two decades, a larger number of research studies emerged to help understand the aetiology and

Continued on next page...
mechanisms of hypertension development in children and adolescents. Although certain conditions merit the measurement of blood pressure in children, the basic screening and awareness thereof would be profound in the general population.

Early reports on paediatric hypertension exist dating back to the early 1940’s in which cases of secondary high blood pressure were recorded due to either kidney disease (1,2), hormone abnormalities involving especially Cushing’s syndrome and hyperthyroidism (3), specific drugs or poisoning, neurological conditions (4), coarctation of the aorta (5), and the list continues when reviewing primary and secondary hypertension separately. Apart from these paediatric conditions, evidence suggested that a family history of cardiovascular disease represents the net effect of shared genetic, biochemical, behavioural, and environmental components (6). This renders a prognostic tool for early onset cardiovascular compromise as well as a favourable setting for primary prevention strategies.

The obesity rate in school children is a major public health concern, with approximately 20% prevalence in the United States (7) and, according to the South African NHANES-1, a combined overweight and obesity prevalence of 13.5% for South African children aged 6-14 years (8, 9). These alarming trends are nursing a larger health burden in the future with major economic and public health implications. With prominent broadcasting corporation channels advertising food of poor nutritional value to children, along with unhealthy food choices in school cafeterias and tuck shops, the overuse of technology-based equipment (and television in particular) (10), reliance on automobiles for transportation, and increasing crime rates in developing countries which reduce participation in physical activities (11), major emphasis should be on earliest primary intervention (which includes government support) to curb a rapidly growing epidemic of early cardiovascular compromise.

The establishment of the May Measurement Month awareness campaign by the ISH was a great leap in the right direction, to screen people from across the world and detect hypertensives unaware of their health risks. The larger these screening campaigns and the more people we can detect with hypertension, the better we can educate the world in terms of self-care and the consequences of high blood pressure. Larger and more ambitious research studies in children should be encouraged and supported by government in order to establish a platform of health reform in countries with a high incidence of cardiovascular disease.

In short, bending the tree while still young is the better practice for a healthier society and where better to start than with the children, the youth and leaders of tomorrow? With an exciting new conference, namely the 1st International Congress of Hypertension in Children and Adolescents (ICHCA) to be held in Valencia, Spain next year, we look forward to hearing about future plans and solutions to support our effort in primary prevention.

- Ruan Kruger

REFERENCES:
The Symposium began with the Oral Award Presentation Session, which included high quality presentations from young investigators from China, India, Australia, Russia, Japan and Singapore presenting on diverse studies in basic, clinical and population science.

This was followed by an inspiring mentorship keynote presentation by Prof Mark Caulfield (Queen Mary University, London, UK), who gave his insights on the importance of mentorship and how to have a successful career in hypertension research. He had several key messages on what young researchers should focus on including team building, persistence and learning from mistakes.

The symposium was followed by the ISH Mentorship and Networking Event in the evening at the Dallas Restaurant and Bar, where attendees actively networked and shared their research experiences. The ISH New Investigator Committee was also very fortunate to attract two more keen Emerging Leaders to the team, Yang Shen and Jiali Wang from China, whose local knowledge will be invaluable for organizing events at the upcoming ISH 2018 Beijing Meeting. Our ISH President Neil Poulter also attended the event to announce the winners of the awards sessions, which were very well received. Two oral prizes were awarded and three poster prizes, one of which was chosen as a favorite by the attendees themselves.

Moderated Poster Award Session

The Symposium also included a Moderated Poster Award Session that was very well attended with presenters invited to give a short presentation to describe their work. This format worked well as it gave the young researchers an opportunity to highlight their work and encouraged discussion amongst attendees.

- Elena Velkoska

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The AHA/ASA Joint Hypertension Scientific Sessions 2017 took place in San Francisco, USA in September. New this year was the successful addition of two clinically-oriented tracks to accommodate the interests of primary care physicians and clinician scientists brought in by the merger with the American Society of Hypertension. Consequently, the number of attendees was nearly double and abstract submission was up 30% this year, making for an intriguing blend of basic and clinical science in hypertension.

SPRINT was once again a major focus of debate. The keynote lecture was delivered by Dr. Robert Carey, who discussed the paradigm-changing conclusions of SPRINT as well as five meta-analyses of randomized clinical trials (comparing more vs. less intensive treatment), all of which showed that blood pressure treatment to a lower target of 120/80 mmHg is more beneficial in terms of preventing cardiovascular disease and death. Also part of the opening sessions was Dr. Brent Egan, who addressed the increasing global burden of hypertension worldwide as well as the impact of lifestyle interventions in controlling this epidemic. These discussions, along with several of the clinical sessions throughout the conference, put into perspective the eagerly anticipated new AHA clinical practice guidelines for treatment of hypertension that are due to be released in this year’s AHA Scientific Sessions in Anaheim, CA in November.

On a similar note, the Primary Care track featured the new AHA pediatric hypertension guidelines. Dr. Joshua Samuelson summarized the key changes in the new document, which include a simplified way to screen and identify adolescents at risk with the emphasis on 24-hour ambulatory blood pressure measurement for evaluation of hypertension, and increased focus on diet and lifestyle intervention as the first line of treatment in this population.

There were several presentations in the basic science track that highlighted novel mechanisms contributing to blood pressure regulation and elevation. Dr. Maria Florencia Martinez discussed the important role of CCCTC-binding factor (Ctcf) in maintaining appropriate renin expression and structural integrity of kidney. Conditional deletion of Ctcf in cells of renin lineage in mice resulted in reduced renin expression and circulating levels, lower mean arterial pressures, and renal remodeling and interstitial fibrosis. Dr. David Harrison and lab members presented intriguing evidence for the relevance of movement of activated bone marrow-derived immune cells, including CD8+ effector memory T cells, to and from peripheral tissues in context of hypertension and end-organ damage. Importantly, they have identified that the sympathetic innervation within the bone marrow niche is key to its regulation and homing of memory T cells during hypertension.

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This year, the International Society of Hypertension New Investigator Committee co-sponsored the Early Career Oral Award Session along with the Trainee Advocacy Committee of the AHA Hypertension Council. Of the six finalists, Dr. Katrina Mirabito Colafella won the first prize. Dr. Colafella, who was also recently featured as an ISH New Investigator of the Month, presented her novel work demonstrating that chronic AT2R stimulation using Compound 21 attenuates angiotensin II-induced hypertension in adult males, but not females. Thus, she argued that AT2R agonists may be a novel antihypertensive therapy for males and aging females. The success of this session bodes well for further collaborative initiatives between the American and International societies in the future. The conference once again also featured a trainee advocacy mixer, allowing for networking opportunities for new investigators with their role models and mentors in the field.

The council recognized Dr. Adam Straub with the Harry Goldblatt Award for his work on Heme redox switches and blood pressure control as a new independent investigator. The Excellence Award for Hypertension Research was given to Drs. Allyn Mark and Richard Roman for their outstanding contributions to the field. Dr. Gregory Fink’s relevant service, research and teaching in the field was recognized via the Irvine Page-Alva Bradley Lifetime Achievement Award.

Overall, the joint sessions were unequivocally considered a success. The merger of ASA brought a unique clinical audience to enhance the experience of the conference attendees, adding more translational perspective and knowledge sharing within the meeting.

- Oneeb Mian

Read New Investigator Spotlight Features

October & November

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Clayton, Australia

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November
Lebo Gafane
North-West University, South Africa

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