HYPERTENSION NEWS

May 2023

Primary aldosteronism

How new treatments and diagnostics may revolutionise treatment

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INTRODUCTION FROM THE PRESIDENT

A new dawn for Hypertension News

BRYAN WILLIAMS
President, International Society of Hypertension

Welcome to this Spring edition of Hypertension News and the first edition of 2023. This new edition marks the changing of the guard and brings to a close, two decades during which Lars Lindholm was the editor of Hypertension News. On behalf of the ISH, I want to thank Lars and the outgoing editorial board for their stewardship of Hypertension News over many years. During that time, Hypertension News has become well established as an important font of information, discussion, and debate about contemporary issues in hypertension. Deciding to change any structure is always challenging, particularly if it has been unchanged for so long, but as Churchill is often quoted, to improve is to change, to be perfect is to change often. The main change is in how the Hypertension News will now function. It will be produced by the Council of the ISH, which is in effect its editorial board. This will seamlessly align the content of Hypertension News with the activities of the ISH around the world. We want our ISH regional advisory groups to generate content highlighting research and other initiatives and activities in their region. We will also highlight the work of the ISH with global partners like regional hypertension societies, the World Hypertension League, the World Heart Federation and the WHO.

As before, a central pillar of Hypertension News will be commentary and discussion of major developments in the field of Hypertension. In this regard, the current edition of Hypertension News is packed with excellent commentaries and reviews of recent major publications in the field of Hypertension, from some of the leading experts in the world. For example, Bill Cushman reflects on the results of the Diuretic Comparison Study from the US VA hospitals system. This is such an important study and particularly important that it was conducted in the US where the use of chlorthalidone is especially popular. Resistant hypertension has become a popular target for many new treatments in development, including both drugs and devices and Michael Weber considers the results of the PRECISION trial of a new endothelin antagonist in resistant hypertension and the wider implications of the study design for future trials. Peter Sever presents some fascinating and provocative data on the relationship between blood pressure variability and longer term outcomes from the ASCOT trial, whilst Francine Marques and Hamdi Jama present some equally intriguing data on the potential role of gut microbial metabolites in lowering blood pressure. Using big data to gain insights into treatment is growing in importance and Reecha Sofat reviews how they used major National Health care data sets to gain insights into the impact of the pandemic on prescribing and treatment of hypertension in the UK.

It is interesting to observe the long overdue and growing interest in the aldosterone axis in the context of hypertension and cardiovascular and renal disease. Of course, this has long been recognised, but we are now on the cusp of a step change, in my view akin to the step change that followed the launch of effective inhibitors of the renin angiotensin system This is being driven by new drug developments and new diagnostic techniques, such as highly specific PET tracers, that promise to transform the diagnostic and treatment landscape. I was recently representing the ISH in Washington DC at a meeting organised by the

Endocrine Society to develop a new guideline on primary aldosteronism, more about that in future issues. On my return to UCL, I was at a meeting reflecting with UCL colleagues on how interesting the field of aldosterone is becoming, when one of them commented "did you know that aldosterone was discovered in this building!". I never knew, and I had walked past, or been in that building many times. It is an example of the modesty of our predecessors that their achievement is recognised by a simple green plaque on the wall of the former Middlesex Hospital Medical School, which is now part of UCL, commemorating the discovery of aldosterone 70 years ago, honouring the pioneering biochemists James Tait, Sylvia Simpson, and Hilary Grundy. Their work was published in Nature in a paper called "Isolation of a highly active mineralocortoid from beef adrenal extract". The plaque sits proudly on what is now called the Courtauld building UCL, at 33 Cleveland Street in London.

So, seventy years on, it is fitting, that in this issue we have a focus feature on some of the new therapeutic developments targeting the aldosterone axis. Hiroshi Itoh reviews the potential of the new mineralocorticoid receptor antagonists in the context of mineralocorticoid receptor associated hypertension, whilst Morris Brown comments of the development of a new aldosterone synthase antagonist, originally tested in resistant hypertension but with many potential applications beyond. This whole area promises to be an exciting field of expansion in the next few years.

Getting back to getting the basics right, one of the many pieces of work the ISH has been involved in recently, as part of global partnership working, is a review led by KDIGO on the importance of standardised and accurate office blood pressure measurement. The output of that review has been published and the recommendations are discussed by the ISH Secretary George Stergiou. Wataru Umishio and colleagues from Japan also discuss the impact of indoor temperature on blood pressure control.

The section on African Voices coordinated by Lebo Gafane-Matemane, is outstanding and highlights major issues around lack of awareness of hypertension, the potential role the ISH and its members can play in training and supporting initiatives in the region, as well as the enormous untapped potential for research in the African continent. This is indicative of the global footprint of the ISH and we want to see more regional flavour from the major continents of the world reflected in future issues of Hypertension News.

The ISH congress occurs every two years and in this issue Hiroshi Itoh bids farewell from the excellent Scientific Congress in Kyoto in October 2022, with his reminiscences on the success of the congress, in what were very challenging times during the tail end of the pandemic. We are all enormously grateful to those who attended the congress, either onsite or virtually, and to the Japanese Society of Hypertension for their outstanding work in supporting the ISH congress 2022. Immediately after the Kyoto meeting, we began to look ahead to the next ISH congress which will take place in September 2024, in the historic and beautiful city of Cartagena. From a personal perspective I think it is long overdue that that the ISH is going to hold a congress in Latin America and having seen the expertise, energy and enthusiasm of the local organising team, I think we are going to have a great meeting in Cartagena in 2024 and I hope to see many of you there is person, I think it is going to be a very special meeting.

Finally, George Stergiou reviews the new ISH management and committee structure, which has also undergone a change cycle after the start of my Presidency. We also feature reports from some of our key committees, all under new leadership, such as the New Investigator Committees and the Women in Hypertension Research Committee, on their ongoing and planned activities.

If when reading this issue of Hypertension News, there is anything you would like to comment on in the articles, or anything you would like to see covered in future issues, please let us know by sending your comments or suggestions to the ISH offices **Helen@ish-world.com**. We look forward to hearing from you.

In closing, we are hugely grateful that all contributors to this issue of Hypertension News have found time in their busy lives to reflect on their recent work and the work of their colleagues and bring their perspective on that work to ISH members. I am personally delighted and grateful to all that have contributed, that this edition of Hypertension News is packed with outstanding contributions and seamlessly continues the fine traditions of this ISH publication.

Bryan Williams - president@ish-world.com

ISH STRUCTURE AND APPOINTMENTS 2022-2024

GEORGE STERGIOU
ISH Secretary

It is longer than half a century since the ISH was established with a global mission to support the advancement of knowledge and contribute to global innovation in hypertension research and its translation into clinical practice and policy around the world. In this time the ISH has developed to become a large organisation with several committees and working groups to carry out specific multidimensional activities of the Society.

See below an organogram of the ISH structure in the term 2022-2024 with new leaders for our Committees, Regional Advisory Groups, and new projects. We are pleased to have a dynamic and truly international synthesis of very efficient and enthusiastic members from around the world, with whom we will work for implementing our current ISH development plan.

ISH Structure 2022-2024

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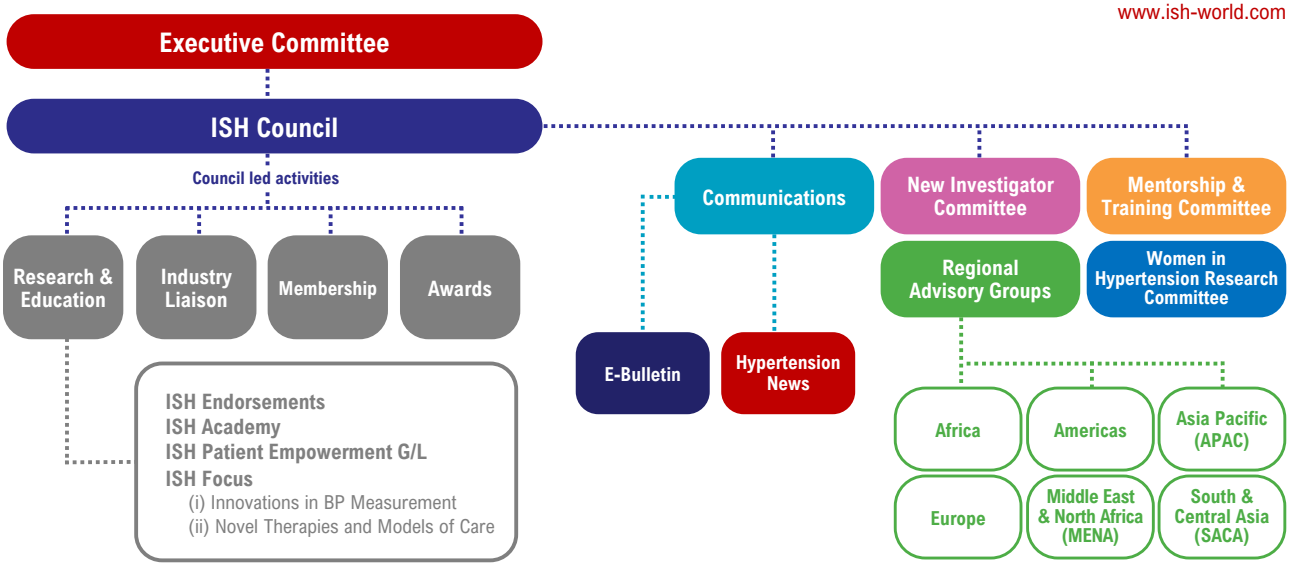


ISH Committees 2022-2024

The ISH follows the guiding principles of integrity and diversity of all international societies and charitable organisations. It has taken unique actions to support inclusivity and representation from all the regions of the world, and has put special emphasis in encouraging active involvement of young people and women. Outstanding initiatives include the ISH Women in Hypertension Research Committee (WiHRC) aimed at supporting women scientists and clinicians in the field of hypertension

and cardiovascular medicine. Also, the ISH New Investigator Network (ISHNIN) and the Mentorship and Training Committee which support young investigators in developing their professional careers. As the ISH is highly interested in helping new leaders in the field of hypertension to emerge, the maximum term in office for all committee chairs is four years.

Awards Committee

George Stergiou
Greece

Communications Committee

Anastasia Mihailidou
Australia

Corporate Liaison Committee

Bryan Williams
UK

ESH-ISH J Hypertens Committee

Maciej Tomaszewski
UK

Finance Committee

Fadi Charchar
Australia

Mentorship and Training Committee

Augusto Montezano
Canada

Membership Committee

Debora Simoes de Almeida Colombari
Brazil

New Investigator Committee

Dean Picone
Australia

Research and Education Committee

Nadia Khan
Canada

Women in Hypertension Research Committee

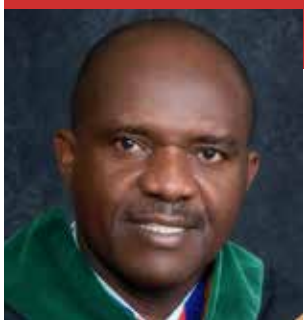
Niamh Chapman
Australia

ISH Regional Advisory Groups (RAGs)

The RAGs are an invaluable asset of the ISH for fulfilling its mission to have global impact, and are crucial for the efficient communication and development of tailored initiatives according to each area's special needs.

See below and to the right the new chairs of the six RAGs for the term 2022-2024, which connect the ISH to major regions of the world.

Africa



Augustine Odili
Nigeria

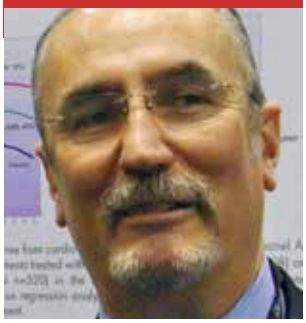
Americas

Cesar Romero
USA

Asia Pacific

Wook Bum Pyun
South Korea

Europe



Claudio Borghi
Italy

Middle East and North Africa

Jafar Alsaid
Bahrain/USA

South and Central Asia

Dorairaj Prabhakaran
India

New ISH Projects

The ISH President Bryan Williams recently initiated the development of three new ISH projects. First, is ISH Focus, which aims to bring together expertise on emerging areas in science and technology. Second is the ISH Academy, which aims to develop a high-quality professional educational platform for hypertension and related cardiovascular disease, including basic and clinical science and with a vision towards providing a basis for accreditation. Third, is ISH Empower, aimed at empowering patients by developing a guideline for patients about what optimal care for hypertension looks like and what kind of care and treatment they should be receiving. This ambitious development program will require considerable resources and time and will certainly help researchers, clinicians, and patients, as well as the ISH in accomplishing its primary mission.

ISH Focus
Blood pressure measurement

Kazuomi Kario
Japan

ISH Academy
Accredited training

Erika Jones
South Africa

ISH Empower
Patients Guidelines

Bryan Williams
UK

PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

Major CVD outcomes with chlorthalidone vs hydrochlorothiazide: the VA Diuretic Comparison Project (DCP)

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The U.S. Department of Veterans Affairs (VA) Diuretic Comparison Project (DCP) primary results were recently published.[1,2] It has been believed by many for decades that the thiazide-like diuretic chlorthalidone (CTD) is superior to the thiazide diuretic hydrochlorothiazide (HCTZ) in lowering CVD events. In fact, several recent hypertension guidelines have recommended chlorthalidone and/or indapamide over HCTZ when diuretics are chosen in the management of hypertension. This preference was based mostly on observational assessment of the MRFIT trial experience, other major trials, such as HDFP, SHEP, and ALLHAT, showing benefit with CTD, compared with fewer trials showing definitive CVD benefits with HCTZ, and a meta-analysis suggesting a 21% lower CVD event rate with CTD vs HCTZ. In addition, CTD lowers BP more at typically used doses of each, especially over 24 hours, and has a much longer duration of action (2-3 days vs <24 hrs). It also has several theoretical advantages in terms of in vitro pleotropic effects. Despite these potential advantages, for many decades HCTZ has been much more commonly prescribed than CTD, especially in the U.S. However, there had never been a randomized controlled CVD outcome trial directly comparing CDT with HCTZ, since such a trial using traditional clinical trial methodology was prohibitively costly.

The VA started a program using the usually less expensive pragmatic or point-of-care methodology, and DCP was the first large pragmatic trial in this program. In DCP, we randomly assigned 13,523 adults age ≥65 years (mean 72 years) who were patients in the VA health system and had been receiving HCTZ at a dose of 25 or 50 mg/d to continue therapy with HCTZ or to switch to CTD at equipotent doses of 12.5 or 25 mg/d, respectively. The primary composite outcome included nonfatal MI, stroke, HF resulting in hospitalization, urgent coronary revascularization for unstable angina, and non-cancer-related death. At baseline, 95% of patients recruited were on HCTZ 25 mg/d, so only 5% were randomized to the higher doses of CTD (25 mg/d) or stayed on HCTZ 50 mg/d. Baseline and follow-up systolic BP in each group was 139 mm Hg. At a median follow-up of 2.4 years, there was little difference in the primary outcome (CTD 10.4%, HCTZ 10.0%; HR, 1.04, 95% CI 0.94-1.16; p=0.45). There were no between-group differences in the occurrence of any of the components of the primary outcome, nor in any prespecified subgroups, except in those who had a history of

MI or stroke: patients in the CTD group had a lower incidence of the primary outcome than patients in the HCTZ group (14.3% vs 19.4%; HR, 0.73; 95% CI 0.57-0.94). The incidence of hypokalemia was slightly higher in the CTD group (6.0% vs. 4.4%).

Since DCP was a pragmatic trial with no local coordinators or investigators, we focused on patients whose doses of HCTZ could be changed to equipotent doses of CTD. Overwhelmingly, when HCTZ was chosen in practice, PCPs used/use 12.5 or 25 mg of HCTZ to treat hypertension. Thus, we included those on 25 or 50 mg of HCTZ in order to convert to somewhat comparable doses of chlorthalidone (12.5 or 25 mg). Therefore, DCP is primarily a comparison of the 95% of participants on HCTZ 25 mg/d vs CTD 12.5 mg/d. These are lower doses than the target doses of these drugs used in the best outcome trials with these agents. For example, 70-80% of participants in SHEP and ALLHAT were on CTD 25 mg/d. Therefore, DCP essentially shows 25 mg of HCTZ has similar outcomes to 12.5 mg of CTD, but I believe the results should not be extrapolated to 12.5 mg of HCTZ (a lower dose than was studied in DCP, but frequently prescribed in practice), or higher doses of each. We plan to look at the 5% subgroup who were on 50 mg of HCTZ vs 25 mg of CTD, but this is too small a subgroup to provide much information and it was not prespecified.

DCP gives us confidence that HCTZ and CTD have similar CVD outcomes over several years at the HCTZ 25 mg and CTD 12.5 mg doses, but we can't extrapolate to other doses. In my own practice, when using HCTZ, I try to use a minimum dose of 25 mg. However, if more BP-lowering is needed, especially if the patient is on multidrug therapy, I will often change the HCTZ 25 mg/d to CTD 25 mg/d, primarily for greater BP-lowering efficacy. One limitation is the few single-pill combination medications available with CTD. HCTZ 50 mg/d is another option, but it has been difficult to get physicians and other providers to keep patients on 50 mg/d, since they have often been taught to limit HCTZ to 25 mg/d, despite guidelines recommending a maximum dose of 50 mg/d.

The better outcomes in the MI/stroke subgroup might lead me to especially use CTD preferentially in such patients, but we must admit that the results must be considered hypothesis-generating and need to be confirmed to be given a strong recommendation.

In conclusion, DCP demonstrates both the considerable strengths, but also the limitations, of conducting pragmatic clinical trials. There is no question many more trials can be conducted less expensively with this methodology than depending on traditional research site-based randomized trials. However, there are many trial questions for which pragmatic trials are not likely to be appropriate. DCP addressed an important question that likely would not have been funded otherwise, and at least strongly suggests these two diuretics in these lower doses have similar CVD outcomes.

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Disclosure: The opinions expressed in this article are those of the author and do not necessarily reflect the position of the U.S. federal government, the Department of Veterans Affairs, or the DCP Study Group.

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PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

The PRECISION Trial: A new endothelin antagonist and new lessons for hypertension trials

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Those of us in the field of hypertension are only too well aware that blood pressure control rates are disappointingly low, even in high income countries. Much of this stems from the dual problems of inadequate prescribing by practitioners and poor medication adherence by patients. Even so, many patients have hypertension that remains uncontrolled despite standard triple therapy, usually a RAS-blocker, amlodipine and a diuretic. To satisfy this need, exciting new drugs as well as device therapy such as renal denervation are in development and soon likely to be available for patients with hard-to-control hypertension.

Endothelin

While we have focused attention in recent years on the pressor effects of the sympathetic nervous system and the renin-angiotensin system, endothelin also possesses powerful blood pressure-raising properties and so is a relevant new target for therapeutic intervention. Studies with endothelin antagonists like bosentan in the 1990s and darusentan about 20 years later were performed in patients inadequately responsive to treatment with 3 or 4 drugs. Promising blood pressure reductions were observed. But, concern over excessive fluid retention, which is an inevitable consequence of blocking endothelin receptors, as well as some inconsistency in blood pressure effects, resulted in the darusentan's commercial sponsor discontinuing its development, to the disappointment of the academic investigators.

Aprocitentan is a new endothelin antagonist with dual ETa/ETb actions. It is believed that its dual action can reduce fluid-retaining effects. A phase-2 study with this agent showed that daily doses of 12.5 and 25mg provided useful blood pressure lowering effectiveness together with an acceptable safety profile. Accordingly, the well-powered phase-3 PRECISION trial was undertaken to confirm and expand those findings.

The PRECISION Trial

This study, published recently in The Lancet (Nov 7, 2022)) was focused on patients with true resistant hypertension, with the expectation that Aprocitentan will be used predominantly (though not necessarily always) as a fourth line drug. Strong attempts were made to ensure that only study subjects taking optimal triple therapy with true resistant hypertension were randomized. After study consent, all previous medications were discontinued during a 4-8 week initial screening period and replaced with a single-pill combination of amlodipine 5 or 10mg, valsartan 160mg and hydrochlorothiazide 25mg for an additional 4 week screening period. And, as a further precaution, placebo was added to the combination therapy to all patients for an additional 4-week single blind run-in period to confirm eligibility.

Double-blind randomization allocated patients equally to placebo, aprocitentan 12.5mg daily, and aprocitentan 25mg daily for the 4-week period to the primary study endpoint. The result, measured by automated office blood pressures, was positive. Aprocitentan 12.5mg was significantly superior to placebo by 3.8/3.0 mmHg and Aprocitentan 25mg by 3.7/4.5 mmHg.

What was entirely unexpected, however, was that despite all the pre-randomization precautions, systolic blood pressure fell by 11 mmHg in the placebo group. Obviously, it fell by even more in the aprocitentan patients, but it's still likely that the real effects of the investigational drug were at least partly diluted by so many patients exhibiting an excessive placebo effect. 24-hour ambulatory blood pressure monitoring provided a somewhat clearer picture of the drug's effect: aprocitentan 12.5mg beat placebo by 4.2/4.3mmHg and 25mg beat placebo by 5.9/5.8mmHg.

After reaching that endpoint, all patients were switched into a single large group, all receiving the same aprocitentan 25mg dose, for a 32 week period to measure the drug's durability and safety.

And then came the highlight of the trial: with all patients now stable, there was a re-randomization, with half remaining on aprocitentan 25mg and half switched to placebo. The endpoint for this comparison was after 4 weeks: the patients remaining on aprocitentan experienced virtually no change in blood pressure; whereas those now on placebo had a significant increase compared with the aprocitentan group of 5.5/5.2mmHg by automated office measurement, and by 6.5/6.7mmHg for 24h ambulatory blood pressure.

Fluid Issues

As expected, oedema/fluid retention was the most common adverse event. Overall, 184 patients on the active drug had fluid retention, but only 8 on placebo (although duration of exposure to the active drug was greater than to placebo). Fluid retention occurred most often in the first few weeks of treatment; 40% of these patients received intensification of diuretic therapy, though only 7 patients discontinued aprocitentan because of fluid retention. This adverse effect was most common in patients with chronic kidney disease.

Of note, the trial allowed patients with uncontrolled hypertension being treated for heart failure to be enrolled, including some whose loop diuretic therapy was replaced with hydrochlorothiazide! Ten patient required hospitalization for fluid issues (all with backgrounds of heart failure, kidney disease or diabetes.) Remarkably, all these patients remained in the study on their assigned treatment after discharge.

What we have learned

Although this trial was designed primarily to study aprocitentan, it also brought to light other interesting issues.

1. Aprocitentan: This drug significantly reduced blood pressure when added to single pill triple therapy in patients with uncontrolled hypertension. An excessive placebo response signaled that too many patients did not have resistant hypertension and so diluted the drug's effectiveness. The main safety issue was fluid retention despite all patients receiving a modest thiazide dose. The study's findings would strongly suggest that replacing hydrochlorothiazide with a more powerful and longer acting agent like chlorthalidone or indapamide would more effectively reduce fluid retention and also enhance efficacy. In fact, it could be recommended, or even mandated, that one of these more powerful diuretics be administered routinely with aprocitentan; perhaps a single pill combination could be considered.

2. Hypertension study design: This trial emphasized the clarity of measuring a drug's antihypertensive efficacy by introducing a randomized placebo comparison after all patients are established on the drug. This approach has been endorsed by the FDA and used in previous trials, and should be considered in forthcoming studies of blood pressure-lowering drugs.

3. We start and end with the prevalent issue of uncontrolled hypertension. This trial, carefully designed to exclude patients with pseudo-treatment resistant hypertension, enrolled 1,965 potential candidates whose blood pressure

and prescriptions indicated treatment resistant hypertension. But 872 of these candidates during the sustained pre-randomization period were excluded for failing to maintain an elevated systolic blood pressure. Even so, these precautions were not sufficient. At baseline 730 patients were randomized, but the drop in systolic blood pressure of 11 mmHg in the placebo group makes it obvious that a large proportion of patients had withheld their medications in order to enter the trial and did not, in fact, have treatment resistant hypertension. This phenomenon of randomizing inappropriate patients has adversely affected several other recently performed studies of blood pressure treatments.

4. One lesson is clear: in an era when patients often measure their own blood pressures and adjust their medications accordingly, we will need to consider measurement of plasma and urine drug levels to determine adherence with protocol medications to maintain the integrity of our clinical trials.[1]

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Michael A. Weber - michaelwebermd@cs.com

Medtronic

Hypertension remains one of the largest unmet needs in healthcare.

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35%

of treated hypertension patients remain uncontrolled.[1,2]

50%

Nearly 50% of patients become non-adherent to therapy within one year.[3]

2x

Non-adherence levels double when patients move from two to three drugs.[4-6]

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PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

Long-term visit-to-visit systolic blood pressure variability is more important than average systolic pressure in predicting cardiovascular outcomes: evidence from the Anglo-Scandinavian Cardiac Outcome Trial

PETER SEVER

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In hypertensive patients, decisions on thresholds for treatment and target blood pressures have traditionally been derived from observational studies and randomised controlled trials of drug treatment. There is overwhelming evidence from the observational studies that the higher the blood pressure the greater the risk,[1] but it is important to point out that at most levels of blood pressure, age is a more important determinant of risk than the level of blood pressure.

It has been widely accepted, based on the results of many individual intervention trials, that the lower the achieved blood pressure, the better the cardiovascular outcome. However, pooled analyses of the trial data raise interesting questions as to whether, indeed, this is always true. From the Blood Pressure Lowering Treatment Trialists Collaboration,[2] this relationship appears to hold for stroke, but for other outcomes including coronary heart disease and total cardiovascular events, larger reductions in achieved blood pressure are not always associated with better outcomes. Moreover, the relationship is strongly influenced by the presence in these trials of subjects with type 2 diabetes, and when these patients are removed from the analyses, the relationship between blood pressure and outcome is much less clear[3]. Perhaps therefore, there are other blood pressure related features that are more important determinants of cardiovascular outcomes.

In 1994, Mancia and colleagues reported that the variability of blood pressure on ambulatory blood pressure recordings predicted target organ damage over a follow-up period of 7.5 years.[4] Shortly thereafter, Otsuka and colleagues, in 1997, reported that circadian amplitude of blood pressure was an important predictor of ischaemic stroke and nephropathy over a follow-up period of 6 years.[5] Thereafter, there were several studies reported from Japan,[6,7,8] showing that variability in office blood pressures predicted cardiovascular events and mortality. Stevens and colleagues have reviewed this important subject and published a meta-analyses of studies of both short-term and long-term blood pressure variability.[9]

The significance of these observations has been largely ignored and long-term visit-to-visit blood pressure variability has been considered an obstacle for the reliable estimation of usual blood pressure and considered as “background noise”. Moreover, clinical guidelines do not recommend treatment for blood pressure variability.

Having been influenced by Rothwell's observations on a cohort of patients presenting with a transient ischaemic attack, that the risk of subsequent stroke was strongly determined, not by mean blood pressure, but by long-term visit-to-visit variability,[10] we collaborated to review the database derived from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in order to test the hypothesis that long-term visit-to-visit blood pressure variability was a more important determinant of cardiovascular outcome than the mean blood pressure achieved during the trial.[10]

ASCOT was a randomised controlled trial in hypertensive subjects, comparing two different treatment strategies, atenolol +/- bendroflumethiazide and amlodipine +/- perindopril.[11] Mean blood pressures were well controlled during the trial following randomisation, but there were small differences in achieved blood pressure in favour of the amlodipine-based treatment by, on average, 2.7/1.4 mmHg. Preliminary analyses suggested that these small differences in blood pressure did not account for differences in cardiovascular outcomes,[12] which were in favour of the amlodipine-based treatment regimen for most cardiovascular outcomes, including mortality. We subsequently re-analysed the database, which included almost one million measurements of blood pressure throughout the 5.5 year follow-up period, and showed that in-trial mean blood pressure was a very poor determinant of cardiovascular outcomes.[10] There was no relationship between in-trial systolic blood pressure and coronary outcomes and only at the highest decile of in-trial systolic pressure was there any association with stroke (Figure 1). On the other hand, when outcomes were related to visit-to-visit systolic blood pressure variability throughout the trial (standard deviation, coefficient of variation of systolic pressure or variation independent of the mean), there was a strong and robust relationship between higher systolic variability and both stroke and coronary outcomes. Moreover, it was clear that there were substantial differences in the treatment effects on long-term blood pressure variability, with a gradual reduction throughout the trial with the amlodipine-based treatment regimen, contrasting with an initial rise in variability as participants were randomized to atenolol and, thereafter, as the trial progressed, a gradual fall presumably due to the introduction of second and third line drugs.[13] Further analyses provided robust evidence that long-term visit-to-visit variability and not achieved mean blood pressure, was the major determinant of the benefit in trial outcomes in favour of amlodipine-based treatment.

Subsequent to the publication of our findings, a number of other trials reported similar observations on the importance of long-term visit-to-visit variability, including ALLHAT,[14] the ADVANCE trial[15] and the African-American trial in subjects with chronic kidney disease[16]. Also, a review and meta-analysis has been published.[9]

At the end of the blood pressure-lowering arm of ASCOT, after 5.5 years follow-up, participants in the United Kingdom were flagged with the Office of National Statistics (subsequently NHS Digital), whereby data on hospitalisations and mortality, could be recorded over the following 15+ years of observation. Outcomes on mortality were derived from death certificates and non-fatal outcomes from electronic records which were classified using conventional ICD codes.

There were initially over 8,500 subjects from England, Wales and Scotland recruited into this ASCOT Legacy cohort, and over the total observation period, almost 5,000 cardiovascular events, including approximately 3,000 coronary events and 1,000 strokes were recorded. In the analyses of these data, which have recently been reported at the ISH meeting in Kyoto 2022,[17] there was a strong positive correlation between long term cardiovascular outcomes and in-trial systolic blood pressure variability adjusted for mean systolic pressure. There was a 20-25% increase in risk for each standard deviation increase in the standard deviation of systolic blood pressure. The importance of these observations is that the relationship with long-term visit-to-visit variability was independent of any differences in in-trial blood pressure as we had previously shown during the original trial. Further analyses (Figure 2), show very clearly that at all levels of systolic blood pressure, higher visit-to-visit systolic blood pressure variability confers a far greater risk. And, importantly, even in those who achieved blood pressures well within the normal range, higher levels of systolic blood pressure conferred substantial additional cardiovascular risk. However, these subjects,

according to contemporary guidelines, would not be considered for any further treatment. We have also reported that visit-to-visit variability is a far more important determinant of renal outcomes (development of chronic renal disease, renal failure and the need for renal replacement therapy), than in-trial mean systolic blood pressure.[17] In these 20-year observations, we also demonstrated that the benefits of the amlodipine-based treatment compared with atenolol-based treatment regimen on cardiovascular events, persisted despite the fact that there had been considerable cross-over of treatments in the post- trial period.

We conclude therefore:

1. That long term visit-to-visit systolic blood pressure variability is a major predictor of cardiovascular and renal events independent of mean systolic blood pressure.

2. That in many individual trials and meta-analyses, mean blood pressures poorly predict outcome.

3. In the long-term follow-up of ASCOT, participants formerly assigned the amlodipine-based treatment demonstrated a persistent reduction in cardiovascular events compared with those assigned atenolol-base treatment.

4. That in a review of antihypertensive drug classes only long-acting calcium channel blockers and, to a lesser extent, diuretics, reduce long-term visit-to-visit blood pressure variability.

5. That the effect of long-acting calcium channel blockers on blood pressure variability is a likely explanation for their long-term outcome benefits compared with other drugs on cardiovascular outcomes in major clinical trials.

6. That the implications of these findings for guidelines on blood pressure management have yet to be established.

Figure 1. Cardiovascular outcomes from ASCOT expressed as hazard ratios for deciles of increasing systolic blood pressure (upper panel) and visit-to-visit systolic blood pressure variability (lower panel).10 For systolic pressure only the tenth decile is significant for stroke outcome (red circle)

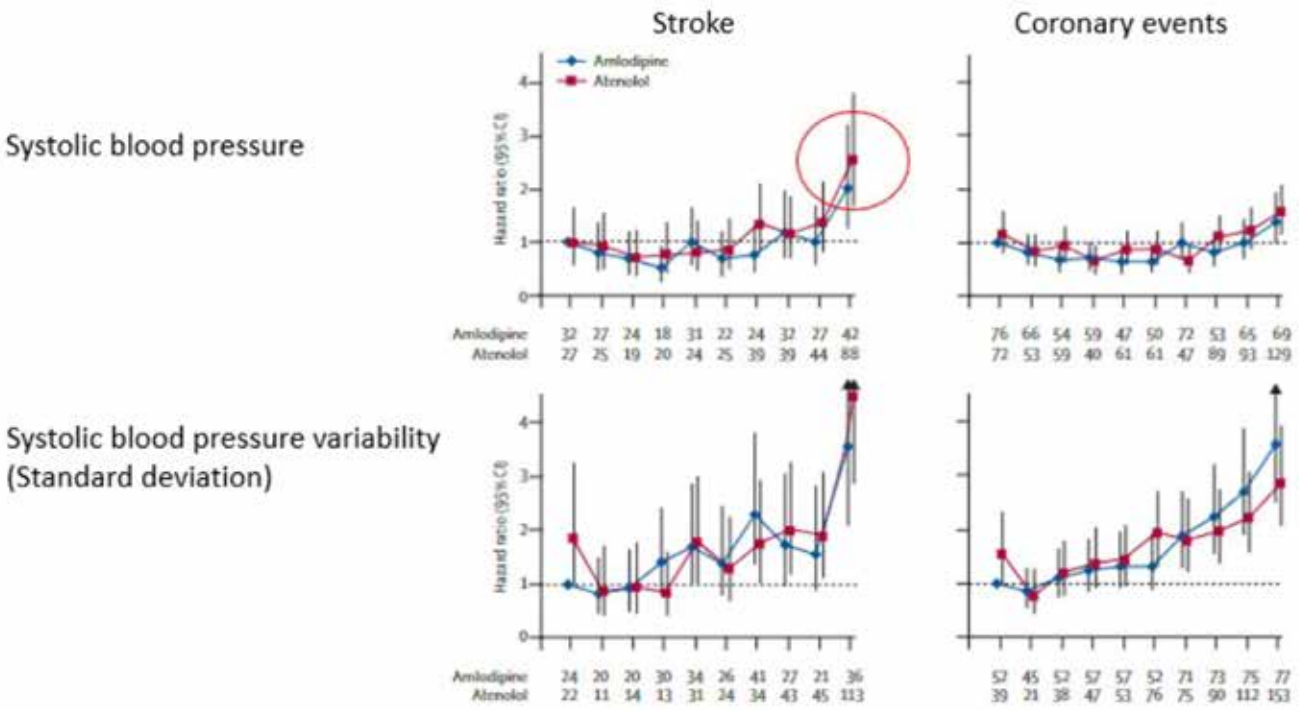
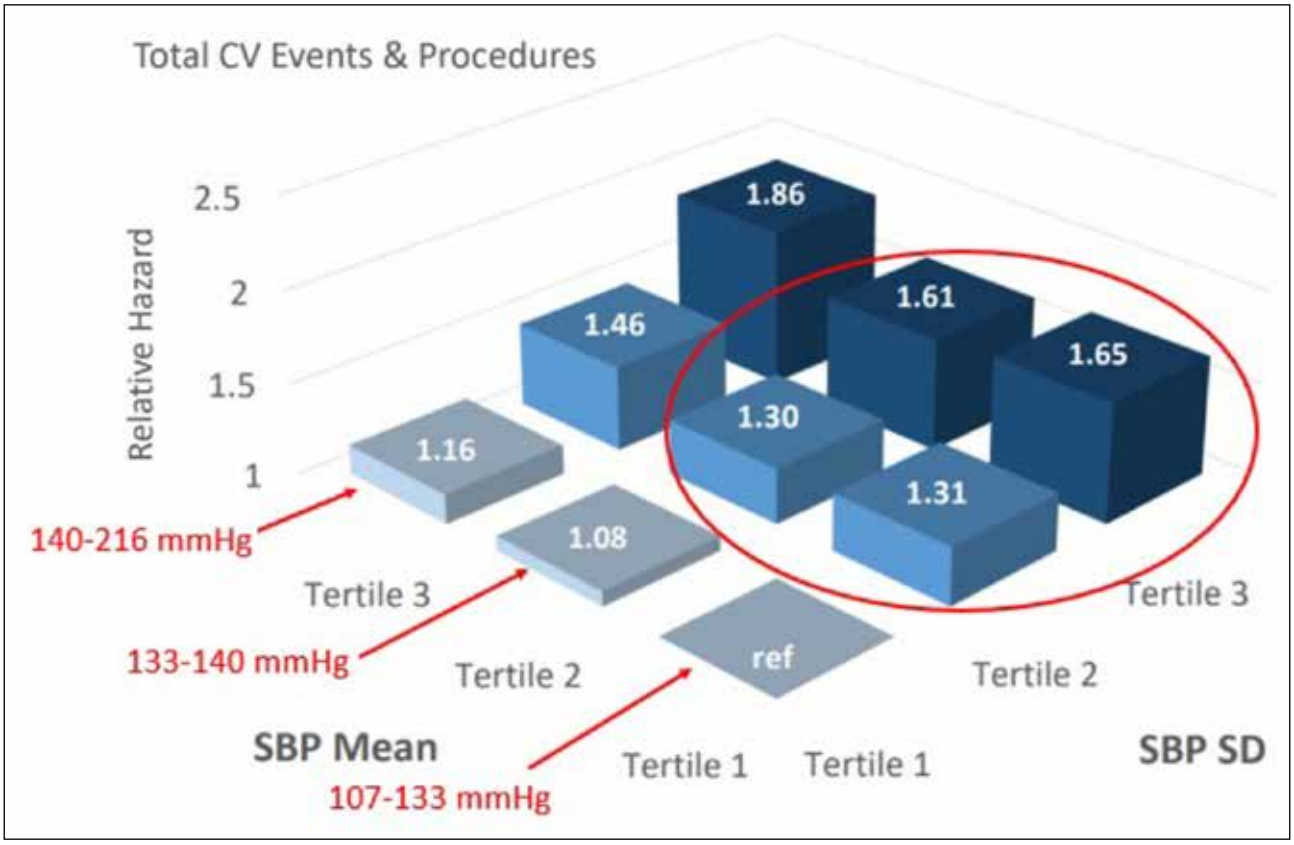


Figure 2. Total cardiovascular events in the 20 year ASCOT Legacy Programme shown by tertiles of systolic blood pressure and tertiles of systolic blood pressure variability (standard deviation SD). Ranges of systolic blood pressure are shown for each tertile. The red circle highlights participants for whom, according to guidelines, no further treatment is advocated. The data are based on almost 1 million measurements of SBP and approximately 5000 cardiovascular events.



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PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

The Impact of the Pandemic on CVD Management

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Reecha Sofat

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide and this is steadily rising.[1] Amongst risk factors for CVD, hypertension remains the most prevalent, although if detected, along with other modifiable risk factors it can act to reduce the burden of CVD. In the UK screening for modifiable risk factors, including hypertension, type 2 diabetes and high lipids was the norm, however the Covid-19 pandemic disrupted this usual screening. Detection and then treatment of risk factors was also disrupted. What is unknown is what the downstream effects of this missed detection and treatment may be on the CVD burden including increased risk of myocardial infarction and stroke.

One way in which risk factor management is actioned is through medicines. In lieu of waiting for increased cases of MI and stroke, using medicines as a proxy for risk factors, we investigated changes in dispensed medicines used to treat CVD risk factors over the course of the COVID-19 pandemic, and assessed the impact of not treating these risk factors on future CVD events.

The UK's comprehensive national medical records track health over the life course for >60 million people in England, Scotland and Wales[2,3,4]. Using these records, we investigated the impact of the COVID-19 pandemic on mediation usage. Specifically, eleven sub-groups of people were analysed, defined by their use of medicines used to treat CVD and its risk factors, such as high blood pressure, high cholesterol and diabetes. Medication records were matched via a non-identifying unique pseudo-identifiers to individual-level socio-demographic characteristics. We analysed trends in first (incident) medication use across 1.32 billion records of community-dispensed CVD medications from England, Scotland and Wales between April 2018 and July 2021. By highlighting monthly trends in incident medication use, we aimed to understand changes in the number of new starters on drugs used to control CVD risk factors of diabetes, hypertension and high lipids.

There was a marked decline in the number of CVD preventative medicines dispensed at the start of the COVID-19 pandemic.[5] Specifically, 491,306 fewer individuals initiated antihypertensive treatment than expected based on 2019 levels. Further analysis revealed that this reduction could result in 13,662 additional CVD events, including 2,281 myocardial infarctions and 3,474 strokes, should individuals remain untreated over their life-course. Incident use of lipid-lowering medicines also decreased by 16,744 patients per month compared to 2019. By contrast, incident use of medicines to treat type-2 diabetes increased by approximately 623 patients per month, although the dispensing of insulin medication remained steady.

Our analysis suggests that the number of first initiation of medicines to prevent CVD greatly declined during the COVID-19 pandemic and has not returned to pre-pandemic levels. This is despite recovery in the dispensing of medications after the initial declines following the first UK lockdown. Whilst these results are indicative of trends in the UK it is of relevance to many countries with similar health systems.

Our results highlight the urgent need for methods to identify and treat individuals who have missed treatment and remain untreated. Without this, large numbers of excess future CVD events will add to the indirect impacts of the pandemic. Hypertension remains the foremost risk factor for CVD and can be easily screened for and actioned through medicines which are cheap and effective. Policy makers and health care leaders need to now focus on recovery from the pandemic and target the health needs of the future generations which if not detected now will increase the burden of hypertension and it's associated increased risk in CVD.

Our work is not without limitations. Importantly, we analysed 'real world' medication data that were not collected for research purposes. It is possible that artefacts may exist within the data due to differences in data collection, processing or transfer, and these may vary over time and by source. Estimates of the impact of a reduction in medicine use on CVD events rely on assumptions that may change over time and in direct response to the pandemic. The final impact of the pandemic on CVD events in the UK is highly dynamic and will be influenced by many factors that could not be captured by our model.

We have shown that using medicines as a proxy for disease can complement investigations using electronic health records and disease diagnostic codes. Such analyses can be incorporated into methods to identify individuals who have missed treatment, which is urgently required to avoid additional future CVD events. This medicines approach provides policy makers with an additional lens to monitor healthcare pathways, providing a rapid response tool in the event of a future pandemic or other similar disruption event.

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PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

Using gut microbial metabolites to lower blood pressure of hypertensive patients

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In January 2023, we published the results of the Microbial Interventions to Control and Reduce Blood Pressure in Australia (MICRoBIA) trial in Nature Cardiovascular Research,[1] where we reported the use of gut microbial metabolites to lower blood pressure (BP) of untreated essential hypertensive patients.

Dietary fibre, particularly fermentable fibre, is a key determinant of the gut microbiome.[2] Commensal gut microbes in the large intestine break down fermentable fibre, producing metabolites known as short-chain fatty acids (SCFAs).[3] Studies by our team[4,5] and others[6] have shown direct supplementation with the SCFAs acetate and butyrate decreased BP in deoxycorticosterone acetate (DOCA)/salt and angiotensin II mouse models. However, the ability of these gut microbial-derived metabolites to treat essential hypertension remained unknown. A major challenge in translating these findings was that, in animal studies, SCFAs are delivered in drinking water throughout the experimental protocol, which was not feasible in humans. Once-off shots of foods high in SCFAs, such as vinegar, were also not an option as they result in a peak of circulating SCFAs after 60 minutes but disappear after a couple of hours.[7] Thus, our biggest hurdle was figuring out a pragmatic and last-longing delivery system for SCFAs that was translatable to humans.

Our novel solution

To address these challenges, we used a fermentable fibre product where the SCFAs acetate and butyrate have been chemically added, called acetylated and butyrylated high amylose maise (HAMSAB). Similar to other types of fermentable fibre, HAMSAB remains intact as it reaches the large intestine. There, it undergoes fermentation by the gut microbiota, releasing high levels of acetate and butyrate.[1] An important property of HAMSAB is that it can be added to food products and consumed orally. Thus, we worked with a research chef and dietitians to develop a suite of foods that contained either HAMSAB or the placebo, including sweet and savoury muffins, frittatas and arancini balls.

What we found

We conducted a double-blind, randomised, placebo-controlled cross-over phase II trial involving 20 treatment-naive hypertensive participants over 3-weeks to test the efficacy of HAMSAB in reducing blood pressure.[8] Our participants were randomised into the HAMSAB-supplemented or placebo arm of the study, followed by a 3-week washout period before being placed on the other study arm.[8] We monitored BP at home and for 24 hours using ambulatory BP monitoring, measured plasma SCFAs, real-time

gastrointestinal transit and pH, and circulating cytokines. We also collected faecal samples from participants before and after each arm of the intervention to analyse their gut microbiota composition.[8]

We determined that HAMSAB resulted in a placebo-subtracted mean reduction of 6.1-mmHg in 24-hour systolic BP, with significant reductions observed in both day and night systolic BP, and central systolic BP.[1] Using home BP data, the BP reduction seems to peak at around 2-weeks after the introduction of HAMSAB.[1] This was associated with a reduction in calculated total peripheral resistance but no changes in stroke volume, cardiac output or heart rate.[1] Plasma acetate and butyrate levels were significantly elevated following the 3-week HAMSAB intervention compared to the placebo arm, as well as a decrease in colonic pH, which confirms SCFA production.[1] Furthermore, HAMSAB shifted gut microbial composition and transiently increased the prevalence of acetate- and butyrate-producing microbes such as Ruminococcus spp. and Parabacteriodetes spp.[1] These changes in microbiome composition were reversed back to baseline after 3-weels of washout when HAMSAB was stopped.[1] Given that SCFAs are anti-inflammatory, we looked at key plasma cytokines associated with hypertension (IL17A, IL1β, IL10 and IL6); however, we did not observe any differences between the HAMSAB and placebo.[1]

The implications

Our proof-of-concept study demonstrates that delivering gut microbial-derived metabolites using HAMSAB is a promising option for lowering BP in patients with essential hypertension. Combined with previous findings showing that untreated hypertensive patients have lower levels of SCFA-producers,[9] our findings suggest the absence of SCFA-producers may impair critical SCFA-dependent BP regulating pathways, such as signalling via the G-protein coupled receptors.[3] Recent evidence has shown a lack of signalling via classic SCFA receptors (e.g., GPR41/43)9,10 and pH-sensing receptors (e.g., GPR65)11 contribute to the development and maintenance of hypertension. Thus, restoring critical microbial taxa that produce SCFAs could be an important therapeutic goal for more optimal BP control.

Although our study demonstrates the BP-lowering effect of HAMSAB, we acknowledge that multi-centre trials with larger sample sizes and longer-term follow-up will yield more conclusive results. Importantly, such a study would provide more insight into the large-scale feasibility of gut microbial strategies to treat hypertension. Further investigations may reveal the proportion of hypertensive patients amenable to this therapeutic approach and identify super-responders that may benefit from HAMSAB supplementation.

Acknowledgements

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ISH BIENNIAL SCIENTIFIC MEETINGS

ISH 2022: Farewell from Kyoto

HIROSHI ITOH
President, ISH2022 KYOTO

On behalf of the committee members of the 29th Scientific Meeting of the International Society of Hypertension (ISH) 2022 KYOTO, I would like to express our sincere appreciation for your cooperation.

With 2,634 participants from 85 countries, ISH2022 Kyoto was held from 12-16, October 2022 in Kyoto, Japan. The ISH2022 Kyoto was held in the hybrid format due to the pandemic. This was the first attempt in the ISH meetings. 1,464 participants attended onsite. On-site participants surely re-discovered the wonderfulness and joy of face-to-face communication with old and new friends. 1,170 participants who attended virtually could also join live discussion through the chat system of the portal site.

The opening ceremony was held with the participation of Their Imperial Highnesses Crown Prince and Crown Princess Akishino. His Imperial Highness Prince Akishino made a strong appeal for the importance of hypertension research.

It was truly our great honor to have this opportunity. We had prepared for the event with all possible security, and were very nervous. I am very relieved that we were able to successfully complete the event.

Following Dr. Dzau's keynote lecture at the opening ceremony, four Plenary Lectures were given during the conference.


ISH2022KYOTO
ISH2022KYOTO
ISH2022KYOTO
The Wisdom for Conquering Hypertension

319 faculty from 50 countries were invited and 1,215 abstracts from 69 countries were presented in the meeting. Under the theme of "The wisdom for conquering hypertension", we especially focused on three main topics which were "Food, AI and Move". The scientific program of ISH2022 Kyoto approached hypertension in a different way from that in the past and we obtained knowledge from broader field. ISH2022 Kyoto provided cutting-edge innovative scientific programs which covered the following 13 categories;

1. Three Main Topics: AI/Dx, FOOD/Nutrition, MOVE/Physical Fitness with the view of correlations with hypertension

2. Hypertension for SDGs Toward 2030 World (Climate, Disaster, Isolation/Mental health etc.)

3. Global Health and Hypertension with Diversity (Racial, Economical difference, medical resources etc.)

4. Life-course and Hypertension (Preconception, DOHaD, cancer etc. and hypertension)

5. Super-aged Society and Hypertension (Sarcopenia, Dementia, Social Capitals etc.)

6. Hypertension Next Generation therapy (Renal Denervation, Single compound pills, Applications etc.)

7. Convergence of Communicable Diseases and NCDs

8. Japan Method for conquering hypertension ("Hypertension Zero Town" etc.)

9. Pathophysiology of Hypertension: Chronicle to the Future

10. Blood Pressure Measurement: Conventional and Future

11. Imaging and Biomarker for Hypertension Management

12. Hypertension Reigning Over Systemic Diseases

13. Genetics, epigenetics, and hypertension

The Gala Dinner, where the new elected ISH Council members were announced, was also a great success, with Japanese Musicians, Ninjas and Samurais entertaining over 250 guests. In fact, all these performers were local organising committee members.

The closing ceremony included PR for ISH2024 in Colombia and the announcement of the ISH2022 KYOTO Zero Hypertension Declaration.

Thank you so much for helping ISH2022 KYOTO. We strongly believe that all participated in the ISH2022 Kyoto could deepen and widen their knowledge and expertise from the sessions, and communication with researchers from all over the world.

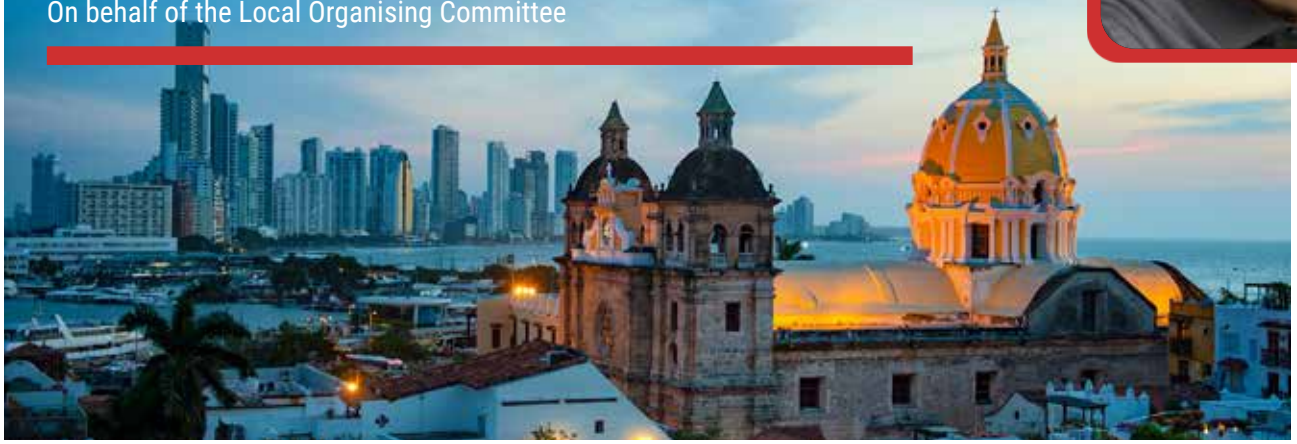
We sincerely hope that the world will be more peaceful and that we can share our values with you. See you again at ISH2024.

Arigato,
Hiroshi Itoh
President, ISH2022 KYOTO

ISH BIENNIAL SCIENTIFIC MEETINGS

Cartagena de Indias: The beautiful and historic city that will host the ISH in 2024

DAGNOVAR ARISTIZABAL
Executive President, ISH 2024, Cartagena de Indias, Colombia
On behalf of the Local Organising Committee



We recently visited Cartagena de Indias for the XIII International Symposium of Cardiology of the Colombian Cardiac Society, a successful meeting with renowned speakers from Europe, US and Latin-America. We experienced Cartagena firsthand as a world class meeting venue. Throughout the year, Cartagena hosts a variety of events that showcase the city's unique character and draw visitors from all over the world. After this delightful time there, we thought of telling you more regarding this great destination, where our next ISH meeting will be held in 2024.

Cartagena de Indias is a stunning coastal city located on the Caribbean coast of Colombia. With its rich culture, fascinating history, and beautiful beaches, it's no wonder that this city has become a popular tourist and meeting destination. Here will explore the accessibility, safety, and accommodation options in Cartagena de Indias.

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Accessibility

Cartagena has an international airport, Rafael Nuñez, which serves as a gateway to the city for travelers. The airport is located just 10 minutes from the historic district, where the main tourist attractions and accommodation offers are located, making it easy to get to your hotel or meeting venue. Many airlines offer direct flights to Cartagena, including JetBlue, KLM, LATAM and Avianca (see graph). Cartagena de Indias is well connected to many international hubs around the world. Here are some of the international flight destinations that have connections with Cartagena de Indias and Bogotá:

Miami: American Airlines and Avianca offer direct flights

Fort Lauderdale: Jet Blue and Spirit offer direct flights

New York: JetBlue and Avianca Airlines offer direct flights

Madrid: Plus Ultra Airlines offers direct flights

Amsterdam: KLM Airline offers direct flights

Panama City: Copa Airlines and Wingo offers direct flights

Orlando: Spirit Airlines offer direct flight

Lima: Latam Airlines offer direct flights

San José: Avianca Airlines offer 4 flights weekly

Sao Paulo: Avianca Airlines offer 3 flights weekly

Santiago: Avianca Airlines offer 4 flights weekly

Guayaquil: Avianca Airlines offer 3 flights weekly

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Security/Safety

Cartagena de Indias is a safe city for visitors, and the government has taken measures to ensure the safety of tourists and locals alike. The city has a dedicated tourist police force, which patrols popular tourist areas, such as the historical center and the beaches. Additionally, many hotels and meeting venues have their own security measures in place, such as gated entrances and 24-hour surveillance. However, like any city, it's important to exercise caution and be aware of your surroundings, especially when traveling alone or at night.

Accommodation

Cartagena de Indias offers a range of accommodation options to suit different budgets and preferences. There are around 200 hotel establishments with around 20,000 beds. From luxury hotels to budget-friendly hostels, there is something for everyone. Many hotels are located in the historic center of the city, which is a UNESCO World Heritage Site and a popular tourist destination. However, there are also hotels located in other areas of the city, such as the beachfront corporate neighborhood of Bocagrande. Overall, Cartagena de Indias offers great value accommodation options for business travelers and tourists alike.

Scientific Venues

Cartagena de Indias ranks 12th in America's ranking of number of meetings per city made by the International Congress and Convention Association (ICCA). The city has a main international convention center, where our congress will be happening and other smaller meeting venues located in exclusive hotel chains. Both the infrastructure of these convention centers and the number of luxury and boutique hotels in the city make Cartagena a great destination for hosting major events.

Tourism

Of course, no trip to Cartagena de Indias would be complete without experiencing the city's rich culture and history. With its cobblestone streets, colorful colonial architecture, and UNESCO World heritage Site designation, the city is a feast for the senses. Visitors can take a stroll around this open air museum of the Spanish colonial period and explore the stunning plazas, churches, and museums. You can also indulge in the local gastronomy, which features a mix of African, Spanish, and indigenous influences, and attend traditional music and dance performances.

This stunning coastal city, on the Caribbean Colombian coast, is a fantastic tourist destination with many cruise ships arriving each week. For those looking for a more secluded experience, there are a number of smaller islands around Cartagena de Indias that can be reached by boat just minutes away. These islands offer pristine beaches, crystal-clear waters, and a chance to get away from the crowds and enjoy some peace and quiet. Whether you're looking for adventure or relaxation, Cartagena de Indias beaches and islands offer something for everyone.

In summary, Cartagena de Indias is the ideal destination for tourism, and also for meetings and conferences. With its convenient location, impressive venues, world-class hotels, and rich cultural experiences, it has everything you need to make your stay an unforgettable memory.

We hope to welcome you in Cartagena de Indias in September 2024!

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FOCUS ON ALDOSTERONE

Selective aldosterone synthase inhibitors: just-in-time delivery for Aldosterone and Aldosteronism's 70th birthdays

MORRIS J. BROWN

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In 1953/4, the Taits in London discovered aldosterone, and Conn the first aldosterone-producing adenoma. He predicted that Primary Aldosteronism (PA), in which one or both adrenals have gone into automode, would be the commonest secondary cause of Hypertension. Estimates from prospective study of newly diagnosed Hypertension are, indeed, 5-13% of all patients.[1,2] But, outside such studies, fewer than 1% of PA patients are diagnosed (e.g. only 79/107,407 patients with Hypertension in UK Biobank). This is a Public Health catastrophe since major cardiovascular morbidity/mortality is twice as high in PA as in Essential Hypertension of similar severity, and potentially reversible.[3,4] Even this statistic underplays the true risk, as PA patients are much more likely to develop treatment-resistant hypertension. PA patients are readily suspected, having a suppressed plasma renin despite treatment with an ARB or ACEi.[5] PA under-diagnosis might largely disappear if renin were routinely measured when hypertension is uncontrolled on these drugs. A clarion call!

Since the British Hypertension Society's PATHWAY-2 study of 2015, it has been clear that targeting the mineralocorticoid axis, with spironolactone or amiloride, trumps conventional antihypertensive drugs in achieving BP control in resistant hypertension.[5,6] But adverse effects, particularly hyperkalaemia, have limited their use and dosage. There are two approaches to protecting target tissue from an undesirable hormone or mediator. One is to block its receptor, or downstream pathway, and the other is to inhibit its synthesis. This is known to Hypertension doctors from the choice between ARBs and ACE inhibitors. For efficacy there is little to choose between these classes, but ARBs avoid the risks of dry cough or angioneurotic oedema. Similarly, aldosterone synthase inhibitors (ASI) have long been a tempting alternative to mineralocorticoid receptor blockade, in the hope of better tolerability and, consequently, effectiveness. This hope has two origins. First is the highly restricted expression of the enzyme, in just a few adrenocortical cells, limiting likelihood of off-target adverse effects. Second is the empirical observation, in human and mouse genetic knockouts, that only loss of both copies of the enzyme gene ('CYP11B2') has a phenotype, largely restricted to infancy; whereas the homozygous knockout of the receptor is lethal.[7]

So why has the ASI class taken so long to deliver? In most domestic species, aldosterone and cortisol are made by the same enzyme. In rodents and primates, the CYP11B1 gene, encoding cortisol synthesis, is duplicated as CYP11B2, encoding aldosterone synthase, and the two enzymes share 93% identity. This has had two consequences. The first was unawareness of molecular events driving the frequency of PA, especially the dramatic disappearance of aldosterone synthase from most of adult human adrenal. This disappearance likely results from excessive salt consumption,

rendering aldosterone largely redundant, but was only appreciated when Dr Celso Gomez Sanchez developed and shared specific monoclonal antisera to aldosterone synthase.[8] PA, I believe, is a maladaptive response to salt excess, consequent on the involution of aldosterone-producing cells when no longer required.[9,10] Only mutation-driven constitutive aldosterone production can save the cells, resulting in physiological clusters responsive to stress hormone or cation fluxes, and in pathological aldosterone-producing adenomas. Darwin in action.

The second consequence of the 93% identity has been the difficulty of inhibiting aldosterone without compromising cortisol synthesis. This is illustrated by LCI699, a Novartis ASI whose development was stopped at phase 2, when ACTH stimulated cortisol levels were reduced. The drug was re-purposed, and is now marketed as Osilodrostat for treatment of Cushing's. But the drought has now ended, and – like we say about London buses – you wait ages for one, then three come along at once. Leading the pack is baxdrostat, a Roche development with 100:1 selectivity for aldosterone vs cortisol inhibition.[11] After Roche paused its cardiometabolic programme in 2014, the drug sat on the shelf until licensed in 2018 to a single-drug US start-up, Cincor. The lack of cortisol inhibition was confirmed in a multiple ascending dose study, and baxdrostat entered a Phase 2 trial of 248 patients with resistant hypertension.[12] Although the lower US vs Europe threshold for diagnosing resistant hypertension resulted in a 10 mmHg lower entry systolic BP than to PATHWAY-2, the primary outcome of placebo-corrected fall on baxdrostat 2 mg was 11.0 mmHg, similar to that on spironolactone 50 mg in PATHWAY-2.[13] There were also dose-related falls, approaching 70%, in plasma and urine aldosterone. The results, presented at AHA and published in NEJM, made Cincor hot property, and shortly afterwards AZ placed a $1.3B bet on the potential value of ASI.

Lorundrostat, similarly, started in Big Pharma – Mitsubishi – before moving to a US start-up, Mineralys. Its phase 2 trial was presented at ACC, but full results are not yet published. In a pre-specified sub-group of resistant hypertension, 30 patients with BMI >30, had a placebo-corrected fall in SBP of 16.7 mmHg.

Dexdrofadrostat (FAD286) is the dextro-isomer of an old drug, fadrozole, whose laevo-isomer inhibits cortisol and oestrogen synthesis. FAD286 long precedes the previous two drugs, and suppressed aldosterone but not cortisol in hypertensive rats (SHR). However, it was not patented and therefore not developed clinically. The breakthrough came with a patented method, by Damian Pharmaceuticals, of separating the isomers with high purity. Its selectivity in SHRs has now been reproduced in volunteers[14] and PA, in which substantial falls in BP and aldosterone were reported in Munich and Kyoto (PIPA7 and ISH-2022).

Hopefully, a judicious blend of academic and commercial competition and collaboration augur long-awaited new treatments for both PA and resistant hypertension – and realisation that patients with the former greatly outnumber the latter. Advent of highly efficacious, well-tolerated once-daily drugs – if confirmed in phase 3 – will also challenge the surgical removal of a whole adrenal gland in order to suppress aldosterone production. With prospective trial evidence that only 30% of adrenalectomies completely cure Hypertension, in a largely identifiable subset of PA patients, the race is on to find less invasive treatments.[15] In my lifetime, coincidentally co-terminous with that of aldosterone, treatment for another small benign lesion, peptic ulcer (PU), has morphed from removal of an organ to a course of omeprazole. If ASIs prove the omeprazole of PA, they will be not just class-of-'23, but class-of-their-own.

Disclosure. MJB was a member of the Scientific Advisory Board of Cincor.

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FOCUS ON ALDOSTERONE

Mineralocorticoid Receptor (MR)-associated Hypertension: Over-activation of MR by 'Greedy Kidney and Guts' for salt and sugar

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Significantly wider roles of mineralocorticoid receptors (MR)

Evolutionally, MR had been developed long before the emergence of aldosterone and possesses high binding affinity to steroid hormones other than aldosterone, including glucocorticoid. MR is activated by high aldosterone, a typical example of which is primary aldosteronism. The activation of MR by glucocorticoid, escaped from degradation by 11β hydroxysteroid dehydorgenase (HSD) type2 through the defect of HSD11B2 is known to cause hypertension (apparent mineral corticoid excess syndrome; AME).[1]

Thus, it is postulated that MR has wider biological activity not restricted to salt retention in the body through the kidney (sodium re-absorption) or the colon (sodium absorption). MR are expressed in the heart, blood vessels, the brain, the skin and macrophages. Significant roles of MR in several organs have been demonstrated in many clinical trials. Spironolactone has been used for more than 60 years. In 1957, the first human trial using spironolactone was performed, and in 1999, the epoch-making trial, the randomized aldactone evaluation study (RALES) study to show the effectiveness of spironolactone for life-saving for heart failure patients was reported. Eplerenone was developed as MR-specific MRB, and again life-saving effect for patients with left ventricular dysfunction after myocardial infarction was reported in eplerenone in post-myocardial infarct heart failure (EPHESUS) trial in 2003. Recent meta-analyses demonstrate the effectiveness of MRB for patients with chronic kidney diseases (CKD) or diabetes mellitus (DM).[2]

MR-associated hypertension

In 2012, we proposed the concept of "MR-associated hypertension", that is, the hypertension caused by over-activation of MR with wide range of plasma aldosterone level.[3] Primary aldosteronism with high plasma aldosterone level is the typical example of MR-associated hypertension but it is not only the cause of MR-associated hypertension. Even in low plasma aldosterone concentration states, MR can be over-activated and MR-associated hypertension occurs. MR blockers (MRB) are quite effective for MR-associated hypertension.

MR-associated hypertension is categorized into hypertension with elevated plasma aldosterone level and with normal or low aldosterone level. In the former category, the plasma aldosterone level usually exceeds 150pg/ml. Primary aldosteronism and aldosterone-associated hypertension exhibit low renin and high aldosterone level and in aldosterone breakthrough phenomenon during

ACE inhibitor or ARB administration plasma renin activity is high. In obesity, obstructive sleep apnea or sleep disorders, plasma renin and plasma aldosterone are in proportion high. In the latter category, in obesity, chronic kidney disease (CKD), polycystic ovary disease, high serum or tissue cortisol level, MR is over-activated in spite of normal aldosterone level.

There are several postulated mechanisms of over-activation of MR. Increased expression of MR, increased sensitivity of MR and we focus upon MR protein stabilization. Other investigators revealed MR over-stimulation through Rac1 by excessive salt intake.[4]

Therefore, several risk factors including left ventricular hypertrophy, diabetes, obesity, metabolic syndrome, salt and stress could activate MR via aldosterone dependent and independent pathways.

We are interested in the activation of MR by salt and sugar themselves. We focus on the significance of MR expressed in the intestines for sodium absorption. Administration of deoxycorticosteroid acetate (DOCA) and high salt induced the up-regulation of epithelial sodium channel (ENaC) β, the target molecule of MR in the intestines. Intestine specific MR knock-out mice exhibited blunted increase of blood pressure by DOCA and high salt loading, indicating the significant role of intestinal MR for sodium absorption and blood pressure regulation. High salt induces up-regulation of intestinal MR activity which is involved in sodium absorption and blood pressure regulation.[5]

We also demonstrated that high sugar induces MR protein stabilization by PKC β activation, O-N-acetylglucosamine (GlcNac) modification or EGF receptor-ERK activation.[6,7,8]

Greedy Organ hypothesis for salt and sugar

In 2021, in relation to excessive salt and sugar intake and occurrence of non-communicable diseases (NCDs), including hypertension, we have proposed "Greedy Organ Hypothesis".[9] Excessive intake of salt and sugar are sensed by the kidney and the intestines. And then, these organs up-regulate sodium-glucose co-transporters, SGLTs and come to absorb salt and sugar greedily. Excessive salt intake through SGLT2 makes the kidney greedy to induce hypertension/CKD. Excessive food intake through SGLT1 make the intestines greedy to induce obesity/DM. Furthermore, there is a "crossing" relationship between "greedy organs" and NCDs, that is, "greedy kidney" can cause obesity/DM and "greedy intestines" can cause hypertension/CKD.

We reported that renal proximal tubular cells sense high glucose levels at their basolateral side and increase uptake of glucose by upregulating SGLT2 expression. Furthermore, high glucose upregulates the expression of gluconeogenic enzymes, such as phosphoenolpyruvate carboxykinase (PEPCK) and Glucose 6-phosphatase and induces gluconeogenesis. We think that these responses of renal tubular cells to high glucose are "greedy".[10]

The intestinal epithelial cells similarly behave to the renal tubular cells. Guts sense high sugar level by T1R3 ("Sweet Receptor") and up-regulate the expression of SGLT1. Recently, we reported that the intestines are also greedy to salt for upregulation of SGLT1. Transient administration of high salt to spontaneously-hypertensive rats (SHR) induced up-regulation of not only sodium hydrogen exchanger 3 (NHE3), but also SGLT1 and this effect persisted after returning to normal salt diet. We elucidated that this effect of transient high salt is caused by overactivation of intestinal renin-angiotensin system.[11]

Greedy Genes and MR-associated hypertension

Greedy kidney and intestines induced by high salt and sugar over-activate MR and induce MR-associated hypertension.

We call the genes to be activated by high salt and sugar and to make organs greedy are "greedy genes". In addition to SGLT1 and 2, the genes for MR and its target molecules, such as epithelial sodium channel (ENAC) can be the greedy genes. Therefore, MRB are effective to alleviate greedy organs to suppress NCDs, including hypertension.

Development of Non-steroidal MRB and their clinical potencies

Recently, esaxerenone was developed with non-steroidal structure which possesses high affinity and specificity to MR and exhibits long elimination half-life. In vitro binding experiment, esaxerenone exhibits around one-order of magnitude higher than spironolactone and two order of magnitude higher than eplerenone binding affinity to MR.[12]

We conducted a double-blind phase III study of esaxerenone compared with eplerenone in patients with essential hypertension in 2020.[13] Esaxerenone 2.5mg elicited comparable hypotensive effect to eplerenone 50mg both in systolic and diastolic blood pressure. Esaxerenone 5mg exhibited significantly a stronger effect than 2.5mg and eplerenone 50mg. 5mg esaxerenone caused 17mmHg in systolic and 8mmHg in diastolic blood pressure reduction. We analyzed the differential effect of esaxerenone on dipper, non-dipper, extreme dipper and riser blood pressure variation patterns. To dippers, it exerted similar hypotensive effect throughout the day.[14]

We also investigated the efficacy and safety of dosage-escalation of esaxerenone from 1.25 to 5mg added to a renin-angiotensin system (RAS) inhibitor in hypertensive patients with type 2 diabetes and albuminuria in a single-arm, open-label study.[15] Five mg esaxerenone induced 20/8mmHg blood pressure reduction in hypertensive patients with diabetes and significantly reduced albumin excretion with no apparent adverse effect, including elevation of serum K level.

We further investigated antihypertensive effects and safety of esaxerenone in patients with moderate kidney dysfunction with eGFR between 30 to 60, as monotherapy or add-on therapy with RAS inhibitors.[16] In both studies, blood pressure was significantly reduced by 18mmHg in systolic and 8-9mmHg in diastolic. Esaxerenone exhibited no serious effect on the elevation of serum K level or the increase of creatinine or decrease of eGFR.

Interestingly, esaxerenone exerted similar hypotensive action in the patients with RAS inhibitors, compared to other groups. This observation indicates that MR can be activatedbeing independent of renin-angiotensin-aldosterone cascade. This clinical observation indicates the existence of MR-associated hypertension.[17]

The effectiveness of another non-steroidal MRB, finerenone was reported in diabetic kidney disease patients around 2020.[18,19] It was demonstrated to exert weak effect on blood pressure but elicit significant suppressive action on inflammation and fibrosis. In FIDELIO-DKD, FIGARO-DKD and the combination analysis of these two studies, FIDELITY demonstrated that albumiuric diabetic CKD patients with median eGFR of 58ml/min and albumin excretion of 515mg/day, taking RAS inhibitors significantly inhibited cardiovascular or renal events with HR of 0.82 or 0.87.[20]

The reason and mechanism of differential action on blood pressure between two non-steroidal MRBs, esaxerenone and finerenone has not been fully known yet.

Positioning of MRB in world guidelines

In the 2020 ISH Guidelines, MRB are recommended as secondary medication. They are preferred for resistant hypertension or hypertension with HFrEF. 2017 ACC/AHA recommended MRB to hypertension with stable ischemic heart disease and HFpEF. 2018 ESC/ESH recommended MRB to hypertension with coronary artery disease, chronic kidney disease, HFrEF, and left ventricular hypertrophy. Our Japanese guideline states that MRB are effective for low renin hypertension and hypertension with chronic heart failure or after myocardial infarction. Only our guideline mentions esaxerenone as follows; Esaxerenone could be carefully administered to diabetics with albuminuria/proteinuria and patients with moderate renal dysfunction, based upon our evidence.

MRB could exert significant effect to suppress over-activation of MR and alleviate greedy organs for salt and sugar, therefore, they should be used more widely in NCDs in the future.

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SPECIAL FEATURES

International consensus on standardized office blood pressure measurement - A call to action by 13 organisations!

GEORGE STERGIOU
ISH Secretary

In the last decade the classic "gold standard" method for measuring blood pressure (BP) in the office or clinic, which has been considered for almost a century as the cornerstone for hypertension diagnosis and management has been seriously questioned, mainly due to its poor reproducibility and the white coat and masked hypertension phenomena.[1] As a result, all the recent guidelines by ISH, ACC/AHA, ESC/ESH, UK NICE, Canada, Japan, Australia and elsewhere have put considerable emphasis on out-of-office BP measurement methods (24-hour ambulatory or home) for the diagnosis and management of hypertension.[2-6] In fact, the decisions for making the diagnosis of hypertension, initiating antihypertensive drug therapy, and titrating therapy for reaching optimal BP control have now been moved out of the office (at home or in ambulatory conditions). Thus, it might be a surprise to many colleagues that in 2023 an international consensus paper exclusively devoted to the old method - office/clinic BP measurement - has been developed and published.[7]

Why should we care about office BP measurement in the 21st century? Well, the reality is that today and in the years to come most people with high BP around the world (in both low and high income countries) will be diagnosed and managed using only measurements of BP in the office. In addition, it took us too long time to accept that the methodology for measuring BP in the office varies, depending on the device, conditions, number of measurements, etc. These different office measurement methods give different BP levels and lead to different conclusions and treatment decisions **(Table 1)**.[8] Thus, it is important to reach global consensus on a 'standardized' office BP measurement aiming at improving its accuracy and thereby the reliability of treatment decisions.

Table 1. Different methods for office blood pressure measurement and their impact on the blood pressure level.[8]

	Setting	Method	Blood pressure
1.	Clinical practice	Manual auscultatory	▲ ▲
2.	Clinical practice	Automated attended	▲
3.	Clinical practice	Automated unattended	▼
4.	Research setting	Auscultatory or automated	▼

Different Methodology ▶ Different BP threshold ▶ Different diagnosis

Numerous guideline publications have provided detailed recommendations for office/clinic BP measurement which essentially are identical **(Figure 1)**.[1-7] Yet regrettably the scientific community has failed to implement the optimal methodology into clinical practice. The 2023 international consensus statement led by KDIGO presents 4 steps for standardized office BP measurement **(Figure 2)**[7]: (i) setting, device, and cuffs, (ii) observer training, (iii) measurement conditions, (iv) procedure and interpretation. Although the manual auscultatory BP measurement is still regarded as the reference method for assessing the accuracy of any novel BP measurement technology, automated electronic (oscillometric) arm-cuff BP devices are currently recommended for office/clinic BP as they are devoid of the common issues with human observer biases and errors.[2,5,7] However, most

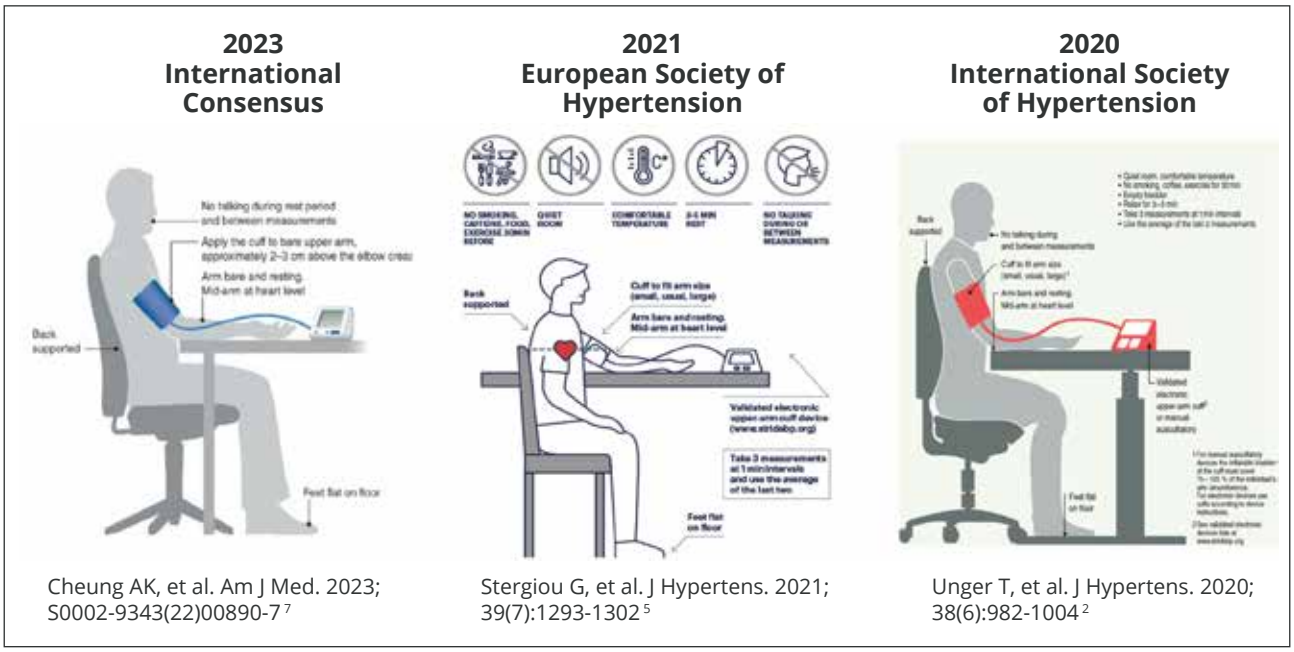

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Figure 1. Recommendations for office/clinic blood pressure measurement.[2,5,7]

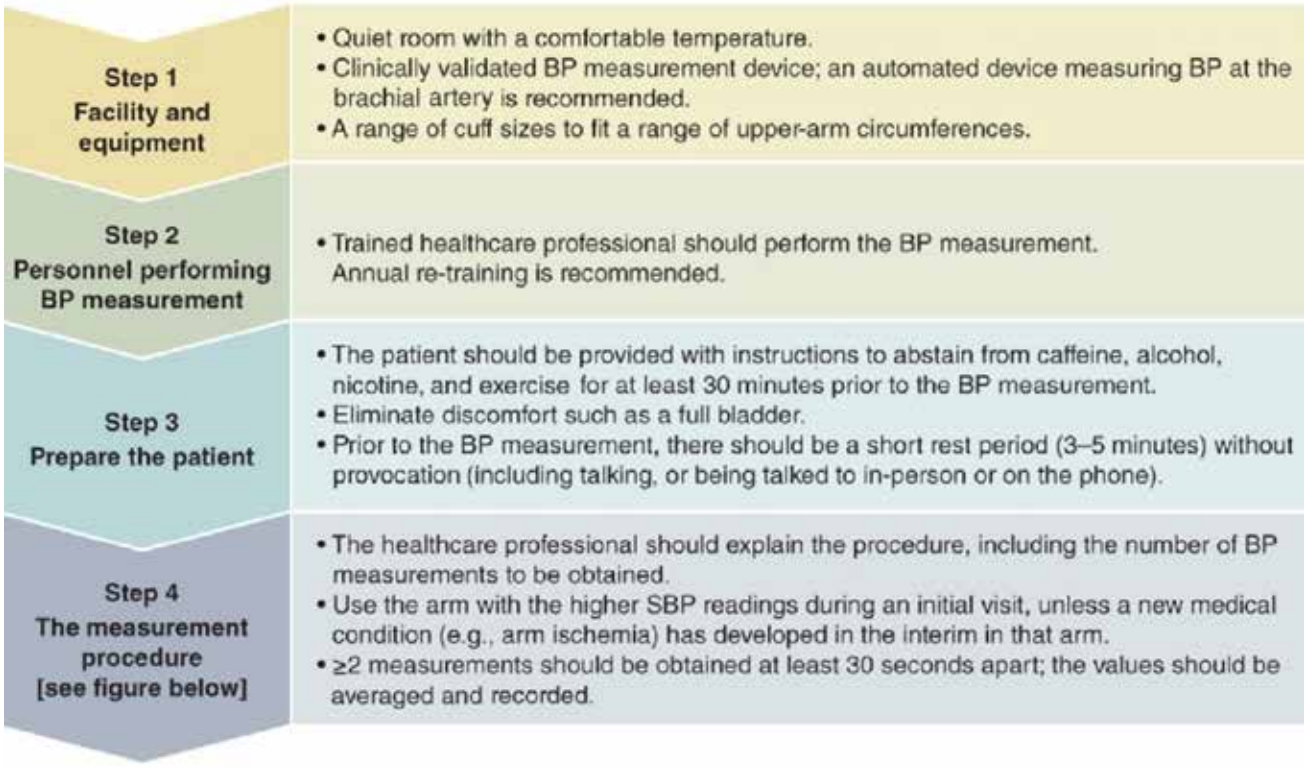
of the electronic devices currently available on the market have not been properly validated for accuracy. The international consensus statement provides a list of scientific organizations providing online lists of validated BP monitors **(Table 2)**.

It is amazing how much time and effort has been put for so long time to achieve optimal BP measurement.[2-7,9,10] This is understandable as BP is an unstable variable with dynamic characteristics of variability and its measurement remains the foundation for diagnosing and treating hypertension. Cheung at al[7] and KDIGO should be praised for an extraordinary achievement, as they managed to bring to the consensus table 25 international experts from around the world representing 13 of the most prestigious scientific organizations in hypertension globally. ISH actively contributed to the development of this statement with four of its officers – Alta Schutte, Maciej Tomaszewski, Bryan Williams, and George Stergiou. We hope and should strive for this initiative to have a global impact in standardizing office blood pressure measurement – at last!

Table 2. Organizations providing online lists of validated blood pressure monitors.[5,7]

Organization	Monitor lists (language)	Scientific association	Website
STRIDE BP	International (English, Chinese, Spanish)	European Society of Hypertension – International Society of Hypertension – World Hypertension League	www.stridebp.org
BIHS	UK, Ireland (English)	British and Irish Hypertension Society	www.bihsoc.org/bp-monitors
VDL	US (English)	American Medical Association	www.validatebp.org
Hypertension Canada	Canada (English)	Hypertension Canada	www.hypertension.ca/bpdevices
Deutsche Hochdruckliga	Germany (German)	German High Pressure League	www.hochdruckliga.de/betroffene/blutdruckmessgeraete-mitpruefsiegel
JSH	Japan (Japanese)	Japanese Society of Hypertension	www.jpnsh.jp/com_ac_wg1.html

Figure 2. Steps for implementing standardized office/clinic blood pressure measurement.[7]



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SPECIAL FEATURES

Indoor temperature and BP control

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Excess winter mortality and the Smart Wellness Housing survey

Excess winter mortality (EWM) from cardiovascular diseases (CVDs)[1] is a global public health challenge, with cold exposure-induced hypertension as a key factor. A previous study reported a greater incidence of EWM in people living in cold homes.[2] However, existing countermeasures aimed at preventing hypertension and CVDs emphasize improvements to lifestyle habits, not life environment.

In 2018, WHO's publication of Housing and health guidelines[3] resulted in increased attention to improving life environment. The guidelines identify 'low indoor temperatures and insulation' as a priority area. Given that in today's society most people spend 60-70% of their time at home, evidence regarding the association between indoor temperature and blood pressure (BP) is essential.

We initiated a nationwide prospective intervention study in Japan, named the Smart Wellness Housing (SWH) survey. Our aim was to quantitatively evaluate the association between indoor temperature and BP in a real-world context. The intervention consisted of thermal insulation retrofitting applied to existing houses. Home BP (HBP) and indoor temperature measures were taken for the 2-week periods before and after the intervention in winter (November-March) of FY 2014 to 2019. We set four research questions, as described in the following sections.

Question 1: Is it warm enough indoors during the winter?[4]

Average temperature readings from approximately 2,200 houses before insulation retrofitting were: living room, 16.8°C; changing room, 13.0°C; and bedroom, 12.8°C, with average minimum temperatures of 12.6°C, 10.4°C, and 11.2°C, respectively. In over 90% of the houses these minimum temperatures were below the 18°C recommended by WHO. The paradoxical relationship was found: whereas the lowest living room temperature (13.1°C) was in Kagawa, where the winter climate is considered mild, the highest (19.8°C) was in Hokkaido, which has the most severe climate in Japan. The reason is that houses in Hokkaido have more efficient thermal insulation and uninterrupted heating. We also found that lower-income householders lived in colder houses. Energy (fuel) poverty is widespread in Europe and North America, where houses are generally better thermally insulated than in Japan. Thus, the problem of living in cold homes concerns not only Japan, but other countries also.

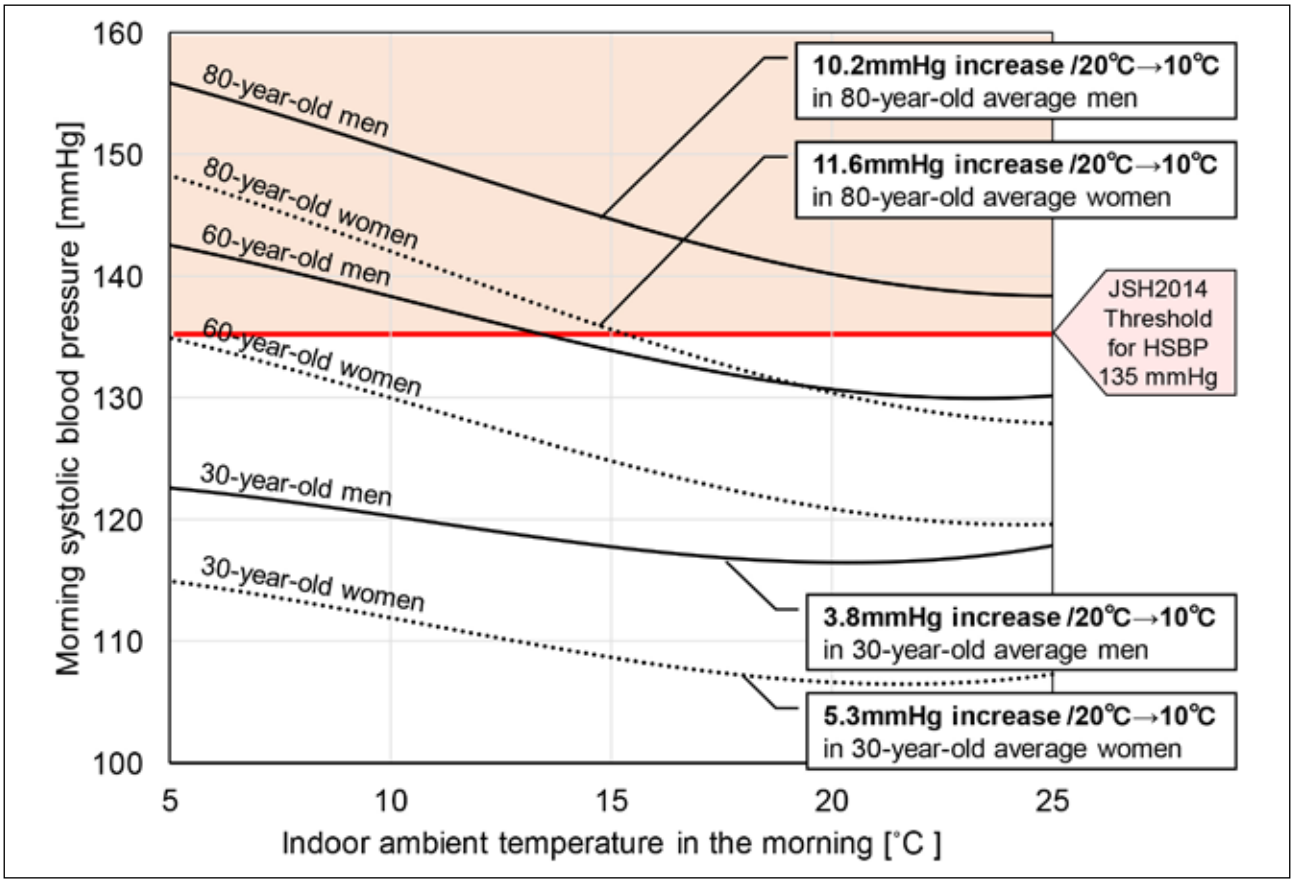

Figure 1. Relationship between indoor temperature and morning systolic blood pressure. (Figure taken from the graphical abstract of Hypertension, 2019)[5]

Question 2: Does higher indoor temperature decrease HBP?[5]

Based on 33,000 data points from 2,900 residents we found a significant inverse association: HBP was lower at high indoor temperatures. Morning systolic BP (SBP) was significantly more sensitive to changes in indoor temperature (8.2 mmHg decrease/10°C increase) than evening SBP (6.5 mmHg decrease/10°C increase) in participants, whose mean age was 57 years. As CVD-related events occur frequently in the morning, morning indoor temperature management may have a major role in reducing CVDs. In addition, although previous studies considered the temperature–BP relationship as a linear function, we showed a nonlinear cubic relationship between morning SBP and indoor temperature **(Fig.1)**. Furthermore, we established that SBP in older residents and women was vulnerable to indoor temperature change. We believe that these findings will contribute to determining optimum home temperature recommendations for each population group.

Question 3: Does stable indoor temperature decrease HBP variability?[6]

The association between indoor temperature instability and BP variability was analyzed using the morning-evening (ME) difference as an index of diurnal variability, and the standard deviation (SD) of 2-week data as an index of day-by-day variability. Compared to residents living in houses with a ME difference in indoor temperature of ≥ 4°C, the ME difference in SBP was less than half this value in residents living in houses with an ME difference < 1°C (9.3 vs 3.9 mmHg). Compared to residents whose houses had an indoor temperature SD ≥4 °C, the SD of SBP was smaller in residents whose houses had an SD <1 °C (9.5 vs 6.3 mmHg).

Question 4: Does insulation retrofitting of houses reduce HBP?[7]

Insulation retrofitting led to a morning indoor temperature increase of 1.5°C. Comparing HBP before and after intervention, morning SBP was significantly reduced by 3.1 mmHg following insulation retrofitting. There was also a dose–response relationship between indoor temperature and HBP, underlining the effectiveness of a substantial improvement in indoor temperature. Analysis by subgroups revealed heterogeneity in the effect of the insulation retrofitting intervention on morning SBP. While the overall average decrease was 3.1 mmHg, the morning SBP of older residents, smokers, and hypertensive patients decreased by 5.0 mmHg, 4.6 mmHg, and 7.7 mmHg, respectively. These results indicate that insulation retrofitting was especially beneficial for subgroups at high risk of CVDs.

New concept of "life-environmental diseases" [8]

We obtained answers for 4 research questions as follows:

A1: Over 90% of houses did not meet the WHO-recommended minimum indoor temperature of 18ºC.

A2: Higher indoor temperature was associated with decreased HBP, especially in older residents.

A3: Stable indoor temperature decreased diurnal and day-by-day HBP variability.

A4: Insulation retrofitting reduced HBP, especially in subgroups at high risk of CVDs.

Residents should keep the indoor temperature high to both reduce and stabilize BP through strategies such as installing effective thermal insulation. We hope that these results will be useful for preventing EWM due to CVDs.

Based on our findings, we propose that hypertension and CVDs might be not only lifestyle diseases but also life-environment diseases (Fig.2). Further, we hypothesize that living in cold homes for a long time has a cumulative effect – which we refer to as a "cold debt" – on blood vessels. The impetus for starting the SWH cohort survey was to clarify whether this cold debt existed or not.

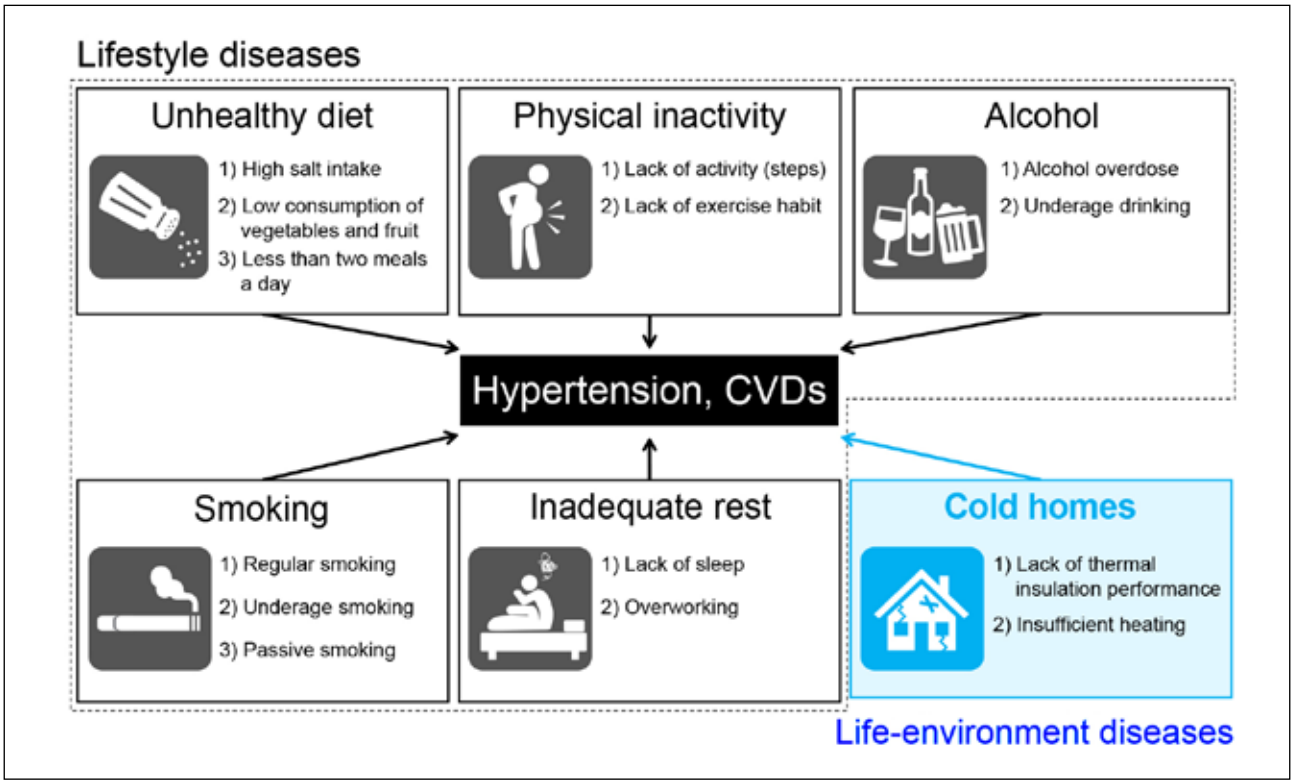

Figure 2. New concept of "life-environmental diseases" (Figure taken from the graphical abstract of Hypertension Res, 2023)8

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AFRICAN VOICES

Introduction

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In this issue, African voices presents three papers covering topics on the progress made in Africa on hypertension research in terms of knowledge generation and approaches to improve management of hypertension. There is a discussion on health systems barriers to hypertension awareness and provision of optimal care in Kenya. Lastly, we look at the pattern of hypertension-mediated organ damage complications in Sudan.

Firstly, Nasheeta Peer and Andre-Pascal Kengne summarise the burden of hypertension and contribution to cardiovascular disease in Africa and give an overview of the progress in research data published from Africa since 1990. The authors further share some findings from South Africa to inform tailored interventions aimed at improving hypertension management in Africa. There is a special focus on how current health systems challenges relating to hypertension care can be mitigated by leveraging existing models used for HIV care such as task-shifting.

In paper 2, Elijah Ogola reports that low hypertension awareness levels remain a public health concern in Kenya, with awareness levels as low as 15%. Poor hypertension awareness is a multifactorial challenge, mainly due to public knowledge and health systems-related barriers. Efforts from national (ministry of health) and global (May Measurement Month) initiatives, have reportedly improved awareness levels. The paper concludes with an emphasis on setting up screening points in places that communities can easily access and not only at primary healthcare facilities.

Paper 3, by Ibtisam Ahmed Ali highlights hypertension as a major risk factor for coronary artery disease (CAD) in Sudan. This paper builds on previous work showing similarities and differences with other North African countries and black populations, respectively, on the pattern of hypertensive target organ complications. The current paper discusses findings of a hospital-based study to assess CAD in hypertensive patients presenting with chest pain in a Sudanese population. CAD was present in a large proportion of the patients (73.3%). Duration of hypertension, along with poor adherence and control were associated with the severity of CAD.

To conclude, the exponential increase in publications from the African continent shows the progress made to tackle the growing burden of hypertension in the past two decades. However, despite efforts to improve hypertension awareness in Africa, screening remains low and care suboptimal. Diagnosis and control are essential to prevent hypertension-mediated organ damage complications and potentially cardiovascular mortality. Indeed, a holistic approach including decentralisation of hypertension screening and care may be the most feasible option to achieve optimal hypertension control in Africa.

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AFRICAN VOICES

Hypertension research in Africa: a gateway to improving awareness of and addressing challenges in care

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Hypertension, a key risk factor for the cardiovascular diseases (CVDs) of ischaemic heart disease (IHD) and stroke, has become a threat to public health globally. Even Africa, with a substantial burden of infectious diseases, suffers from a high and burgeoning burden of hypertension and subsequent CVDs. In 2019, IHD and stroke contributed to 11% of mortality in the World Health Organisation Africa Region. Notably, almost half (48.9%) the mortality attributable to IHD and stroke in ≥15-year-old Africans occurred in those <70 years of age.[1] This represents an unacceptable high burden of premature deaths in the working age population who are likely family breadwinners. Poor management of hypertension in Sub-Saharan Africa, as reported by the NCD Risk Factor Collaboration, likely contributed to the high burden of premature CVD mortality in the region with only 13% of women and 9% of men with hypertension controlled on treatment.[2]

Nevertheless, there is a growing awareness of hypertension as a major public health issue in Africa as reflected in the incremental increase in publications emanating from the continent.[3] For example, per 10-year period from 1990 onwards, publications in Sub-Saharan Africa on hypertension prevalence increased from 32 (1990-1999) to 65 (2000-2009) and rose exponentially to 317 (2010-2019) publications in recent years. These data demonstrated an initial doubling of publications followed by an almost 5-fold exponential increase between the latter two decades and may likely signal a growing awareness of hypertension as a serious problem in Africa. The most publications over the 30-year period (1990 – 2019) examined were from South Africa (n=81) with publications more frequent in recent years.[3] The increase in publication numbers may correlate with the rise in hypertension prevalence in South African men and women from 27% and 31%, respectively, in 1998 to 45% and 48% in 2016.[4] Notably, while remaining suboptimal, hypertension control among the treated increased from 17% to 26% in men and from 21% to 30% in women between 1998 and 2016 and may be related to an increasing awareness of the growing hypertension burden in the country.[4]

However, numerous challenges exist to optimal hypertension care in Africa at the governance, healthcare system, healthcare provider and patient levels.[5] For example, health systems are poorly structured and sub-optimally funded, healthcare workers are overburdened and inadequately trained, and basic equipment such as sphygmomanometers to measure blood pressure and essential medications are frequently in short supply, etc. Several solutions have been proposed including the reallocation of care from doctors to those less skilled such as nurses or trained community health workers. Such task-shifting restructuring, together with ongoing training and monitoring of lower-level healthcare workers, has the potential to improve hypertension and CVD care.[5]

Novel approaches may be implemented for specific vulnerable populations such as patients with human immunodeficiency virus (HIV) who now have prolonged lifespans following the successful rollout of antiretroviral therapy in Africa and are developing hypertension similar to general populations. Considering the high HIV burden in Africa, incorporating routine blood pressure screening and hypertension care in HIV clinics for patients in regular contact with healthcare services may ensure that a substantial proportion of the population receive optimal hypertension treatment. The successes of and lessons learnt from HIV management in Africa, which includes task-shifting described above, may be leveraged to improve hypertension and CVD care on the continent.[5] For example, the contrasting approaches to HIV and hypertension care was highlighted in the same patient population who were found to be adherent to their antiretroviral therapy but not to their antihypertension medication.[6] This may likely be attributed to specific strategies employed in HIV programmes; adherence to antiretroviral therapy improved when this was emphasised during patient education and counselling sessions. However, the latter are lacking in hypertension and CVD management and harnessing such lessons learnt from HIV care in Africa will likely improve hypertension control.[6] Other initiatives may include decentralising hypertension management with community outreach programmes led by nurses and community health worker teams. This may likely improve patient access to care by removing barriers associated with transportation costs, time spent travelling long distances and waiting in clinic queues; it may enable easier access to blood pressure screening and treatment services. Research will be required to identify and adapt the optimal model of decentralised hypertension care in each setting.

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In summary, ensuring effective management of and optimal adherence to treatment for hypertension and other CVDs requires a holistic approach with a need to understand and address the unique and complex multifactorial influences in each setting. Ongoing review and regular monitoring of strategies implemented will play a major role in optimising efficiencies and cost-effectiveness of hypertension and CVD care.

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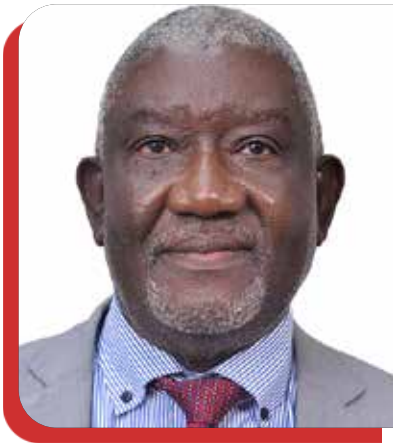
AFRICAN VOICES

Lack of awareness: a major barrier to control of hypertension in Africa



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Background

Raised blood pressure (BP) is the leading cause of global morbidity and mortality.[1] Africa has the highest age adjusted prevalence, which is still increasing.[2] Robust evidence exists for the reduction in cardiovascular (CVD) morbidity with adequate BP control. However, control rates globally remain poor, being poorest in Africa.[1] A meta-analysis of African studies showed control level of just 7% (3). A recent survey in Kenya showed a control rate of less than 5%.[4] The biggest contributor to poor control is lack of awareness. For example, in the African meta-analysis, only 27% of the participants were aware of their BP status.[3] In the Kenyan study it was about 15%. Lack of awareness is therefore the greatest barrier to the population control of elevated BP and reduction of hypertension related morbidity. In recognition of this fact, the International Society for Hypertension (ISH), in 2017 launched the May Measurement Month (MMM) programme, a global screening initiative to raise awareness.

Reasons for poor awareness

The poor awareness rates in hypertension are multifactorial. Fundamental to this is the fact that hypertension is asymptomatic. Simply put, unless BP is measured, a simple procedure indeed, a diagnosis of hypertension cannot be made. The measurement of BP, simple as it is, is hostage to several factors, especially in low income countries as in Africa. The public healthcare system is overstretched; overburdened and under resourced. It is essentially designed to tackle acute illnesses. The orientation of the system and the training of the healthcare workers is focused mainly on communicable diseases. Even in circumstances where there is frequent interaction with the healthcare system, BP is often not measured. It is for example, not tenable that a healthy looking middle aged man walks into a busy emergency department asking for his BP to be checked. Yet the facilities to offer health screening are simply not there. There is similarly a lack of understanding by the public of the asymptomatic nature, yet catastrophic consequences of hypertension if untreated. This is reflected also in primary healthcare workers as we recently showed.[5] This limits the ability of the public to initiate measurement of BP.

Initiatives to raise awareness

However, it is not all doom and gloom. In Kenya, in 2013, we embarked on a multiple component programme to improve hypertension control.[5] It involved a screening component that screened about 6 million subjects and also training of primary healthcare workers in hypertension treatment including a simplified treatment algorithm. From 2017, Kenya joined the MMM programme and we have participated in each subsequent year.[6,7,8] Around the same time the ministry of health (MOH) launched the non-communicable disease strategic plan followed by launch of national CVD guidelines, a joint project of MOH and the Kenya Cardiac Society. We have seen a rise in awareness rates in the MMM survey from 30.7% in 2018 to 34.7% in 2019.[7,8] It has further risen to 45.9% in 2021 (unpublished data). We believe the observed rise in awareness rates is a consequence of the various activities by the various stakeholders over the past several years.

Conclusions

Lack of awareness is a major barrier to adequate control of BP, hence measures to raise awareness are a major plank in the fight against hypertension. Public education to make patients aware of the asymptomatic nature of the disease as well as the consequences would encourage the public to initiate self-measurement. Easy availability of measuring points should be ensured e.g. in pharmacies, malls, markets and places of worship as well as in any public gatherings. Every health encounter should be an opportunity to have a BP measurement. Primary healthcare workers should be trained on the significance of BP measurement and availability of functional sphygmomanometers ensured. These continuous activities can be supplemented by opportunistic screening such as MMM.

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AFRICAN VOICES

Pattern of presentation of coronary artery disease in hypertensive patients in Sudan

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Hypertension is a common disease worldwide and is emerging as a public health problem in most developing countries. The disease is characterised by complications resulting in target organ involvement, associated with high morbidity and mortality. In the Sudan, the pattern of hypertensive target organ complications was found to be comparable to that of neighbouring North African countries, but distinct from that shown in black individuals outside the African continent.[1] Hypertensive heart disease, rheumatic heart disease, ischaemic heart disease (IHD) and cardiomyopathy constitute more than 80% cardiovascular diseases in Sudan.[2] Hypertension, either systolic/diastolic or isolated systolic, is considered a major risk factor for coronary artery disease (CAD). Hypertensives have a threefold increase in cardiac death (due to either coronary events or to cardiac failure).[3]

Evaluating chest pain in hypertensive patients presents challenges because besides CAD, left ventricular hypertrophy (LVH) is a cause of chest pain and shortness of breath.[4] A hospital-based study in Ahmed Gasim hospital in Khartoum, north Sudan aimed to assess CAD as a cause of chest pain. The study investigated the pattern and severity of CAD and associations between ECG, echocardiography, and coronary angiography findings. We recruited 135 known hypertensive patients presenting with chest pain aged between 39 – 90 years, with mean age of 59 years, and SD of 10 years and 60.7% of the study population were men. The exclusion criteria were smoking, diabetes and family history of CAD. Age, gender, duration of hypertension and body mass index (BMI) were considered as covariates. Hypertension period ranged between 6 months and 30 years, with a mean of 10.4 (SD of+- 6 years). In 33.1% of the patients, BMI was > 30 kg/m2. CAD was assessed through abnormalities in ECG, echocardiographic measurements, and cardiac catheterization. Coronary angiography results showed that 73.3% of the patients had CAD, of whom 26.7% had three coronary vessel disease (3VD). Left anterior descending (LAD) artery was the main presentation, followed by right coronary artery (RCA), circumflex artery (CX), then lastly the left main (LM).

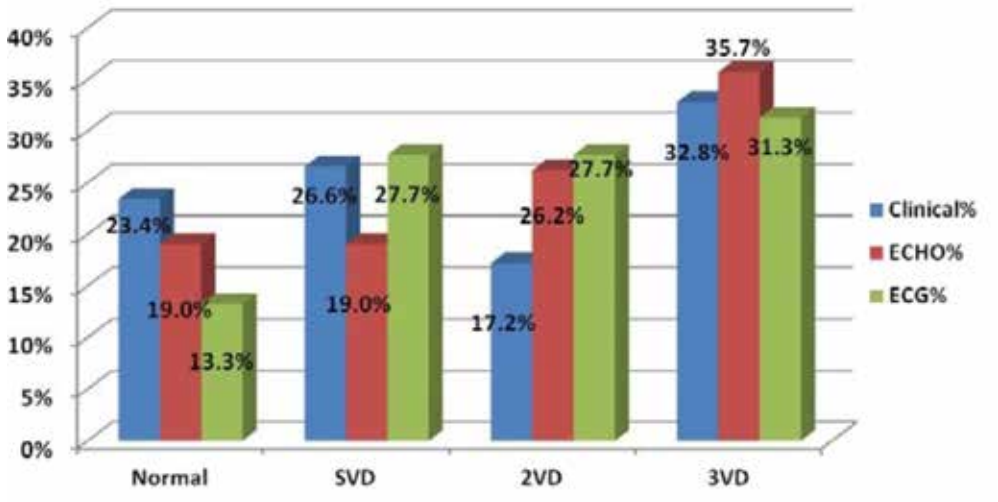

Figure 1: The pattern of coronary involvement in the study population

Abbreviations:
SVD, single vessel disease;
2VD, 2 vessel disease;
3VD, 3 vessel disease

The overall ranking of severity as assessed through the recommendation for treatment was-percutaneous coronary intervention (PCI) in 31.4%, coronary artery bypass graft (CABG) in 21.6%, 33% and 25% of these patients have had hypertension for more than 10 years. The LAD is the commonly involved artery due to the bulk of muscles supplied. Strong association between ECG LVH and CAD was found. These results are comparable with the data from the Second National Health and Nutrition Examination Survey (NHANES II) that suggesting that the presence of ECG LVH is a strong predictor of future cardiovascular death.[5] Duration of hypertension with the poor control and lack of compliance with medication is directly related to severity of CAD as in other studies.

In conclusion, the main cause of chest pain in hypertensive patients was found to be CAD (73.3%). Aging, BMI, duration, and magnitude of hypertension had strong and frequent association with CAD. LAD was the most evident, followed by RCA then the CX, the LM was the least. A further observation was that ECG LVH is strongly associated with CAD more than echocardiographic LVH.

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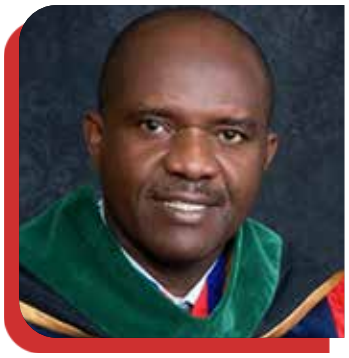
AFRICAN VOICES

Health workers from across Africa trained and mentored in ISH initiative



94 health workers from across Africa have received training and mentorship as part of a new ISH initiative aimed at improving hypertension care across the continent.

The African School of Hypertension for Non-Physician Health Workers was set up by the ISH Africa Regional Advisory Group (RAG) and was first delivered between August and December 2022. It offers training on diagnosing and managing hypertension, and on referring patients to specialist physicians when needed.

The aim of the course was to enable non-physician workers including nurses, pharmacists and community health workers to carry out some of the roles that traditionally only physicians have done. To be eligible for the course, students had to be working in a non-physician healthcare role and be employed in a registered health facility. The first students, coming from Nigeria, Kenya, Gambia, Cameron, Malawi, Sudan, Tanzania and Ghana, have just received course completion certificates from the ISH.

The course is divided into two phases: two months of online lectures taking place every Saturday, followed by a two-month period of mentorship with experienced physicians. Lectures are pre-recorded and uploaded onto the OMRON Academy (an e-learning program for healthcare professionals developed by OMRON in collaboration with leading medical societies, including the ISH), with course faculty members available during lectures to answer questions live. Faculty members were drawn from the RAG membership and other ISH members in Africa.

Africa RAG Chair Professor Augustine Odili, said: "There is a high prevalence of hypertension in Africa and historically only physicians have treated hypertension. But this is not sustainable and there is a need for other healthcare professionals to deliver care. 'Task sharing' with non-physician health workers already happens in other areas of healthcare in Africa, such as malaria, HIV and obstetrics care, and this is what we want to encourage in hypertension too. This is a key reason we set up the school."

Dr Adeyeye Akintunde, Course Director and ISH Fellow, said: "We had really strong engagement and attendance from students at all sessions, and students benefitted from the chance to speak live with course faculty at the same time as watching the online lectures. We are providing ongoing mentorship to students, and we have also developed an online app enabling students to stay in touch with lecturers and other course attendees."

Dr Godsent Isiguzo, Deputy Course Director and ISH Fellow, said: "There has been extremely positive feedback from course attendees. We will now be conducting in-depth feedback with attendees and we will take on board this feedback for future course sessions."

President of the ISH, Professor Bryan Williams, said: "It is very gratifying to see the success of this course and the impact it will have both in terms of workforce development and patient care. Africa is a focus for the ISH, and we want

to do everything possible to support educational and other initiatives made by ISH members and experts in Africa to improve hypertension care in the region."

The Africa ISH RAG will run the course again as there is high demand for future places.

Prof Odili said: "We hope to see this course grow and grow – to help develop our healthcare workforce and to improve care for patients with hypertension across our region."

Find out more about the ISH Regional Advisory Groups.

COURSE ORGANISERS AND RAG MEMBERS

Faculty Members and Mentors

OMRON ACADEMY

Names	Country	Status
Prof. Hind Beheiry	Sudan	Faculty Member/Mentor
Prof. Albertino Damasceno	Mozambique	Faculty Member
Dr. Reuben Mutagaywa	Tanzania	Faculty Member/Mentor
Dr. Lucie Mbulaje	Malawi	Faculty Member/Mentor
Dr. Ayodipupo Oguntade	Nigeria	Faculty Member
Dr. Abiodun Moshood Adeoye	Nigeria	Faculty Member
Prof. Basden Onwubere	Nigeria	Faculty Member
Dr. Akintunde Abiodun Adeseye	Nigeria	Faculty Member/Course Director
Prof. Anastase Dzudie	Cameroon	Faculty Member/Mentor
Dr. Godsent Isiguzo	Nigeria	Faculty Member/Mentor
Prof. Augustine Odili	Nigeria	Faculty Member
Dr. Lamin	Gambia	Mentor
Dr. Alfred Dokku	Ghana	Mentor
Dr. Florence Akumiah	Ghana	Mentor
Dr. Louis Avorkliya	Ghana	Mentor
Prof. Elijah Ogola	Kenya	Mentor
Dr. Akinyemi Aje	Nigeria	Mentor
Dr. Ayoola Yakeen	Nigeria	Mentor
Dr. Adejumo Oluseyi	Nigeria	Mentor
Dr. Manven	Nigeria	Mentor
Dr. Sebastian Marwa	Tanzania	Mentor
Dr. Exon	Tanzania	Mentor

Course administration

Uzochukwu Maureen Amaechi
Joseph Chinonso Okereke
Ifeanyi Emmanuel Nwude

COMMITTEE REPORTS

Uniting and supporting New Investigators

DEAN PICONE

Chair of the ISH New Investigator Committee (Australia), outlines committee activity and priorities for 2023 and 2024

On behalf of the New Investigator Committee, I would first like to acknowledge the fantastic work of the immediate past Chair, A/Prof. Brandi Wynne, and past members, Dr. Manja Zec, Dr. Mariane Bertagnolli, Dr. Nicolas Renna and Dr. Lyudmila Korostovsteva. The past committee brought New Investigators together through incredibly challenging years with the ISH Live events, continued to promote outstanding early career scientists through the New Investigator Spotlight and Our Fellows Work.

A personal highlight from my time on the previous committee was the Reconnecting New Investigators symposium, held at ISH 2022 in Kyoto. The symposium had a strong focus on networking after several years of communication through our screens. We also had the privilege of learning about the publication process from esteemed senior investigators A/Prof. Dylan Burger, Prof. Rhian Touyz and Prof. Alta Schutte. The committee received fantastic feedback about the symposium and it was wonderful to see friends made at this event spending time together for the duration of the conference.

Top row from left to right: Dean Picone (Australia), Mega Febrianora (Indonesia), Chloé Landry (Canada)
Bottom row from left to right: Neusa Jessen (Mozambique), Charlotte Mills (UK), Rikeish Muralitharan (Australia)

The current New Investigator Committee met for the first time in early April. Our committee is comprised of ISH members from different global regions, and varied career stages. Our mission is to promote the interests of new investigators in hypertension research globally by inclusive collaboration, promotion and networking.

A priority for the committee will be to deliver a series of inclusive activities and events at the ISH 2024 meeting in Cartagena. Our aim is to unite New Investigators to form new friendships and collaborations that last well beyond the life of the meeting. Be sure to keep an eye out in the coming months for more information!

The committee will continue to promote outstanding New Investigators through the Spotlight initiative. We aim to grow the initiative so that New Investigators featured in the Spotlight have an opportunity for wider promotion of their work through the Hypertension News and online capacity building events. Previous Spotlights can be viewed on the ISH website, including winners of our Reconnecting New Investigators awards, Dr George Siopis, Dr. Dhashani Sivaratnam and Dr. Zach Blaikie. If their research sparks interest for you, contact details for these investigators are contained within the Spotlight article.

Other initiatives of the committee will include forming connections with new investigator networks from hypertension, cardiovascular and non-communicable disease organisations and scientific activities.

I feel honoured, and a great responsibility, to lead the New Investigator Committee to deliver our mission. Our committee will be highly collaborative and inclusive, and in that spirit, we welcome suggestions and feedback on our activities. Please do not hesitate to get in touch with us via **nic@ish-world.com**

Dean Picone - nic@ish-world.com

COMMITTEE REPORTS

Promoting women in hypertension research: science, communication and capacity building

NIAMH CHAPMAN

Chair of the ISH Women in Hypertension Research Committee (Australia), writes about plans for the committee over the next two years.

Women in Hypertension Research

The Women in Hypertension Research Committee (WiHRC) has the mission to encourage, support and inspire women in hypertension research. As Deputy Chair of the WiHRC, I had the fortune of learning from the leadership of Professor Muscha Steckelings where the WiHRC launched a dedicated network, delivered talks in hypertension sessions at international meetings, completed a scientific review and provided several valuable career development sessions.

These achievements are the result of a collective effort from previous committee members and the generous leadership of Muscha. It has been a joy to be part of such a productive and enthusiastic committee and my hope is to sustain the momentum of the committee. For my term as Chair, the WiHRC will focus on three core activities of science, communication and capacity building.

Scientific activities to support a women-focused research agenda to address knowledge gaps in hypertension

On behalf of the WiHRC, Dr Lizzy Brewster recently led a comprehensive review of hypertension in women, highlighting knowledge gaps in the field, and the lack of consideration of female-specific risk factors for hypertension in clinical guidelines. This review summarises known differences in hypertension, draws attention to the important link between reproductive health and cardiovascular health for clinical history taking and highlights knowledge gaps to improve our understanding of hypertension among women. This work demonstrates a need for a women-focused research agenda for hypertension, which will be a major focus on the committee for the next two years led by Dr Lizzy Brewster as the Science Working Group Lead.

From left to right: Ulrike Steckelings (Denmark/Germany), Lizzy Brewster (Netherlands-Suriname), Hind Beheiry (Sudan).

Top row from left to right: Yan Li (China), Joanne O'Donnell (Australia), Mansi Patil (India)
Bottom row from left to right: Ching Siew Mooi (Malaysia), Buna Bhandari (Nepal), Pensee Wu (UK)

Communications to increase the visibility of women in hypertension research

Through the launch of the Women in Hypertension Research (WiHR) Network we have reached more than 135 ISH members to encourage, support and inspire women in hypertension research. A specific component of this is celebrating women's success through the 'Spotlights' and providing detailed insight into the barriers women overcome to pursue research careers as shown in the 'Lived Experience' articles. Recent spotlight features on new committee members and previous Lived Experience articles from Anna Shalimova (Ukraine), Amela Jusic (Bosnia and Herzegovina), Lucia Davie Mbulaje (Malawi) and Hind Beheiry (Sudan) can be found on the WiHR webpage.

The WiHRC will continue to celebrate the achievements of women in hypertension research across all ISH communications platforms. The communications working group of the WiHRC will be led by Dr Mansi Patil, who made a substantial contribution to committee communications for the last two years.

Capacity building to support women to progress in research

The previous committee delivered well attended career development sessions both virtually and in-person at the ISH Kyoto meeting. These sessions and the networking afterwards highlighted the demand for practical advice to support career progression. The WiHRC hopes to offer a career development session in Cartagena, Colombia 2024. In addition, we hope to offer virtual sessions outside of ISH meetings. Dr Ching Siew-Mooi is leading the capacity building working group to develop these activities, which we look forward to sharing with you in the future.

Please email **wihrc@ish-world.com** if you are interested in joining the WiHR Network or would like to find out more about our activities.

Niamh Chapman - wihrc@ish-world.com

ISH COUNCIL MEMBERS & Co-opted Council Attendees

Bryan Williams (UK)
ISH President

Hiroshi Itoh (Japan)
ISH Vice President

George Stergiou (Greece)
ISH Secretary

Fadi Charchar (Australia)
ISH Treasurer

Nadia Khan (Canada)
ISH Officer-at-Large

Maciej Tomaszewski (UK)
ISH Immediate Past President

Claudio Borghi
(Italy)

Dylan Burger
(Canada)

Rafael Castillo
(Philippines)

Myeong-Chan Cho
(South Korea)

Tazeen Jafar
(Singapore)

Kazuomi Kario
(Japan)

Dorairaj Prabhakaran
(India)

Cesar Romero
(USA)

Ulrike (Muscha) Steckelings
(Denmark/Germany)

Augustine Odlili
(Co-opted Council Attendee, Nigeria)

ISH CORPORATE MEMBERS

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