HYPERTENSION NEWS

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Lifestyle changes and hypertension

ISH position paper sets out new evidence

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INTRODUCTION FROM THE PRESIDENT

Hypertension takes centre stage at the United Nations

BRYAN WILLIAMS

President, International Society of Hypertension

This issue of Hypertension News is packed with new information and reports which illustrates how vibrant the field of hypertension research is. As I write, at the United Nations in New York, Dr Tedros Adhanom Ghebreyesus, WHO Director-General, Michael Bloomberg the WHO Global Ambassador for Noncommunicable Diseases, and Tom Frieden, President and CEO of Resolve to Save Lives, were heading up the launch of its first-ever report on the devastating global impact of high blood pressure, along with recommendations on the ways to tackle the under-detection, treatment and control of hypertension across the world. The full WHO announcement can be accessed on their website.

The report contains many facts which are familiar to readers of Hypertension News. Nevertheless, reading them again doesn't make them any less palatable. The report estimates that 1 in 3 adults now have hypertension across the world and makes the notable claim that 4 out of every 5 people with hypertension are not adequately detected and/or treated, and that if countries across the world could scale up coverage and improve care, then 76 million deaths could be averted between 2023 and 2050. I suspect this is an underestimate. The ISH has been engaged with our many other partners in the generation of this report, fully endorse it and congratulate the WHO and many colleagues who contributed to it.

This announcement at the United Nations comes on the heels of recently released guidelines from the European Society of Hypertension on the management of hypertension, first presented at the ESH Congress in Milan in June. The coincidence of these two events begs the inevitable question as to whether these new guidelines will change the lamentable global detection, treatment and control of high blood pressure. I suspect they will not. This is not a criticism of the guideline – far from it. The ISH endorsed the guideline and members, including myself, contributed to it. It is merely an observation that we have had many iterations of guidelines and whilst they do provide an important reference source and distillation of new data, they do not drive implementation of care for patients. In fact, I doubt the vast majority of patients are even aware of the recommendations of how their hypertension should be treated according to best practice today.

We need simplicity and better communication and empowerment of patients if the silent killer is to be stopped in its tracks. The HEARTS programme from the WHO , with its pragmatism and simplicity, is a step in the right direction. But we need to do more and with this in mind, the ISH is pioneering a new approach in developing a new kind of guideline, that will use a consensus of existing treatment recommendations and involve patients to understand how we can better inform and empower patients about how their blood pressure should be measured, how they should be treated, what lifestyle interventions are helpful, what drugs they should be receiving, what tests should be performed and what good control of blood pressure looks like. Patients can then calibrate whether they are receiving optimal care, and if they are not receiving optimal care, they can start to ask why not? Empowering patients also disempowers policy makers to resist change and to make the kind of improvement needed to change the current situation in which so many people are denied treatment or receive poor treatment.

Empowering patients is also a theme in the recently released ISH position statement on lifestyle measures that can help prevent hypertension and improve the control of blood pressure in those who are treated. This was endorsed by the World Hypertension League and the European Society of Hypertension and was recently published in the Journal of Hypertension. This publication received huge media attention across the world including a dedicated slot on the BBC world service. This is discussed in this issue of Hypertension News.

The interest this publication has generated also tells us that patients and the public are very interested in learning more about blood pressure and effective means to improve their health. We need to capitalise on that and the opportunities social media provide, if we are to make a real difference. Guidelines alone will not achieve that and neither will the current models of care. We have to embrace what technology and the digital age are bringing to simplify the approach to chronic disease management and alas, much of this won't need a doctor centric approach. This won't be palatable for all, but it is the only way to deliver effective care to many millions of people.

Bryan Williams - president@ish-world.com

This is clearly a topic for our age in many areas of medicine which are going to change in the face of emerging technologies and AI. We need to embrace this change and there will be a strong focus on new systems and models of care for hypertension in the upcoming ISH congress in Cartagena.

Speaking of Cartagena, a small group of ISH officers have recently completed our first site visit to Cartagena in Colombia which is where we will host our next ISH congress in September 2024 (see images below). Let me tell you, the location is wonderful, enchanting, vibrant and exciting, as well as a wonderful cultural venue, and along with our colleagues in Colombia and Latin America, we are putting together a very exciting programme. If you have never been to that part of the world, this is your chance. This will be a congress and a venue that will be a unique experience and opportunity for many and we hope to see you all in Cartagena next summer. With this in mind, it is timely that we have a series of stimulating and informative articles from Latin America in this issue of Hypertension News, amongst many other outstanding contributions.

Enjoy!

FROM THE SECRETARY

Our progress in the term 2022-2024

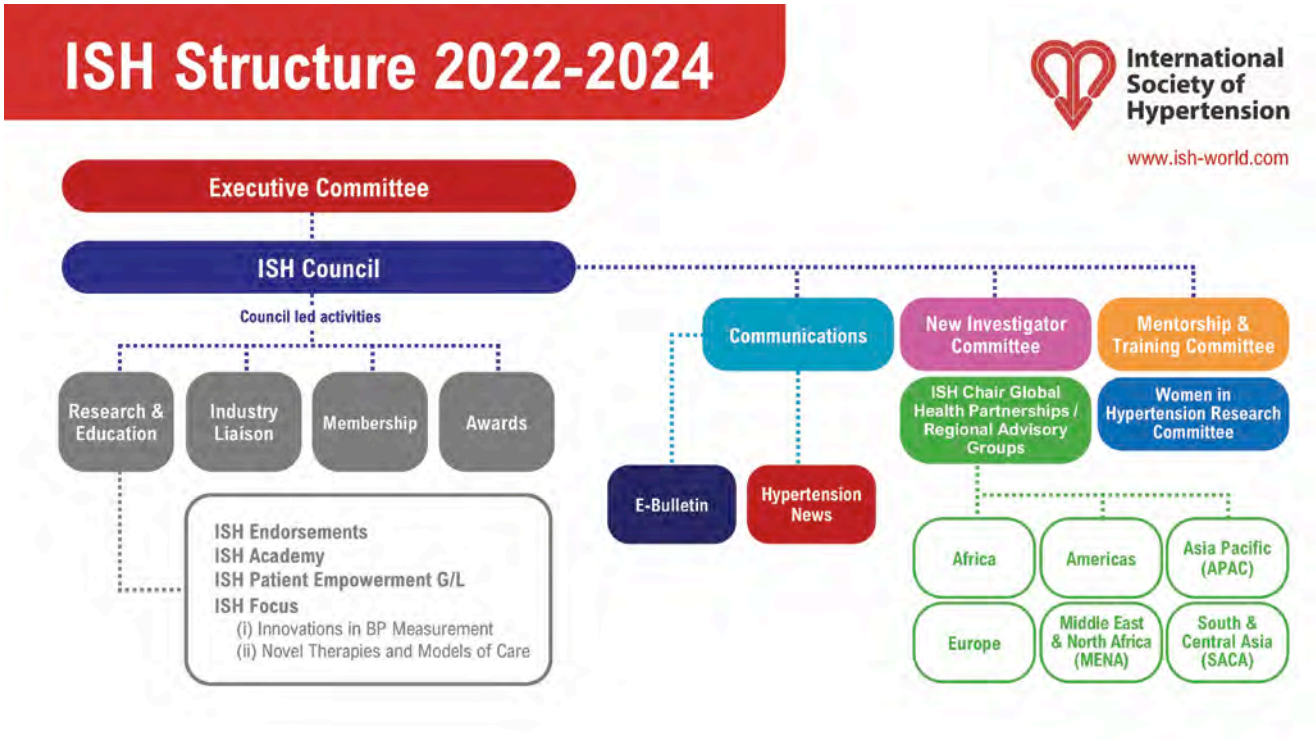
GEORGE STERGIOU

Secretary, International Society of Hypertension

It is almost one year since the current ISH council started its two-year term with Bryan Williams as president. The first meeting of the council took place in October 2022 in the wonderful city of Kyoto, Japan on the last day of the 2022 ISH meeting. It was a great time for a new team to take over, after a memorable meeting, thanks to immense efforts by Hiroshi Itoh and his local organizing team. The "Wisdom for Conquering Hypertension", introducing three essential elements for controlling hypertension - "food, move, and AI" - was the take home message from this meeting. October 2022 is also memorable as the time when COVID-19 was eventually defeated, with visa restrictions for visiting Japan lifted just as we arrived in Kyoto for the ISH meeting.

During the 2020-2022 term, the ISH council with president Maciej Tomaszewski and secretary Bryan Williams put considerable energy and time into tidying up important structural and functional issues within the ISH. These tasks were not too visible, pleasant, or rewarding, but were vital for the smooth and secure operation of the ISH. As Bryan played an important role in these tasks, he was more than ready to take over as the new ISH president, and in the first meeting of the new council in Kyoto he presented his vision and plan for his 2022-2024 presidency.

We are now halfway through the 2022-2024 term, and all the organizational changes and new initiatives and projects as envisioned by Bryan have been established, which leaves us one more year for execution. Here I present our progress with the outstanding ISH activities and what you should expect to see happening within the ISH until the end of this term.



Executive Committee: Council Members

Bryan Williams
President / UK

Hiroshi Itoh
Vice President / Japan

George Stergiou
Secretary / Greece

Fadi Charchar
Treasurer / Australia

Nadia Khan
Officer-at-Large / Canada

Maciej Tomaszewski
Past President / UK

Council Members: Co-opted Council Attendees

Claudio Borghi
Italy

Myeong-Chan Cho
South Korea

Tazeen Jafar
Chair ISH-Global Health Partnerships / Singapore

Kazuomi Kario
Japan

Prabhakaran Dorairaj
India

Cesar Romero
USA

Ulrike (Muscha) Steckelings
Denmark/Germany

Augustine Odlili
Co-opted Council Attendee / Nigeria

ISH New Investigator Committee (NIC)

The ISH NIC chaired by Dean Picone is currently working hard on a number of collaborative activities with the ISH Mentorship and Training committee (MTC) and the ISH Women in Hypertension Research Committee (WiHRC). Details of their plans will be announced later in the year. They are also planning broader outreach activities and reviewing awards offered by the committee. Their New Investigator Spotlight continues to be published monthly. This is a great opportunity for new investigators to gain exposure to the international hypertension community! They are always on the lookout for new candidates – check the nomination criteria here.

ISH Women in Hypertension Research Committee (WiHRC)

This Committee chaired by Niamh Chapman works hard to promote the research of women in hypertension through spotlight features in ISH communications, and social media posts. Recently, they set up a science working group, which aims to improve the management of hypertension among women by actively identifying knowledge gaps and advocating for women-specific hypertension research. They will also promote the implementation of existing knowledge into clinical guidelines. Members of the ISH WiHRC recently published a comprehensive review highlighting knowledge gaps in the field of hypertension in women (Chapman N, et al. Hypertension. 2023 June; 80:1140-1149). They are currently working on an ISH position paper to present key research questions on hypertension in women, which is co-led by Niamh Chapman, Lizzy Brewster, and Muscha Steckelings.

Mentorship and Training Committee (MTC)

The ISH MTC chaired by Augusto Montezano supports young investigators in developing their professional careers and helps new leaders in the field of hypertension to emerge. In the last year the MTC has wrapped up a successful season of podcasts, where many researchers representing all corners of the globe were interviewed. The MTC is now preparing a new season of podcasts where, in addition to the classic mentorship interviews, hot topics related to career development will be discussed. To increase its outreach, the MTC is currently developing a series of workshops/webinars and social media activities to be launched soon.

ISH Capacity Building Network (CBN)

The ISH New Investigator Committee (NIC), ISH Mentorship and Training Committee (MTC), and ISH Women in Hypertension Research Committee (WiHRC) are working together on a new Capacity Building Network (CBN). The purpose is to create an inclusive and supportive environment for society members, and thereby offer career development and networking opportunities for early-career researchers and those from under-represented backgrounds.

The CBN will be co-led by the NIC, MTC and WiHRC Chairs with oversight from a Steering Group including an ISH Council member and RAG representatives. They will collaborate on networking events, careers development sessions, spotlight interview features, and more, and will meet twice per year to inform CBN strategy and formally endorse activities. We will be sharing more information about the Network soon.

ISH Communications Committee (Comms)

ISH Communications Committee chaired by Anastasia Mihailidou organised two video interviews following the launch of the latest ESH guidelines in June. These interviews with ISH and ESH officers explored the development and impact of the ESH guidelines - including the ISH 2020 global guidelines. The Committee has also developed infographics with essential information for patients with hypertension. Currently they are working on improving the organisation of our website and on supporting the 2024 ISH conference.

ISH Membership Committee

The ISH Membership Committee chaired by Debora Simoes de Almeida Colombari is very active behind the scenes, as it continues to review and approve applications for membership. Recently, a big focus of the committee has been on reviewing the membership structure for the ISH aiming at having a simpler scheme for our membership categories. They are also considering new benefits for our members, and some joint initiatives with other Committees which will help the ISH to further engage existing members of the Society, as well as to have more people interested in hypertension and related cardiometabolic research and treatment to become members of the ISH.

ISH Regional Advisory Groups (RAGs)

To serve efficiently its global mission, the ISH has six RAGs to connect with major regions of the world aiming at developing tailored initiatives according to each area's needs. For the 2022-2024 term, chairs of the ISH RAGs are Augustine Odili (Africa), Cesar Romero (Americas), Wook Bum Pyun (Asia Pacific), Claudio Borghi (Europe), Jafar Alsaid (Middle East and North Africa), Prabhakaran Dorairaj, (South and Central Asia). In the last year we had several new educational activities and publications from our RAGs. Tazeen Jafar is currently coordinating all the ISH RAGs to best engage them in their ISH activities and plans. Tazeen is currently chairing the ISH Global Health Partnerships and writes about her role in this issue of ISH Hypertension News.

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

Prabhakaran Dorairaj
India

ISH projects in development

As announced last year by the ISH president during our first council meeting in Kyoto, we have initiated the development of the following new ISH projects: ISH Academy, ISH Empower, and ISH Focus.

ISH Academy

Erika Jones is leading this major ISH project which aims at developing a high-quality professional educational platform for hypertension and related cardiovascular disease for clinicians and scientists. We are developing an online educational modular course that will be freely available to Society members and tailored to specific audiences. The initial basic course material is being developed. Material will be ISH accredited and formatted and a certificate of achievement will be awarded. Speakers and presenters will represent ISH global and gender diversity.

ISH Empower

This project led by Bryan Williams aims at developing guidelines for patients with hypertension. The development of hypertension guidelines for doctors has now reached a point of overflow, and what is needed is their implementation at patient level. This ambitious development program is in the design phase and will require considerable resources and time. It will certainly help researchers, clinicians, and patients, as well as the ISH in accomplishing its primary mission.

ISH Focus

Kazuomi Kario is leading the first ISH Focus group on blood pressure measurement, which aims at bringing together expertise on emerging areas in science and technology in this area. The project is starting with the development of a review and statement on the current status with blood pressure measuring methods and devices, and the potential of novel technologies under development, including cuffless blood pressure measuring devices and AI applications.

Next ISH meeting preparation: Cartagena 19-22 September 2024

As you know, our next meeting will take place in Cartagena, Colombia, from 19-22 September 2024. Cartagena has a beautiful walled old town by the sea, founded in the 16th century. Although we have shown you some wonderful photos of the city, these photos say too liitle about what the ISH meeting in Cartagena will be like. I visited Cartagena with Bryan Williams and Fadi Charchar in the last weekend (15-16 September) and we now know.

Cartagena is amazing! The old city is full of well restored colorful colonial buildings, its people are smiling and ready to dance, the food is delicious, and the atmoshere is lively and joyful. It is a very popular travel distination and safe for tourists. The conference venue is located in the historic center of the city on the seafront.

We couldn't have a more efficient local organising scientific committee! Dagnovar Aristizabal-Ocampo is the heart of the meeting. Together with Patricio López-Jaramillo and Cesar Romero, they are our guarantee for a great ISH meeting in every aspect! Dagnovar deals meticulously with all the organisational details for a successful meeting and we are working together to develop a rich scientific program for clinicians and basic scientists. We already have a long list of very attractive proposals from our ISH Committees and from our members and friends. Latin America has a super-active community in hypertension which is expected to contribute hugely to the success of the meeting.

Without question, the 2024 ISH meeting in Cartagena will be exceptional, and different from any other you have attended! This is your chance for an extraordinary experience combined with great science!

As you can see, in the 2022-2024 ISH term we are fortunate to have dynamic leadership and an enthusiastic and efficient team of officers from around the world. We are committed to execute our current ISH development plan, aiming at increasing the global impact of our society. If you are an ISH member and you are interested in getting involved in any of our committees, regional advisory groups, or projects, I encourage you to contact the relevant Chair or Lead.

Dagnovar Aristizabal-Ocampo
Executive President
ISH 2024 Congress

Patricio López-Jaramillo
Honorary President
ISH 2024 Congress

Cesar Romero
Chair of Americas ISH
Regional Advisory Group

PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

The ISH lifestyle rules for healthy blood pressure – news on the latest ISH position paper

PRISCILLA PRESTES AND FADI CHARCHAR

Health Innovation and Transformation Centre, Federation University Australia

In the latest Position Paper to be published by the International Society of Hypertension (ISH), the society has focussed its attention on the huge importance of lifestyle to blood pressure control. Changes in lifestyle measures such as diet and exercise are the most important choice individuals can make regarding their health. Although simple and effective, lifestyle can be hard to decipher and to adhere to. This is further complicated by the fact 'not one-size-fits-all' due to our genes and where we live.

The ISH selected a group of experts from 18 countries, to tackle the topic. These experts had a broad range of expertise including in important emerging areas such as precision medicine, behavioural modification, microbiome and digital health. The experts worked together on published evidence to deliver a set of contemporary and easy to implement lifestyle management recommendations for hypertension.

The recommendations are a comprehensive guide for both patients with hypertension and those at risk of developing the condition. In writing it the authors tried to offer international perspectives on each of the sections. Furthermore, following each set of recommendations there is a unique section on how these can be implemented.

So what do the experts say?

The diagram below summarises the recommendations presented in the paper. These include the usual suspects, such as weight management, increased levels of exercise, eating a balanced diet low in sodium, in addition to smoking and alcohol cessation. The authors also delve a bit deeper with each recommendation and include examples to reach the ideal consumption of potassium and fibre, and types, intensity and duration of exercise.

So what is new in these recommendations?

1) Holistic approach - We suggest a holistic approach for the effective management of blood pressure. In addition to diet and exercise clinicians/individuals should consider limiting stress and pollution exposure and improving sleep quality. We offer some suggestions on how these could be implemented. We also recommend careful use of non-prescription medication and nutritional supplements.
2) Digital technologies – We recommend the potential of using digital aids to monitor, track and increase exercise, calculate meal composition, help mindfulness and improve overall habits.
3) We include a discussion on the quality of food and how to improve our microbiome. We discuss the fact that the quality of food should be considered and the replacement of whole foods over processed food.
4) We talk about popular new methods of weight loss such as fasting and their benefits.
5) For most sections we include ways to change behaviour and how to encourage this change from an early age and the importance of patient centred and collaborative care.

6) We also include sections on international perspectives and how public and health regulators have an important role to play in prevention of blood pressure.

We also discuss genomics and the advent of individualized recommendation in lifestyle change. The article, commissioned by ISH is endorsed by the World Hypertension League (WHL) and European Society of Hypertension (ESH). This was further reviewed by 8 international leaders in hypertension.

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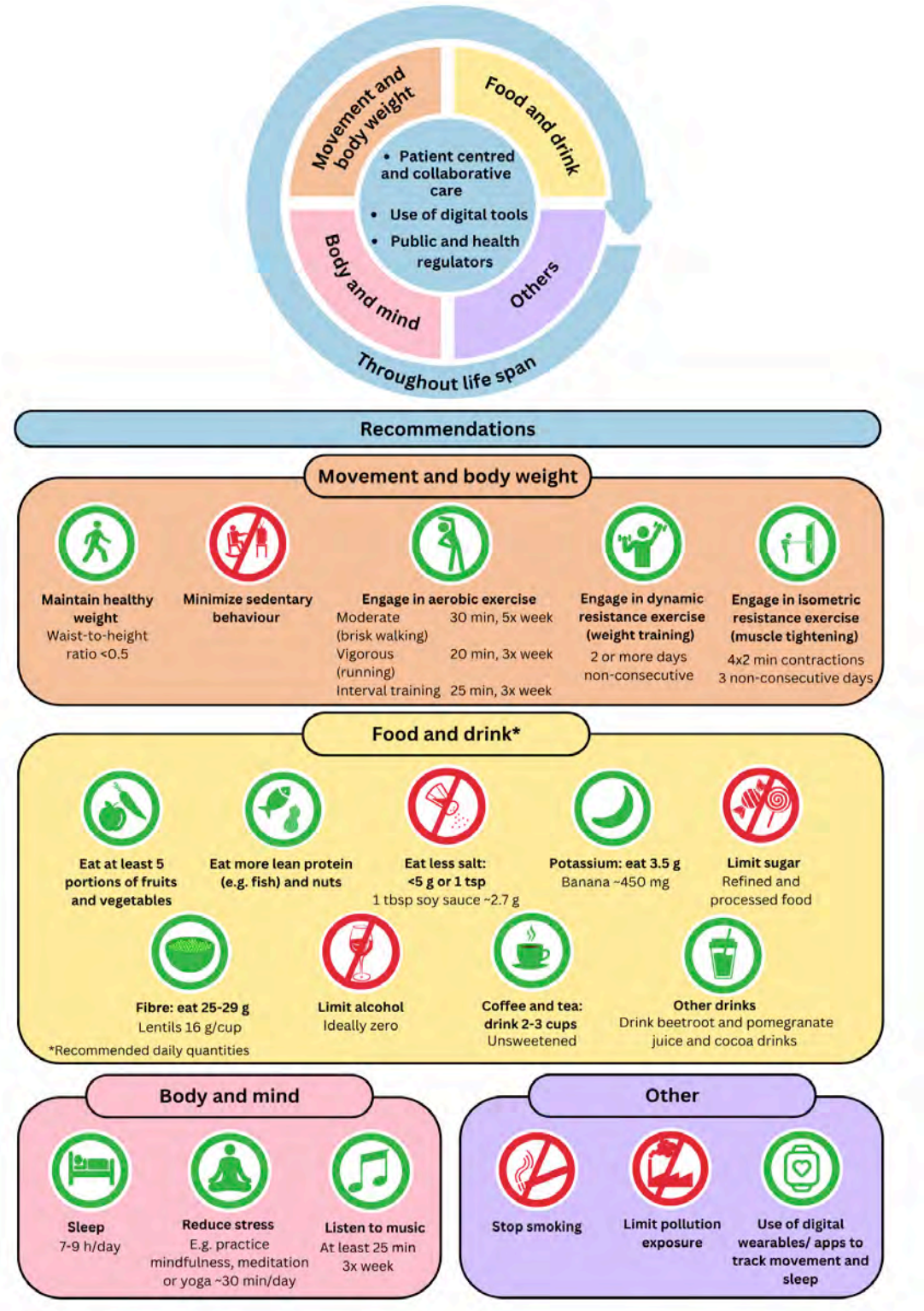

PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

Ambulatory blood pressure is better associated with the risk of all-cause and cardiovascular mortality than clinic blood pressure

ALEJANDRO DE LA SIERRA,* NATALIE STAPLIN AND LUIS M. RUILOPE

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High blood pressure is recognized as the most important risk factor for premature death and disability. The relationship has been ascertained mostly based on blood pressure (BP) values obtained in the clinic. However, several aspects of clinic BP measurement, such as a lack of standardization in daily practice, the fact that it represents only a very short time frame, and the well known "white coat" phenomenon, are all claimed as responsible for an imperfect relationship between clinic BP and prognosis.

Ambulatory blood pressure monitoring (ABPM) is currently recommended in most hypertension guidelines. Obtained BP estimates reflect repeated measurements during an extended period of time (24 hours), which includes daily activities of an individual, including the most important sources of variability (activity-sleep). Previous epidemiological data from population-based studies, relatively small clinical studies and pooled analysis of the previous smaller studies indicate that ABPM-based BP estimates are more strongly associated with cardiovascular morbidity and mortality than clinic or office BP. However, some uncertainty exists regarding which estimate, i.e., 24-hour, daytime or nighttime BP, is better associated with cardiovascular prognosis. In addition, the relationship between new BP phenotypes, especially white-coat and masked hypertension and prognosis is not well established.

Mortality associations from the Spanish ABPM Registry have been recently published in the Lancet[1]. The Spanish ABPM Registry was developed two decades ago to promote a widespread use of ABPM among Spanish physicians and nurses attending patients with hypertension[2]. More than 200 primary care centers were involved in this project. They were instructed in the use of an ABPM monitor and the data obtained from the monitors was automatically uploaded to a central server, along with basic demographics and clinical information, which included a standardized clinic BP value obtained through the mean of two consecutive measurements. The system created an immediate report of the results of the ABPM procedure, which was transmitted to the health care provider.

From March 1, 2004 to December 31, 2014, 59124 patients (47% women, mean age 59 years) were selected from the Spanish ABPM database. The selection was based on the following criteria: an ABPM record of enough quality (more than 70% of valid readings during a 24 hour period and at least 1 valid measurement per hour), complete essential clinical data, including age, sex, concomitant cardiovascular risk factors and diseases, and clinic BP measurement, and linkage to the vital registry of the Spanish National Institute of Statistics (which was used to ascertain vital status and determine the cause of death according to the International Classification of Diseases [ICD-10]).

Associations between systolic BP indices and mortality in all patients were J-shaped, particularly for clinic BP, but log-linear after excluding patients in the fifth with the lowest BP values. In the Cox regression model adjusted for clinical confounders (age, sex, BMI, smoking status, diabetes, dyslipidemia, and previous cardiovascular disease) all systolic BP estimates (clinic, 24-hour, daytime and nighttime) were associated with all-cause and cardiovascular mortality, although the magnitude of the associations was clearly greater for all ABPM measures compared to clinic BP. After adjustment for 24-hour BP, clinic BP was no longer associated with all-cause or cardiovascular mortality, whereas hazard ratios for ABPM estimates were essentially unmodified after adjustment for clinic BP. Simultaneous adjustment for daytime and nighttime BP revealed that nighttime BP, but not daytime BP maintained the association with all-cause or cardiovascular mortality. Compared to clinic systolic BP, 24-hour systolic BP was almost five times more informative about the risk of death, and nighttime systolic BP six times more informative.

With respect to diastolic BP, most of the relationships with mortality were U-shaped, with a higher risk of all-cause death in patients in the lowest fifth of BP, most notably for clinic diastolic BP. The exception was nighttime diastolic BP, where those in the highest fifth had 27% higher risk of mortality in comparison with the lowest fifth.

The study also assessed the risk of mortality in the BP phenotypes obtained combining normal or abnormal values of both clinic and 24 hour BP. In comparison to those patients with BP in the normal range (normal both office and 24 hour BP) those with masked hypertension (normal clinic but elevated 24 hour BP) or sustained hypertension (elevated clinic and 24-hour BP) had a higher risk of all-cause and cardiovascular mortality, which was similar in both groups (24% higher risk in both groups for all-cause mortality, and 37% and 38%, respectively for masked and sustained hypertension in relation to cardiovascular death). Interestingly, white coat hypertension (elevated clinic, but normal 24-hour BP) was not associated with a higher risk of death. In the confounder-adjusted model, patients with white-coat hypertension appeared to have a lower risk of death (10% and 11% lower for all-cause and cardiovascular death respectively). However, after excluding about 2000 patients from the BP in the normal range category who had a clinic diastolic BP < 70 mmHg (possibly reflecting more advanced pre-existing cardiovascular disease), white coat hypertension was not either protective or harmful for all-cause or cardiovascular death. In this latter analysis, the risk of death associated with both masked and sustained hypertension relative to patients with BP in the normal range was even more highly elevated.

These results emphasize the importance of ABPM in the risk assessment of patients with hypertension. They come from the largest cohort of patients studied to date, and it represents a European population of patients attending primary care centers and managed according to the usual clinical practice. The use of ABPM measurements to guide treatment in patients with hypertension with respect to prevention of cardiovascular outcomes has not been examined in randomized clinical trials, and it is unlikely that such a trial would occur. However, the information provided by ABPM in terms of risk assessment cannot be neglected and such information could help in guiding clinical and therapeutical decisions of patients with hypertension.

The mortality data of this large population from the Spanish ABPM Registry also allows for evaluation of other aspects of ABPM, which can be of interest in their relation to prognosis, in addition to the magnitude of BP elevation. The issues of short-term BP variability, including the circadian variability, as well as the particular BP behaviour in specific subgroups of patients, such as resistant hypertension, diabetics, or patients with previous cardiovascular disease, not included in the Lancet publication, are going to be evaluated in the near future.

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PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

Inflammatory mechanisms of hypertension – perspective for novel biomarkers and therapeutic targets

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The role of inflammation and immune activation is well-established in diseases like coronary artery disease and heart failure, but its significance in hypertension has only recently been emphasized. While we understand inflammation's impact on hypertensive cardiac, vascular, and renal damage, the immune mechanisms behind the origins of hypertension are less defined. Unravelling these mechanisms is crucial for developing new therapeutic strategies targeting inflammation in CVD. This is important as, despite earlier advancements in hypertension treatment, in recent years, there has been minimal progress in creating completely new classes of treatment. Moreover, our focus has been on targeting blood pressure instead of tackling the underlying pathophysiology.

Immune mechanisms of hypertension

Historically, the immune system's role in hypertension has been underexplored, but revelations over the last fifteen years have spotlighted the connection.[1-3] Earlier research already in the '60s and '70s hinted at this association, but it was only with the utilization of recombinase-activating gene knockout mice in 2007 that the immune system's causal role was concretely demonstrated in hypertension.[1,4] Since then, this relationship has been underscored by hundreds of studies showing the involvement of a broad range of immune cells, such as T cells, monocytes, macrophages, dendritic cells, B cells, and NK cells, in the initiation and progression of high blood pressure.[2, 5] These cells show features of activation in experimental hypertension, and mice lacking any of these immune cells exhibit altered hypertensive responses to various stimuli, including salt, angiotensin II.[5,6] Such a range of cells involved is not surprising, considering that immune cells act in concert to modulate inflammation and immune defence. The origins of immune activation in hypertension are still under broad debate. Factors like oxidative stress-derived neoantigens, NLRP3/inflammasome, and even dietary salt are known contributors to immune activation in hypertension and can be modulated by intrinsic T cell mechanisms including microRNAs.[6] Moreover, the immune cell, and especially T cell activation, is modulated by the central nervous system with the prominent role of sympathetic outflow as well as innervation of spleen and bone marrow as key reservoirs of immune cells.[7] Upon activation, immune cells target critical organs - arteries, kidneys, heart, and brain. This is because, in hypertension, these organs express high levels of chemokines, inviting immune cell infiltration.[8] Once there, immune cells can modify key hypertension-related mechanisms, including reducing nitric oxide availability, leading to endothelial dysfunction or modulating sodium transporters in the kidney. In doing so, they not only elevate blood pressure but also induce vascular remodelling, renal and cardiac damage, and even cognitive impairments. Notably, specific cytokines like IL-17, IFN-γ, and TNF-α play crucial roles in this process, while others like IL-10 offer protective effects.[3]

Clinical evidence

Importantly, since the discovery of these mechanisms in various animal models in mouse or spontaneously hypertensive rats, their relevance

to human disease have been questioned. Importantly, clinical observations further validate the inflammatory mechanisms of hypertension.[1,2,9] Conditions with immune-mediated inflammation, such as psoriatic arthritis and periodontitis, have a significantly heightened risk of hypertension. Chronic inflammation serves as a nexus between these conditions. In primary hypertension patients, markers of inflammation, like C-reactive protein and various cytokines, are elevated, correlating with an increased risk of hypertension onset.

Additionally, genetic studies offer valuable insights. Polymorphisms in molecules crucial for T cell activation, like CD247, have been linked to hypertension. While traditional genetic studies provide a limited scope, systems biology methodologies are casting a wider net. For instance, integrative gene network expression data with blood pressure data has spotlighted genes, such as the negative regulator of T cell activation, SH2B3/LNK, as top key drivers of hypertension. This gene is also one of the top GWAS hits for hypertension. Mechanistic work has shown that LNK, along with its associated network, regulates inflammatory responses in hypertension. Differential gene expression analyses in multiple cohorts have emphasized genes associated with cytotoxic T cells and natural killer cells as significant in regulating blood pressure. The kidneys' multi-omic studies in hypertensive patients have identified critical signalling pathways of the innate and adaptive immune responses, including interferon-γ signalling.[10] More importantly, robust Mendelian randomization studies in the ≈750 000 UK-Biobank/International Consortium of Blood Pressure-Genome-Wide Association Studies patients, have indicated strong, potentially causal associations between lymphocytes and increased blood pressure in large human cohorts.[11] Growing genetic data also indicates a potential causal relationship between inflammatory conditions like periodontitis and hypertension.[12]

In recent years, infections, including COVID-19, CMV, malaria, and oral periodontal infections, have been identified as non-traditional risk factors for cardiovascular diseases (CVD). Studies suggest links between, CMV and increased hypertension related to inflammation. Moreover, it is likely that hypertension exacerbating COVID-19 symptoms may also reflect the immunopathogenesis of hypertension. Furthermore, while a recent meta-analysis indicated that HIV-positive individuals generally have a lower risk of hypertension than those without HIV, regional variations exist, possibly due to differences in AIDS progression and antiretroviral therapy usage.

In summary, both clinical, genetic, and multi-omics data stress the intricate interactions between genes tied to inflammation and T cell activation in hypertension's onset and progression.

Biomarker and therapeutic perspective

Our understanding of immune mechanisms in hypertension has grown significantly over the past 15 years, but translating this knowledge to patient benefits requires more work. While some classical immunomodulating therapies may offer some promise, the evidence is not strong.[9] Moreover, the CANTOS trial suggests that a generic 'one-size-fits-all' immunosuppression might not be ideal for treating CVD and also hypertension. Instead, tailored approaches based on specific immunometabolic factors might be more effective. Our analysis of CANTOS cohort indicated that while IL-1β targeting did not affect blood pressure, it conferred protection from clinical events, specifically in hypertensives.[13] The interactions between vascular and immune systems and the brain-immune-vascular axis also offer insights into hypertension's root causes, paving the way for targeted treatments.[14]

Potential treatment strategies include using nanoparticles for localized immunosuppressant delivery and bioelectronic medicine for controlling inflammation. Advancements in these techniques might revolutionize hypertension's immunosuppressive therapies, offering personalized treatments. Non-pharmacological interventions, like treating periodontal inflammation, may offer simple and cost-effective approaches. Intensive therapy for periodontitis may offer additional advantages by targeting inflammation linked to hypertension. In a recent randomized clinical trial, we have demonstrated that intensive periodontal therapy, but not conventional oral hygenization, improves blood pressure control in patients with uncontrolled hypertension.[12] This was accompanied by improvements of vascular function in hypertensive individuals.[12]

Patient stratification using inflammatory biomarkers and molecular imaging techniques

is another priority. Such tools can help classify patients for tailored treatments and offer insights into immune cell activities within blood vessels. Emerging technologies like single-cell and spatial multiomics promise to further elucidate inter-cellular communications, allowing to better link immunity to classical mechanisms of high blood pressure.

It's also vital to focus on the immune response's broader impact, like preventing cardiac, renal damage, or dementia onset in at-risk patients. Targeting inflammation in patients with hypertension will likely decrease complications from hypertension, improving overall patient health, as evidenced by the CANTOS trial. With the advent of treatments like renin inhibitors, it's also key to understand how they impact hypertension's inflammatory aspects.

In sum, addressing hypertension's immune complexities requires pinpointing specific pathways, localized treatments, improved patient stratification, and a holistic view of its effects. Adopting these strategies promises better comprehension and novel, previously unexplored aspects of care for hypertension patients.

Acknowledgments

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PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

Potassium-enriched salt – a plausible option for every patient with hypertension

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Guidelines advise that every patient with a diagnosis of hypertension should reduce their dietary sodium intake. But many don't receive this advice and most continue to eat the same amount of sodium. The reasons for this are not that doctors are slack and patients recalcitrant, but rather that doctors don't want to waste their time giving patients advice that they can't action. The usual behavioural changes recommended to reduce dietary sodium intake are just too hard to achieve - patients can't relearn to cook with less sodium, can't retrain their taste buds to season with less sodium and can't change decades of shopping habits to choose foods from the supermarket shelves with less sodium.

The difficulty of reducing dietary sodium intake has now dramatically reduced. This is because there is clear evidence that a like-for-like switch to potassium-enriched salt can lower blood pressure and reduce the risks of stroke, major cardiovascular events, and premature death. For the first time doctors have a sodium reduction intervention that they can recommend and be confident that patients will be able to implement. While the headline result of the landmark 2021 Salt Substitute and Stroke Study[1] was the protective effect against stroke (**Figure**), the 92% of people still using the salt substitute after 5 years was perhaps the real game changer.

The Salt Substitute and Stroke Study

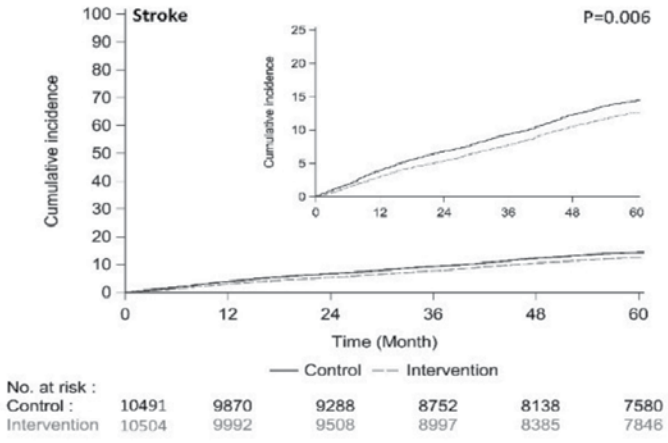
20,995 randomised, 4.7 years mean follow-up.

Random assignment:

- Potassium-enriched salt (75% NaCl and 25% KCl) vs.
- Regular salt (100% NaCl)

Main results:

- 14% reduction in stroke (p=0.006)
- 13% reduction in cardiovascular disease (p<0.001)
- 12% reduction in premature death (p<0.001)
- 92% still using potassium-enriched salt at study end
- No hyperkalemia or other adverse effects
- Use of potassium-enriched salt cost saving



Potassium enriched salt, sometimes also referred to as a 'salt substitute' or 'low sodium salt', is a product that can be used as a direct switch for regular table salt. Regular table salt comprises 100% sodium chloride, but potassium-enriched salt replaces some of the sodium chloride with potassium chloride. The proportion of potassium chloride varies and some salt substitutes also have other components like magnesium sulphate[2]. The potassium-enriched salt used in the Salt Substitute and Stroke Study was a 25% potassium chloride and 75% sodium chloride mix and with this composition most people can't taste a difference, or if they can, it's so minor that they are happy to accept it.[3] High patient acceptability of switching to potassium enriched salt is a consistent feature of the trials done to date.

Potassium-enriched salt works, not just because it reduces sodium intake but also because it increases potassium intake. And in some circumstances the effect of the potassium supplementation is probably as important as the effect of the sodium reduction.[4] Potassium has a demonstrated antihypertensive effect in its own right[5] and most of the world's population don't get near anywhere enough potassium in their diet. It is estimated that during hominid evolution daily consumption of potassium was about 10g per day but average global intake is now less than a third of that.[6]

There has also been concern raised about the potassium in salt substitutes. This is based on the possibility that potassium-enriched salt could cause hyperkalemia in patients with seriously impaired kidney function, or amongst those using medicines that raise blood potassium levels.[7] While harm has never been shown in a trial, most studies have been done in patients under management for hypertension.[8] In this setting advice to use potassium-enriched salt is moderated by a clinician able to advise against use where contra-indicated. Modelling studies suggest low risks and large net benefits from population-wide use of potassium-enriched salt, even in those with chronic kidney disease,[9] but risk mitigation has been objectively demonstrated in the hypertension management setting and this is the obvious place to start.

The magnitude of the benefit achieved from potassium-enriched salt will vary with the amount of dietary salt that can be switched. In turn, this will differ depending on sources of sodium in the diet and with starting dietary sodium and potassium intake levels. Individual effects on blood pressure will be moderate but most people are likely to get some reduction. In the Salt Substitute and Stroke Study the average systolic blood pressure lowering of just 3.3mmHg reduced stroke risk by 14%, major cardiovascular events by 13% and premature death by 12% (**Figure**).

Scaling use of potassium-enriched salt will be a significant challenge. Most hypertension management guidelines recommend sodium reduction, though less comment on potassium supplementation and only a very few advise on potassium-enriched salt. Clinical guidelines need to be updated alongside raising awareness amongst the clinical community. In parallel, potassium-enriched salt needs to be much more accessible to patients. While currently available in over 40 countries worldwide, potassium-enriched salt is hard to find on the supermarket shelf and constitutes just a fraction of salt sales. It is often marketed at a significant price premium[2] though almost always at a cost highly competitive with even the lowest cost drug therapy. The higher price is because potassium chloride is about four times the price of sodium chloride, so the ingredients for a product comprising 25% potassium chloride and 75% sodium chloride will be about twice as expensive as regular salt. However, salt is a very low-cost commodity, and even at two or three times the price of regular salt, potassium-enriched salt should be an affordable proposition in many countries.

After decades of failing to reduce sodium intake, potassium-enriched salt offers a highly feasible new opportunity to reap large health benefits. It has been projected that a population-wide switch to potassium-enriched salt in China alone would avert almost one million strokes and heart attacks every single year.[9] And if used widely across the 1.2 billion people with hypertension worldwide, similarly large benefits are likely. Please be in touch if you're interested in helping us to make this happen (lfisher@georgeinstitute.org.au).

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NEW DIMENSION SERIES

Sustainable Development Goals (SDGs) for Hypertension Zero in the era of Anthropocene

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In the past few years, the world has been turned upside down by the coronavirus pandemic and up to August 2023 more than 7 million people died of the COVID-19 infection. Even in these circumstances, noncommunicable diseases (NCDs), including hypertension, are still one of the uppermost global health burdens, since about 70% of deaths in the world (57 million deaths/year) are attributed to NCDs. There also emerges a concern that COVID-19, a communicable disease, will create another pandemic of NCDs .[1] This prediction stems from the harsh and important experiences gained from the Great East Japan Earthquake that occurred on March 11, 2011 and the subsequent nuclear accident at the Fukushima Daiichi Nuclear Power Plant. A survey of the evacuees reported that even two years after the disaster, their blood pressure remained significantly elevated by ~4–5 mmHg on average, and the incidence rates of obesity, diabetes and dyslipidemia, as well as hypertension, remained 1.2–1.5 times higher than before the disaster.[2] These facts would be plausibly yielded from Fukushima residents' constant unstable mental health caused by the sudden death of those close to them, fear of their own death, stress of being confined to a temporary house with their family members all day long, feelings of detachment/isolation from friends and others, job loss and economic difficulties and so on. This lesson taught us that NCDs, such as hypertension, are caused by the change of natural environment surrounding us and new modality for the treatment of hypertension is required. "New Normal" hypertension medicine should be expected, such as a new field of hypertension research and medical practice to cope with combined disease types of communicable and noncommunicable diseases, specific to each person's particular lifestyle and life environment. A new disease entity in hypertension, including a physical and mental stress-induced hypertension or cardiovascular dysregulation produced by discordance between human host and micro-organisms should be recognized.[1]

In 2000, Paul Crutzen, a Nobel laureate in chemistry, and others proposed the "Anthropocene" (the new era of humankind) as a new geological epoch. This idea emphasizes that while humankind has long been subject to natural perils, in the course of "human evolution," human activities themselves have come to conversely threaten nature, and subsequently, the life of humankind. We are now facing pressing issues that have never been seen before, such as climate change including global warming, loss of biodiversity due to mass extinction, an increase in waste plastic or the accumulation of residues from fossil fuel combustion or nuclear tests. The COVID-19 pandemic can be placed in this category since its persistence is attributable to unavoidably close personal interaction.[3]

In the era of the Anthropocene, "Sustainable Development Goals" (SDGs) are advocated. They are a set of global goals established by the United Nations (UN) to cope with social, economic, and environmental challenges in various aspects. The SDGs were adopted by the UN in September 2015 as part of the 2030 Agenda for Sustainable Development. The goals aim to create a more

sustainable and equitable world by addressing key issues the world is now facing.

The 17 Sustainable Development Goals are as follows:

1. No Poverty
2. Zero Hunger
3. Good Health and Well-being
4. Quality Education
5. Gender Equality
6. Clean Water and Sanitation
7. Affordable and Clean Energy
8. Decent Work and Economic Growth
9. Industry, Innovation, and Infrastructure
10. Reduced Inequality
11. Sustainable Cities and Communities
12. Responsible Consumption and Production
13. Climate Action
14. Life Below Water
15. Life on Land
16. Peace, Justice, and Strong Institutions
17. Partnerships for the Goals

Different stakeholders, that is, governments, businesses, civil societies, and individuals are encouraged to work together to protect our planet and ensure prosperity for all by 2030. Sustainable development means meeting the needs of the present, whilst leaving no one behind and without compromising the ability of future generations to meet their own needs, which is considered to be the most important message for this movement.

It is evident that global health and SDGs are closely related and interdependent. SDG 3 (Good Health and Well-being) is included as one of the SDGs to reduce maternal and child mortality, combat infectious diseases, achieve universal health coverage, and address NCDs, including hypertension. Thus, trials dedicated to conquering hypertension, one of the most serious NCDs, carried out so far have been an effective enabler for the achievement of the SDGs. Actually, it is expected that the NCD countdown 2030 campaign (aiming for the reduction of mortality by 30% by 2030 compared to 2015) is expected to gain several health benefits; the reduction of not only NCD related complications but also dental caries, domestic violence, infectious diseases, road traffic injuries/falls etc. In addition, it is postulated to yield other non-medical benefits; reduction in environmental pollution, poverty or improvements in built environments, economic growth and productivity, local food production etc.[4]

I believe, however, that in the era of the Anthropocene, all efforts to realize SDGs in multiple ways, which are not directly related to reducing high blood pressure, could conversely be a new approach for Hypertension Zero (**Figure. 1**).

Figure 1

SDG 1 (No Poverty) and SDG 2 (Zero Hunger) are related to promoting food security and access to nutritious food. Healthy and balanced diets are encouraged. SDG 4 (Quality Education) can enhance health literacy and awareness to help individuals understand the importance of preventive measures, lifestyle modifications, and regular health check-ups. SDG 6 (Clean Water and Sanitation) is vital for preventing waterborne diseases, SDG 7 (Affordable and Clean Energy) can improve access to healthcare facilities and medical equipment. SDG 8 (Decent Work and Economic Growth) can improve access to healthcare and resources for managing NCDs. Economic growth can also lead to better healthcare infrastructure and more investment in research and development to prevent NCDs. SDG 10 (Reduced Inequality) includes reducing health inequities, ensuring access to healthcare services, and reducing barriers for vulnerable and marginalized populations. We should know that clear differences exist in NCDs mortality rate between high income and low-income countries.[5, 6] SDG 11 (Sustainable Cities and Communities) includes healthy urban planning and infrastructure that can promote active lifestyles and better access to healthcare services. SDG 13 (Climate Action), which is the emerging and urgent issue among SDGs, is directly linked to health and includes countermeasures against extreme weather events, rising sea levels, and disruptions of ecosystems. SDG 17 (Partnerships for the Goals) underscores the importance of collaborative international cooperation and partnerships for tackling global health challenges that transcend national boundaries.[7]

I have separated the interrelation between Hypertension Zero approach (the challenge for the conquest of hypertension) and achievement of SDGs into three categories as shown in Table 1. That is, hypertension in relation to the life environment (category A), to diversity (category B) and to the next generation (category C). Each category contains many issues to address, which conventional hypertension research and clinical practice have not paid so much attention.

In category A, for example, the current trend of accelerated global warming and climate change has a profound impact on the epidemiology of hypertension and cardiovascular diseases, especially on the elderly.[8] The ambient temperature, which is related to not only the inhabitants' geographical situation but also the housing environment.[9] The Ukraine conflict definitely would affect people's blood pressure all over the world. Approximately 50-70 million individuals in the USA complain of insomnia. Nowadays, sleep science has been remarkably advanced and the relation of diurnal blood pressure alteration and the quality of sleep (nonrapid eye movement; NREM sleep or REM sleep etc.) is gradually elucidated with the development of a new evaluation modality of sleep or sleep modulation drugs.[10, 11] In category B, in addition to disparity of economic situation or food availability, which are posted in SDGs, loneliness should be significant in hypertension research and clinical practice. Loneliness is apt to be occasionally stigmatized or ignored but is associated with a 26% increase of premature mortality.[12] The extent and causal associations of loneliness/social isolation and health-related behaviors especially in the elderly should be explored.[13] In category C, passing the baton to our next generation with sustaining our planet in sound conditions is the most vital issue in SDGs. "First 1000 days in life" (1000 days since fertilization) focusing upon *in utero* embryo development and epigenetic modulation by maternal factors has attracted many people's attention. Obesity is a pandemic health problem globally that produces various metabolic syndrome-associated diseases[14], but in Japan, emaciation in young women is the most serious problem. About 20% of women in their twenties show BMI below 18.5, due to distorted ideal body image, and the ratio of low-birth-weight baby is 9~10% in Japan. These babies bear the risk of developing metabolic diseases and cardiovascular diseases along with psychological disorders in later life. Taste sensation is the important determinant for food preference including a craving for salt and is cultivated in childhood. Food education and sophistication of our taste sensation, the research of which has been recently much progressed, should be highlighted.[15, 16]

In this context, in the ISH Hypertension News, New Dimension Series, we welcome papers, reviews or commentaries related to SDGs and Hypertension from our Society members to cultivate this new field of hypertension research and clinical practice, which could be the "Moonshot" for conquering hypertension.[17]

Table1.

Interrelation between SDGs and Hypertension Zero

 # Category A: Hypertension and Life Environment

Hypertension & Global Warming,
- Disaster (Earthquake, Flood) Air Pollution, Decarbonization, War
- Housing (light, noise, vibration...)
- Sleep Condition etc.

 # Category B: Hypertension and Diversity

Hypertension & Genetic Ancestry
- Poverty/Economic Disparity
- Food Availability
- Loneliness, Social Isolation etc.

 # Category C: Hypertension and Next Generation

Hypertension & DOHaD (Developmental Origins of Health and Disease)
- Emaciation in Women
- Pregnant Women's Health
- Dietary Education, Taste Favor etc.

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SPECIAL REPORTS

What has the Study of Hypertension in Pediatrics-Adult Hypertension Onset in Youth (SHIP AHOY) taught us about high blood pressure in the young?

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Despite the impact and costs of hypertension (HTN) in adults, limited research has been focused on the early stages of primary HTN, when greater opportunities to modify or attenuate the disease exist.[1] Using the updated normative date in the 2017 American Academy of Pediatrics guideline[2], at least 10% of adolescents have elevated blood pressure (BP) or HTN[3], and it is predicted that the health burden of premature cardiovascular (CV) disease will increase. Adolescents with high BP are generally asymptomatic, and HTN related CV events are distant. Consequently, therapies for most hypertensive adolescents are restricted to lifestyle interventions unless a secondary cause or concurrent condition is detected.[2] Emerging cross-sectional evidence now indicates that hypertensive target organ damage (TOD) is detectable in adolescence. However, while it is generally accepted that the origins of adult CV disease reside in the young, many fundamental questions about high BP in adolescence remain unanswered, including at what BP level do cardiac and vascular pathology begin to appear, and how prevalent is HTN-related target organ damage [TOD] in youth. In fact, the U.S. Preventive Services Task force recently published an evidence-based review which stated that no direct evidence currently exists that routine BP measurement identifies adolescents at increased risk for development of adult CV disease.[4]

SHIP-AHOY design

The Study of Hypertension in Pediatrics-Adult Hypertension Onset in Youth (SHIP AHOY) project was designed to address these knowledge gaps and develop an evidence base that would inform future childhood HTN guidelines. A cohort of adolescents with BP levels ranging from normal to stage 1 HTN were recruited and divided into 3 strata based on clinic BP:

- Low-risk: systolic BP < 80th percentile;
- Mid-risk: systolic BP > 80th but < 90th percentiles; and
- High-risk: systolic BP >90th and <99th percentile.

In contrast to adult HTN definitions that are linked to hard CV events, BP levels in children and adolescents have been classified using statistical cut-points- thus, HTN is defined as BP >95th percentile (age, sex, and height adjusted) and elevated BP >90th% (and <95th%). However, the risk for future HTN or concurrent TOD could also be increased at lower BP levels. Indeed, existing data suggest that adolescents with BP as low as the 90th percentile may be at increased risk for TOD[5], and adolescents with BP as low as the 80th percentile have increased risk for HTN in early adulthood. For these reasons adolescents with levels across the BP spectrum were included in SHIP-AHOY to determine if the BP risk level has been underestimated.

TOD measures in SHIP-AHOY included echocardiographically determined left ventricular mass index (LVMI) as the primary outcome, plus pulse wave velocity (PWV), urinary albumin excretion (UAE) and cognitive function as secondary outcomes. In addition to clinic BP by auscultation, 24-hour ambulatory BP was measured to determine BP phenotype, and metabolic measures of CV risk, including lipids and insulin resistance, were assessed.[6] The overarching hypothesis was that TOD among adolescents with high-risk BP would be common, and that the prevalence and severity would be greater at higher levels of BP. The findings from SHIP-AHOY to date have largely supported the original study hypothesis and provide significant new information on the development of BP-related TOD in youth. In the paragraphs that follow, highlights of the published data from SHIP-AHOY will be summarized.

Left ventricular hypertrophy

There were two main questions regarding left ventricular hypertrophy (LVH) addressed in SHIP-AHOY: prevalence and prediction according to BP level. In an analysis of data from 303 SHIP-AHOY participants, it was found that nearly 20% of youth with BP in the upper end of the BP distribution presented with LVH, defined as LVMI ≥38.6 g/m2.7.[7] The prevalence of LVH increased with increasing BP level, such that only 13% of those with low-risk BP had LVH compared to 21% of those with mid-risk BP and 27% of those with high-risk BP. In the same study, the level of clinic BP associated with development of LVH was investigated. In this analysis, the 90th percentile of systolic BP had a reasonably high specificity (0.75), with little loss of sensitivity (0.44) compared with lower systolic BP percentiles. This leads to the suggestion that children and adolescents with sustained clinic BP above the 90th percentile should have echocardiograms to assess for LVH.[7]

In addition to clinic BP level, the relationship between results of 24-hour ambulatory BP monitoring (ABPM) and LVH have been examined in SHIP-AHOY.[8] The predictive ability of both pediatric and adult ABPM thresholds for predicting the presence of LVH was examined in 327 SHIP-AHOY participants. Using logistic regression, adult ambulatory BP cut-points performed better than the pediatric criteria that were previously recommended for ABPM analysis.[8] The adult mean wake cut-point of 130 mmHg, for example, had a better balance between sensitivity (42%) and specificity (75%) than the mean wake 95th percentile BP level (sensitivity 23%, specificity 85%) found in the pediatric normative ABPM data currently in use. Additionally, BP load, the percentage of readings above threshold, which had previously been used to classify pediatric ABPM studies, did not improve prediction of LVH when added to the model.[8] These findings have led to a major revision of the consensus recommendations for analysis of pediatric ABPM studies[9], and example of how findings from SHIP-AHOY are already influencing the field of childhood hypertension.

Cardiac function

In addition to the 2-D and m-mode echocardiographic measures commonly used to assess for LVH, echocardiograms performed in SHIP-AHOY also included advanced echocardiographic approaches to assessing left ventricular function, including tissue Doppler, pulse wave Doppler and calculation of global longitudinal strain (GLS) and ejection fraction.[6] Using these data, the SHIP-AHOY investigators were able to determine whether there were any sub-clinical changes in cardiac function as participants' BP level increased from the low-risk to high-risk levels. Indeed, subclinical changes in both systolic and diastolic function were seen: Ejection fraction and peak GLS were lowest in those with the highest BP level, and diastolic function as reflected in the E/e' and e'/a' ratios was impaired compared to those in the low-risk BP groups.[10] Systolic and diastolic BP percentiles proved to be significant determinants of several of these cardiac function parameters.

Cardiovascular risk factors

Traditional CV risk factors such as high BP, dyslipidemia and insulin resistance are well-established as being linked to adult CV outcomes, but it is uncertain whether a similar relationship exists in youth. As part of SHIP-AHOY[6], fasting

lipids, glucose and insulin were obtained. Insulin and glucose were used to assess insulin resistance by means of the Homeostasis Model Assessment equation (HOMA-IR), and other variables such as lipid and BP levels were classified according to accepted pediatric criteria.[11] The number of abnormal values for these risk factors was then examined as potential predictors of various TOD measures, including LVH, systolic and diastolic cardiac function, and vascular stiffness as assessed by carotid-femoral pulse wave velocity (PWV). Participants with a greater number of CV risk factors had higher LVMI and PWV and greater impairment of systolic and diastolic function compared to participants with no CV risk factors. Generalized linear models demonstrated that the number of CV risk factors was significantly associated with higher LVMI, higher PWV, and alterations in several markers of diastolic function.[11]

Vascular stiffness

Increased vascular stiffness is felt by some investigators to precede the development of other manifestations of BP-related TOD, and previous studies have shown that youth with even slightly elevated BP can be shown to have increased PWV, an accepted marker of vascular stiffness.[5] In SHIP-AHOY, vascular stiffness was assessed by measurement of carotid-femoral PWV and by calculation of various parameters of aortic stiffness, strain and distensibility by echocardiography.[12] These markers of vascular stiffness were then examined as potential predictors of TOD measures such as LVMI, left ventricular systolic and diastolic function, and urine albumin excretion. PWV increased across the BP risk groups described earlier. Aortic distensibility, distensibility coefficient, and compliance were greater in the low-risk group than in the mid-risk or high-risk groups. After controlling for BP, PWV and aortic compliance were significantly associated with systolic and diastolic cardiac function and urine albumin excretion.[12] Although the cross-sectional nature of SHIP-AHOY does not permit conclusions to be drawn about causality, these findings support the concept that changes in vascular stiffness are involved in the causal pathway of adverse CV outcomes.

Conclusions and future directions

Taken together, the findings from SHIP-AHOY reviewed here provide convincing evidence that early markers of adult CV can be detected in youth, beginning at BP levels that are currently classified as normal. Incorporation of these data into future iterations of pediatric hypertension guidelines will hopefully facilitate efforts to reduce the burden of adult CV disease.

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Continued overleaf

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Diagnostic inertia: A remediable cause of resistant hypertension

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Blood pressure control is poor worldwide. The many reasons for this include therapeutic inertia (resistance of the patient or the physician to initiating or increasing intensity of therapy), consumption of substances that aggravate hypertension, such as salt, licorice and nonsteroidal anti-inflammatory agents (with the exception of sulindac), non-compliance, and diagnostic inertia (the failure to ask the question "Why is this patient's BP not controlled with usual therapy?").

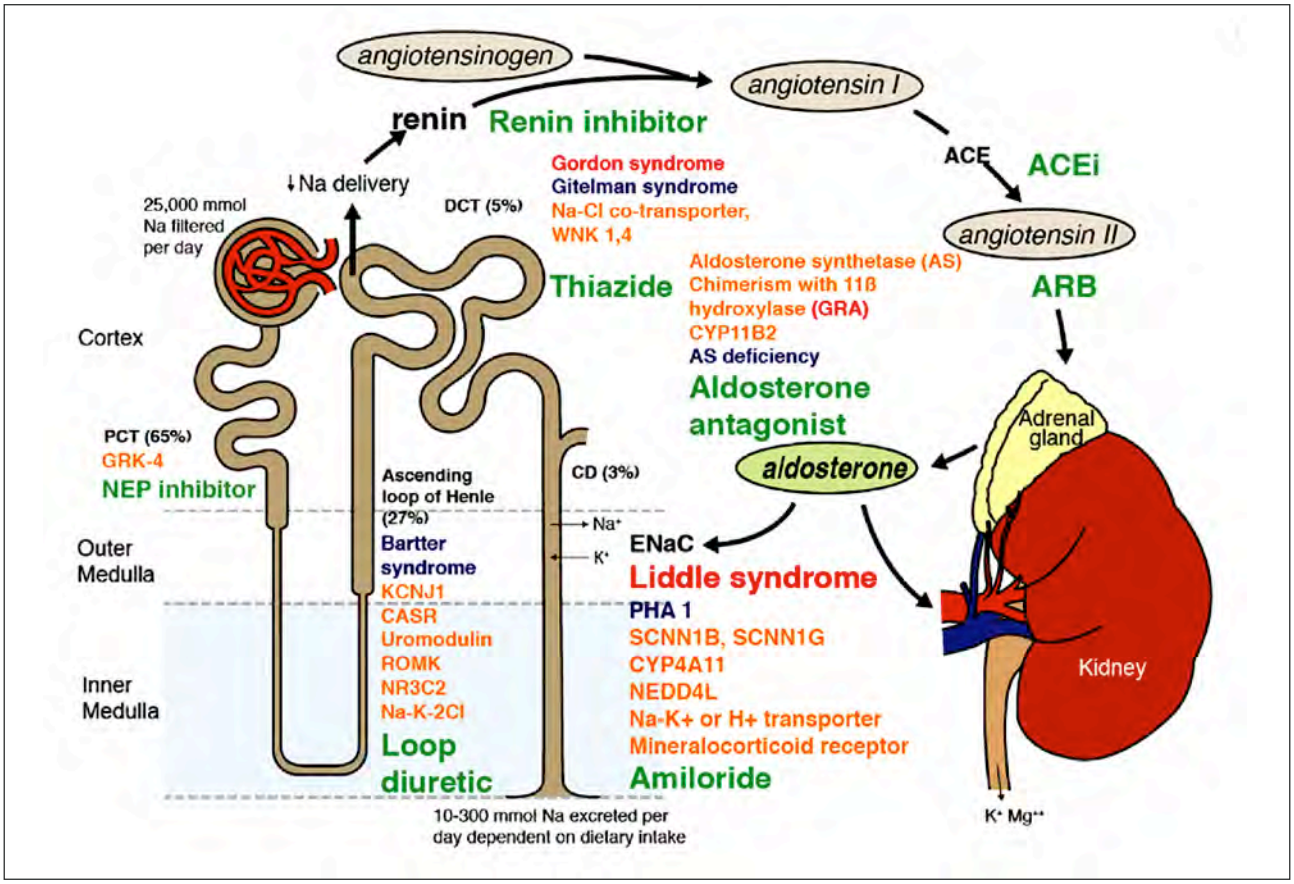
Diagnostic inertia is all too prevalent. Primary aldosteronism is an important example: Brown et al.[1] reported that 22% of patients with resistant hypertension had primary aldosteronism (PA), for which the specific treatment is aldosterone antagonists. Primary aldosteronism is greatly neglected: there are variants of at least 6 genes that predispose to PA: CYP11B2, KCNJ5, ATP1A1, ATP2B3, CACNA1D and ARMC5.[2] However, Cohen et al. reported that only 1.6% of patients with resistant hypertension attending hypertension clinics in the Veteran's Administration system were investigated for PA.[3]

Hypertension guidelines commonly recommend that a mineralocorticoid antagonist be added if blood pressure is not controlled by usual therapy. Eplerenone improves blood pressure resistance among patients with hyperaldosteronism.[4] In the PATHWAY-2 study, amiloride was as efficacious as a mineralocorticoid antagonist.[5] However, among patients with a Liddle phenotype (low renin/low aldosterone), amiloride is more efficacious than mineralocorticoid antagonist.[6] Guidelines do not mention Liddle syndrome, and only refer to amiloride as an alternative to mineralocorticoid antagonists for treatment of PA.

Hypertension due to overactivity of the renal epithelial sodium channel (ENac) is even more neglected than PA.[7] Although true Liddle syndrome (due to variants of SCNN1B) is rare, there are at least 5 other genetic variants that result in a Liddle phenotype (low renin/low aldosterone): GRK, NEDD4L, CYP4A11, NPPA, and UMOD.[2] In the Jackson Heart Study, 15.8% of patients had a Liddle phenotype, vs. 9.3% with a PA phenotype. The specific treatment for a Liddle phenotype is amiloride. (Triamterene, a possible alternative to amiloride, causes urinary casts and is implicated in interstitial nephritis.) The physiology of these issues was reviewed in 2018. (**Figure 1 overleaf**)

In the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, African-Americans were more likely to have uncontrolled hypertension, even though their hypertension was more likely to be diagnosed, more likely to be treated, and more likely to be treated more intensively. Among African-Americans, hypertension is prevalent among 48% of those born in the US, vs. 27% of those born outside the US. This supports the hypothesis put forward by Grim and others, that there was an advantage conferred by salt and water retention, for survival of the sequence of events entailed in slavery: capture, long marches to barracoons awaiting transport, ocean crossings with vomiting and diarrhea, then survival in the first few years of working in the hot sun. Among slaves transported to Brazil, mortality was 19% to 30% during the Pacific crossing, and in total, mortality was 63% to 85% during embarkation, voyage, arrival, and the initial adaptation period.

Physiologically individualized therapy based on renin/aldosterone phenotyping (PhysRx) markedly improves blood pressure control, as reported from a study in Africa.[8] At the Nigerian site, where patients with uncontrolled hypertension were randomized to PhysRx vs. usual therapy, and amiloride was available, blood pressure was



markedly improved by PhysRx: "Systolic control was obtained in 15% of UC [Usual Care] vs. 85% of PhysRx (P = 0.0001), diastolic control in 45% vs. 75% (P = 0.11) and control of both systolic and diastolic pressure in 15% vs. 75% (P < 0.0001) even though the renal function was worse at that site", and baseline blood pressures were higher. The biggest change in medication in the study was that 19% of patients allocated to PhysRx were switched to amiloride. In the Jackson Heart Study, a Liddle phenotype was more common than a PA phenotype (15.9% vs. 9.3%).

Plasma renin and aldosterone should be measured in a stimulated condition (i.e. while taking a diuretic, angiotensin converting enzyme inhibitor or angiotensin receptor antagonist), and should be interpreted in the light of the medication being taken at the time of blood sampling.[9] In patients with severe hypertension, it is not safe to withdraw all medication for the purpose of achieving "purity" in such testing; one of my patients, a young man, died from an intracerebral hemorrhage when an endocrinologist did so.

Alternative approaches

In patients with resistant hypertension, a common approach is to simply keep increasing the number and doses of medications. This may be carried to extremes; one patient I saw was taking atenolol 200 mg three times/day, amlodipine 20 mg twice/day, HCTZ 25 mg daily, terazosin 10 mg twice/day, and minoxidil 20 mg twice/day, with a blood pressure of 250/150 mmHg. After adding amiloride 30mg twice a day and spironolactone 100mg daily, and tapering off atenolol for plasma renin testing, his blood pressure came down to 220/120 mmHg. His hypertension, which was due to primary aldosteronism with bilateral adrenocortical hyperplasia, responded well to bilateral adrenalectomy. Renal denervation is sometimes also considered. A pooled analysis of sham-controlled trials of ultrasound renal denervation (uRDN) reported BP decreases of < 7 mmHg. These benefits are very small in comparison to what is achieved by PhysRx. I suggest that renal denervation should never be considered unless hypertension remains resistant to PhysRx.

Conclusion:

Diagnostic inertia is an important and all too common remediable cause of resistant hypertension.

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Table 1. Physiologically individualized therapy[a] based on renin/aldosterone phenotyping

	Primary aldosteronism/ Inappropriate secretion of aldosterone	Liddle phenotype (overactivity of ENaC)	Renal/renovascular
Renin	Low[b]	Low	High
Aldosterone	High[b]	Low	High
Primary treatment	Minerallocorticoid antagonist (spironolactone or eplerenone); sometimes amiloride[d] Rarely, adrenalectomy[e]	Amiloride	Angiotensin receptor blocker[c] or renin inhibitor Rarely, revascularization

a It should be stressed that this approach is suitable for tailoring medical therapy in resistant hypertensives; further investigation would be required to justify adrenalectomy or renal revascularization.

b Levels of plasma renin and aldosterone must be interpreted in the light of the medication the patient is taking at the time of sampling. 9 In a patient taking an angiotensin receptor blocker (which would elevate renin and lower aldosterone), a plasma renin that is in the low normal range for that laboratory, with a plasma aldosterone in the high normal range, probably represents primary hyperaldosteronism, for the purposes of adjusting medical therapy. c. Angiotensin converting enzyme inhibitors (ACEi) are less effective because of aldosterone escape via non-ACE pathways such as chymase and cathepsin.

d To avoid gynecomastia from spironolactone if eplerenone is not available, or if blood pressure control is inadequate with mineralocorticoid antagonist alone. Caution regarding hyperkalemia must be observed if amiloride is added to mineralocorticoid antagonist.

e Primary aldosteronism is commonly/usually due to bilateral adrenocortical hyperplasia [10]

(Reproduced with some updates by permission of Elsevier from Spence JD. Lessons from Africa: the importance of measuring plasma renin and aldosterone in resistant hypertension. Can J Cardiol 2012; 28:254–257.)

FOCUS ON LATIN AMERICA

Exploring Hypertension and Latin Culture: Insights from the Americas

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In anticipation of the upcoming ISH scientific meeting in Cartagena next year, this edition of Hypertension News offers a glimpse into Latin culture and its resonance in advancing hypertension research within the region.

Latin America is a tapestry woven with celebratory culture, friendship, and camaraderie. The scientific meetings hosted here are not just gatherings; they are vibrant forums where young investigators and clinicians thrive.

Traditionally, countries in this region grapple with budget constraints in healthcare—often investing 30% to 50% less of their GDP compared to nations like the USA, UK, or Europe. Yet, their cardiovascular mortality rates are on par, or even lower, in some cases like Peru, Colombia, or Chile. Hypertension treatment rates hover around 90% in the aware patients in Brazil and Argentina, and some instances report control rates nearing 70%. However, the regional average remains below 50%. "Reverse innovation" emerges as a concept that could address inequalities by implementing low-income strategies in high-income countries.

Within this issue, we've invited some eminent Latin-American investigators and clinicians to share their perspectives. Dr. Elizabeth Muxfeldt from Rio de Janeiro, Brazil, delves into renal denervation for resistant hypertension. Overseeing a sizable program spanning two decades, with almost 1200 patients, her team's work has contributed to impactful publications in the field.

Dr. Patricio Jaramillo, hailing from Bucaramanga, Colombia, brings to light pioneering research on using isometric exercise to reduce blood pressure—a cost-effective and globally applicable approach. He holds a distinguished reputation as a clinical and epidemiological researcher, even serving as the honorary president of the 2024 Cartagena meeting.

However, Latin America's influence goes beyond clinical research. Did you know that Argentina boasts three Nobel Prizes in medicine and physiology? Dr. Houssey, one of these laureates, established a foundational research legacy working in endocrine hypertension. His mentees later coined "angiotensin," once called hypertensin. Brazil unveiled the first ACE inhibitor, and since then, the renin-angiotensin system has evolved into a complex entity, with ongoing revelations about its effects. Dr. Mariela Gironacci from the University of Buenos Aires presents captivating research exploring the protective dimensions of this system, along with its potential applications in mental health and hypertension.

Furthermore, Dr. Carlos Vio from Chile shares fresh insights into vasoactive systems and their interplay with potassium homeostasis, aligning with the burgeoning evidence of potassium's antihypertensive effects.

Lastly, to provide an authentic portrayal of the Americas' reality, two clinical nephrologists specializing in hypertension share their perspectives. One practices within an upscale healthcare system, while the other operates in a low-income setting. Surprisingly, similarities overshadow differences, not only professionally but also in the realm of humanity.

Within these pages, you'll discover the rich fabric of Latin American contributions to hypertension research. From the rhythms of Rio to the intellectual vigor of Colombia, this region promises an expanse of innovation and cultural vibrancy that's rewriting the narrative of hypertension research.

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FOCUS ON LATIN AMERICA

Renal denervation in resistant and refractory hypertension: where are we and where are we going?

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Resistant hypertension is defined as the absence of blood pressure control despite the use of three or more anti-hypertensives, preferably including a thiazide diuretic, a renin-angiotensin-aldosterone system (RAAS) inhibitor and a calcium channel blocker. Its pathophysiology is based on hyperaldosteronism status with resulting volume overload. Therefore, the fourth drug prescribed for resistant hypertensives must be a mineralocorticoid receptor antagonist, preferably spironolactone.[1]

On the other hand, refractory hypertension is defined as uncontrolled blood pressure despite the use of five or more drugs, including a long-acting thiazide diuretic and a mineralocorticoid receptor antagonist, preferably spironolactone.[2] Considering that these patients use a potent double diuretic block associated with RAAS inhibition, both volume overload and hyperaldosteronism status are already being effectively treated. Thus, in pathophysiological terms, sympathetic hyperactivity is the primary responsible for refractoriness to treatment. In this regard, the pharmacological treatment starting with the fifth drug is based on sympatholytic drugs. Those may be a beta-blocker (preferably selective beta-blockers with vasodilating action, such as carvedilol and nebivolol, which also present the advantage of not altering the metabolic profile), an alpha blocker (doxazosin) or a central alpha agonist (clonidine). However, this sympathetic blockade is not always enough to effectively reduce sympathetic hyperactivity and control blood pressure. Furthermore, an excessive number of anti-hypertensive drugs is a meaningful determinant of lower adherence to pharmacological therapy for several reasons, including the side effects of this high number of drugs.[3]

Therefore, non-pharmacological procedures arise aiming to achieve blood pressure control, thus reducing cardiovascular morbimortality among these individuals. Renal denervation is one of the most promising therapies to decrease sympathetic activity. This technique is primarily recommended in cases of true resistant hypertension, refractory hypertension, and patients intolerant to usual anti-hypertensive medications.[3]

We are aware that afferent renal sympathetic nerves stimulate juxtaglomerular cells, which, in turn, increase renin release, decrease renal perfusion, and increase sodium reabsorption. On the other hand, afferent nerves signal these changes to the central nervous system (CNS), activating sympathetic reflex and leading to vasoconstriction, increased blood pressure, and worsening of hypertension-mediated organ damage (HMOD). Therefore, renal sympathetic nerve ablation not only aims to increase renal blood flow but especially to modulate this signaling between the kidneys and the CNS, reducing the sympathetic hyperactivity responsible for resistant and refractory hypertension.[3,4]

The initial procedures of renal denervation used radiofrequency ablation, and the main procedure was the three phases of the Simplicity study. In 2014, the study's third phase – Simplicity-3 – was interrupted early as it failed to reduce ambulatory blood pressure, which led to an initial decrease in clinical trials assessing the efficacy of renal denervation. Afterward, initial negative results were attributed to technical issues related to the

amount of energy employed and the application site of the radiofrequency. Multiple statements were published aiming to establish a unique protocol for the denervation technique and for conducting clinical trials.[3,5] Recently, an ultrasound renal denervation was developed. It was projected to maximize nerve covering using circumferential ultrasound energy. This technique appears to be less dependent on the operator's individual skills.[4] Both techniques came off as very safe, without evidence of renal artery lesion nor short- or long-term reduction of renal function, especially among patients with eGFR > 40 ml/min/1.73m2.[6] However, the actual decrease of blood pressure with the two ablation techniques is still quite controversial.[3] In a recent metanalysis, Pisano et al (2021) evaluated the results of renal denervation in resistant hypertensives. The study also showed that this procedure can moderately reduce 24-hour ABPM systolic and diastolic blood pressure in 5.29 mmHg and 3.75 mmHg, respectively, without affecting office systolic blood pressure.[7] There is no evidence that renal denervation can reduce the risk of major cardiovascular events or hospitalizations.[7] Furthermore, the long-term anti-hypertensive effect is still uncertain, and it is also unclear which patients may really benefit from renal denervation.[3]

All things considered, currently, there is evidence that renal denervation may work as an adjuvant treatment for resistant and refractory hypertension, especially in patients without advanced chronic kidney disease. Moreover, it is essential to perform renal denervation in specialized centers with qualified personnel to guarantee adequate selection of patients as well as the technical quality of the procedure.[3]

As in most Latin American countries, our center does not perform renal denervation in clinical practice but only in a research context. We still need to define better which patients could really benefit from this procedure. But above all, we must provide specific training for our staff concerning this technique so that we can present more robust results in the future.

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FOCUS ON LATIN AMERICA

Isometric exercise in the management of hypertension

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide and hypertension (HT) is the main modifiable risk factor.[1] It has been shown that HT has an attributable population fraction for CVD of 22.3% and 18.7% in Latin America.[2,3] Physical training is key for HT control. Cardiovascular disease primary prevention guidelines recommend 90 -150 minutes per week of dynamic aerobic exercise accompanied by dynamic or isometric resistance exercises 2 to 3 times per week.[4]

We recently published the results of the Effect of Isometric Strength training in individuals with metabolic syndrome in the workplace (EEFIT) according to its initials in Spanish.[5] A randomized, controlled clinical trial in which the effects of two isometric exercise interventions, one on the upper limbs and the other on the lower limbs, on blood pressure levels in patients with grade I HT who had not started pharmacological treatment was evaluated. Seventy- seven participants were randomized to a handgrip strength intervention group (n= 28), a wall squat intervention group (n= 27), or a control group (n= 22). In addition to the intervention, all participants received recommendations consisting of modifications in the four main risk factors for chronic non-communicable diseases (unhealthy diet, tobacco use, sedentary lifestyle, and harmful alcohol consumption). The interventions were performed at the participant's workplace under the supervision of a physiotherapist. The handgrip strength group performed isometric contractions of 30% of their maximal strength for four sets of 2 minutes with a 2 minute rest between each set;

Effect of two different isometric exercise programs during office hours for blood pressure control

A) Initial squat evaluation **B) Squat training at 95 degrees** **C) Grip force training**

Cohen D.....Lopez-Jaramillo P. J Clin Hypertens 2023;25 (4):380-387

the wall squat intervention group was required to hold the position at an angle between 95°-135°, for a total training of 14 minutes duration. The study was divided into two phases, each lasting 12 weeks, in the first phase, the intervention was performed 3 times a week and in the second phase, one session was performed weekly. At the end of the first phase, we observed a decrease within-groups in mean systolic blood pressure (SBP) of -11.2 mmHg (SD 12.5; p<0.001) in the handgrip strength group and -12.9 mmHg (SD 10; p<0.001) in the wall squat group, a significant difference compared to the control group where the change was -0.4 mmHg (SD 12.6; p=0.86). At the end of the first phase, significant differences in SBP were observed between handgrip strength and the control group with a mean SBP of 10.3 mmHg (95% CI 2.8 - 17.8) and between the wall squat group and control with a mean SBP of 11.7 mmHg (95% CI 4.1 - 19.3). In the follow-up phase, the mean SBP of the handgrip strength group and the squat group was 129.3 mmHg (SD13.5) and 126.5 mmHg (SD 9.2), respectively; showing that the benefit of isometric exercise performed in the first phase was maintained even with the decrease in training frequency to one session per week.

Our results agree with those of a recent meta-analysis of observational and interventional studies. The analysis included 1,286 participants and showed that isometric exercise produces a significant reduction in SBP (-6.97 mmHg, 95% CI -8.77 to -5. 18) and diastolic blood pressure (DBP) (-3.86 mmHg 95% CI -5.31 to -2.41, p < 0.0001) measured in the office. Additionally, effects were seen as well in central SBP and DBP (-7.48 mmHg; 95% CI -14.89 to -0.07 and -3.75 mmHg; 95% CI -6.38 to -1.12) and 24-hour DBP (-2.39 mmHg; CI -4.28 to -0.40). Importantly, there was no evidence of an increased risk of adverse events such as joint pain, muscle pain, dyspnea and/or tachycardia with the intervention.[6]

Isometric exercise requires a short weekly time and can be performed at the workplace without additional equipment or with portable devices (dynamometer), which gives it an advantage compared to aerobic exercise. However, more studies with a larger number of participants are still required, which is why we are implementing the EEFIT-2 study, an international multicenter program to evaluate the effectiveness of wall squat training in a real-life condition and its contribution to the improvement of HT control rates.

The implementation of isometric exercise programs in hypertensive patients appears to be a feasible, low-cost, safe intervention that can have clear benefits in improving HT control rates, which globally and particularly in Latin America reach only 18%.

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New concepts of protective RAAS arm and the implication for novel therapies in the future

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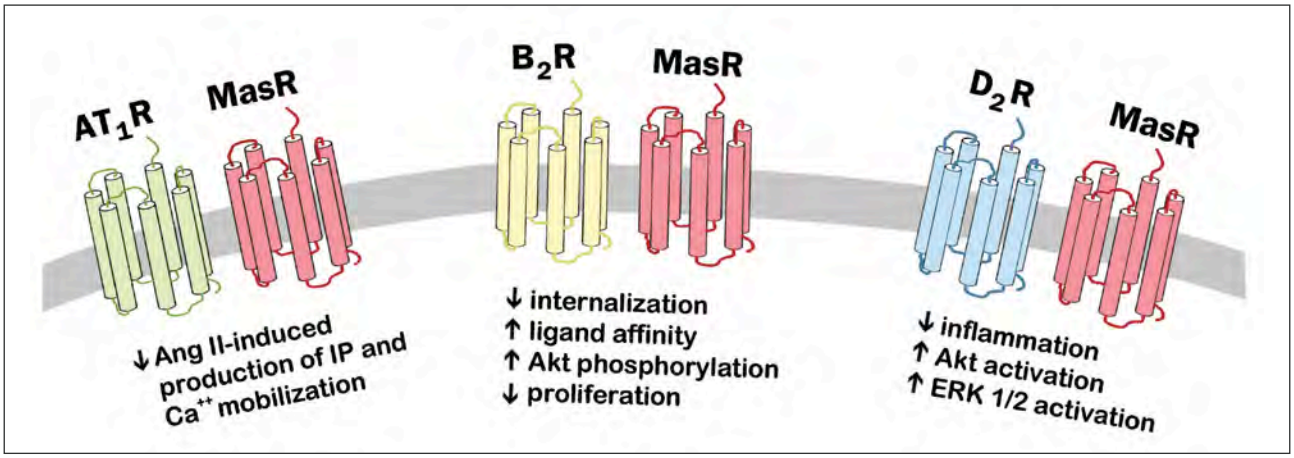
Hypertension is a hallmark of cardiovascular dysregulation and a significant risk factor for cardiovascular disease and mortality. Managing hypertension through blood pressure-lowering drugs has emerged as an effective approach to reducing the risk of cardiovascular events.

One critical target in the treatment of hypertension is the renin-angiotensin system (RAS), which plays a pivotal role in blood pressure control and fluid homeostasis. The RAS is a complex system composed of various components, but current understanding suggests it consists of two distinct axes with opposing functions.

The "pressor" axis is primarily constituted by angiotensin II (Ang II), the Ang II type 1 receptor (AT1R), and the angiotensin-converting enzyme (ACE). This axis mediates numerous effects of Ang II, including pressor, trophic (cell growth and proliferation), proinflammatory, fibrotic (scar tissue formation), and oxidative effects. In various cardiovascular diseases, overexpression of this axis has been linked to deleterious outcomes.

Conversely, the "depressor/protective" axis is represented by Angiotensin-(1-7) [Ang-(1-7)], its receptor Mas (MasR), and angiotensin-converting enzyme 2 (ACE2). ACE2 catalyzes Ang II degradation into Ang-(1-7), which ultimately acts through the MasR. The depressor axis exerts beneficial effects, including vasodilation, anti-inflammatory actions, and anti-fibrotic properties. In contrast to the pressor axis, the Ang-(1-7)/MasR/ACE2 axis has been associated with protective actions in various cardiovascular diseases, such as ischemic stroke and neurocognitive disorders.[1] These protective effects are attributed to reducing oxidative stress and inflammation, improving outcomes in affected individuals.[1]

Moreover, the RAS extends beyond its role in blood pressure regulation and electrolyte balance. Evidence suggests that RAS components also affect higher brain functions, including cognition, memory, anxiety, depression, and neurological disorders. For instance, an overactive pressor axis has been linked to cerebrovascular diseases, such as stroke, and neurodegenerative conditions,



including cognitive impairment, dementia, Alzheimer's disease, and Parkinson's disease. On the other hand, the Ang-(1-7)/MasR/ACE2 axis has demonstrated neuroprotective effects, particularly in ischemic stroke and neurocognitive disorders, by safeguarding neurons and oligodendrocytes through a MasR-mediated pathway.[1,2]

The locus coeruleus (LC), a brainstem nucleus containing norepinephrine (NE), is essential for regulating various brain functions, such as attention, arousal, emotion, cognition, and the sleep-wake cycle. Ang-(1-7) decreases NE release[3,4] and induces downregulation of tyrosine hydroxylase[5], an enzyme involved in NE biosynthesis in neurons from the hypothalamus and brainstem. This reduces NE production, resulting in potential anxiolytic and protective effects on neurological disorders.

Overall, these recent data on the protective arm of the RAS open potentially new approaches to mental health issues, especially in patients with cardiovascular diseases, where with one intervention, we may tackle two problems.

G-protein-coupled receptors (GPCRs) are a large and diverse group of transmembrane signaling proteins, and they are the targets of approximately one-third of approved and clinically prescribed drugs. Thus, MasR belonging to the G-protein-coupled receptors (GPCRs) family, holds significant therapeutic potential. Upon agonist stimulation, GPCRs undergo internalization and trafficking within cells, leading to various signaling pathways and biological responses, and MasR is not the exception.[6-8] Interestingly, MasR undergoes differential trafficking inside neurons from hypertensive but not normotensive rats: it is translocated to the nucleus.[8]

Notably, MasR has been observed to form constitutive heterodimers with other receptors, such as AT1R,[9] dopamine type 2,[10] and bradykinin type 2 receptors (B2R).[11] These interactions influence receptor function and alter ligand binding properties, potentially leading to long-lasting protective effects in cardiovascular and inflammatory processes. For instance, the interaction between MASR-B2R results in delayed sequestration of the MasR from the plasma membrane and an increase in the affinity ligand binding properties of MasR.[11] We also have observed MASR-B2R in other tissues such as endothelium, kidney, and mesenteric vascular beds.[11]

Thus, receptors are in constant dynamism, undergoing dynamic interactions with each other and with G proteins, as well as with the surrounding cytoskeleton, other structural components, and other receptors leading to the formation of receptor heteromers explaining the diversity in MasR receptor function.

We believe that advancing our understanding of the protective arm of RAS and its receptors regulation offers promising opportunities for new therapeutic development. Beyond the conventional approach of designing drugs solely to activate or inhibit single GPCRs, there is a growing focus on regulating specific receptor signaling pathways or effectors at precise subcellular locations and timeframes. Targeting receptor-dependent signaling pathways holds particular promise for cardiovascular disease treatment and warrants further investigation.

In conclusion, hypertension's significance as a risk factor for cardiovascular disease underscores the importance of understanding the complexities of the renin-angiotensin system and G-protein-coupled receptors. These molecular mechanisms offer exciting possibilities for developing novel and more effective therapeutic strategies, leading to improved patient care and outcomes in various diseases, particularly those related to cardiovascular health and neurological function.

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FOCUS ON LATIN AMERICA

Hypertension, dietary potassium, and renal vasoactive systems, matters with South American flavor

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Renal vasoactive hormones contribute to kidney excretory function and blood pressure regulation, and more attention has been placed in the vasoconstrictor renin angiotensin system (RAS), and less to the vasodilator sodium excretory kallikrein kinin system (KKS) although bradykinins received an important recognition after the discovery that they are degraded by Angiotensin-I Converting Enzyme (ACE) or Kininase II and contributed to the therapeutic effects of ACE inhibitors.

The history of angiotensins and bradykinins have grounds in South America, since pioneers in the field such as Mauricio Rocha-Silva (Brazil), Eduardo Braun-Menendez (Argentina), Hector R. Croxatto (Chile), posted the concept that the imbalance between vasoconstrictors (angiotensins) and vasodilators (bradykinins) hormones would determine hypertension.

Nowadays we know that pathophysiological alterations of these vasoactive hormonal systems contribute to chronic kidney disease and salt-sensitive hypertension.

The relation of dietary potassium with kallikrein emerged when we discovered – by using ultrastructural immunohistochemistry with high resolution electron microscopy- the origin of renal kallikrein exclusively in the connecting cells (CNTc) of the connecting tubule. These CNT cells have abundant sodium/potassium-ATPase on their basolateral side, and ROMK potassium channel in the apical pole, and constitute a main site of potassium regulation and secretion. With a high dietary potassium, the CNTc hypertrophies, secrete more potassium, and increase the synthesis of kallikrein and bradykinin receptors, and the production of bradykinin. This mechanism contributes to the natriuretic and hypotensive effect of the potassium-rich diet, in addition to the inhibitory effect on the activation of sodium chloride cotransporter NCC.

Abundant epidemiological studies show that higher dietary potassium intake (evidenced by higher urinary potassium excretion) is associated with lower blood pressure and lower cardiovascular risk. Our current diet is characterized by a high sodium content and a low potassium content, therefore increasing dietary potassium may be as important as reducing sodium intake. Dietary potassium has been shown to regulate the activity of the thiazide-sensitive sodium-chloride cotransporter (NCC) in the distal convoluted tubule.

In humans, kallikrein excretion varies in direct relation to potassium intake, and there is a high correlation between urinary potassium and urinary kallikrein. Therefore, potassium deserves serious consideration, not only because it is an important kallikrein regulator but also because of the therapeutic implications of a high-potassium diet.

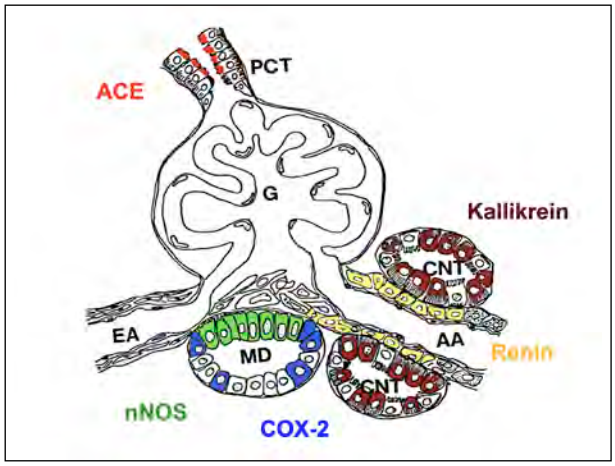
It is well established that high potassium intake dephosphorylates the thiazide-sensitive sodium/chlorine cotransporter (NCC) located in the distal convoluted tubule, thus inducing natriuresis, a mechanism mediated by Kir4.1 potassium channel. More recently we have described a similar effect of bradykinin which dephosphorylates the thiazide-sensitive sodium/chlorine co-transporter (NCC) located in the distal convoluted tubule, thus inducing sodium excretion.

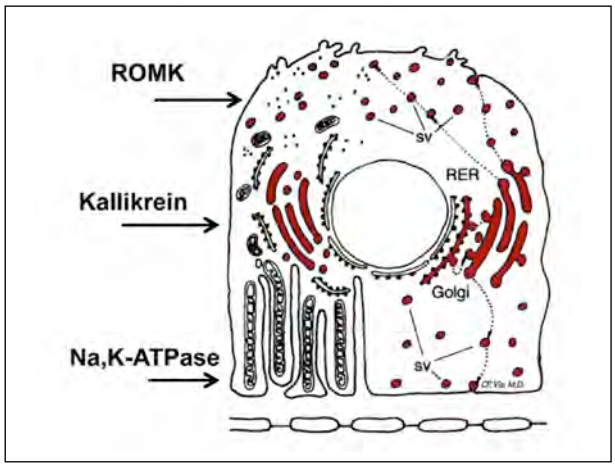
Several studies in hypertensive humans have shown that dietary potassium supplementation significantly increases kallikrein, urinary sodium excretion, and lowers blood pressure. The therapeutic implications in the management of hypertensive patients are of great importance, particularly in those who are sensitive to salt. The partial replacement of sodium salts by potassium salts in the diet has an additive effect with the double benefit of reducing sodium intake and stimulating KKS at the same time. This change in dietary salt content (less sodium and more potassium) has been shown to be effective in reducing blood pressure and deaths from coronary and cerebral vascular accidents in large-scale studies in Finland, and recently in a large population in China.

The high sodium diet corresponds to a relative value, it is generally accepted that the normal sodium diet corresponds to an intake of 100 mmoles/day, however, changes in eating habits have meant that the usual sodium diet is close to 150-200 mmoles/day corresponding to a high sodium diet.

On the other hand, an adequate diet in potassium corresponds to our ancestral diet, which because of civilization and food preservation was changed to a diet rich in sodium. However, our body is not adequately adapted to handle the high-sodium diet, characteristic of our current diet, resulting in sodium-sensitive hypertension. This occurs in subjects with normal kidney function and in subjects with minimal kidney injury. Since sodium restriction is unrealistic as processed foods are high in sodium, the increased intake of potassium can be promoted in the population which in the long term may constitute the main non-pharmacological measure of prevention of high blood pressure and kidney damage.

There is consensus in the world that our modern diet is potassium deficient, consumption from a balanced diet with meat, fruits and vegetables provides approximately 150-200 mmol/day, but data shows that current potassium intake is close to 50 mmol/day. This moderate potassium deficiency cannot be detected in blood levels but is associated with the development of high blood pressure, cerebral vascular infarction, osteoporosis, and kidney damage.





Animal or vegetable cells from natural, unprocessed foods have an intracellular concentration of 140 mEq of potassium and 10 mEq of sodium. Therefore, natural foods are rich in potassium and contain little sodium. However, processed foods have 5-10 times more sodium than potassium. Today, it can be stated that in industrialized countries, a large part of the population is exposed to a low daily intake of potassium, a situation correlated with the development of salt-sensitive hypertension.

There is strong evidence that the beneficial health effects of a low-sodium diet with adequate potassium are synergistic, and both factors are necessary, since 1928, studies by Addisson have shown that potassium salts lower blood pressure and eliminate sodium.

High blood pressure affects 20-30% of the population and contributes to the leading cause of death in men and women. Depending on the characteristics of the population, 40-70% of hypertensives are sensitive to salt (sodium). Less

than 50% of hypertensives know their condition and only 10-20% have their pressure controlled, the Chilean National Health Survey 2010 shows similar numbers to those in the literature.

With similar numbers around the world, one can wonder if we are missing an important factor in the management of hypertension. Especially since we have, as never before in history, a wide variety of effective antihypertensive drugs.

We believe that the forgotten factor is the potassium content of the diet whose importance has been relegated in favor of the importance placed on sodium content, but both sodium and potassium are closely linked in their health effects.

Current sodium and potassium intakes are very different from the physiological intakes that have prevailed during mammalian evolution. Foods consumed by terrestrial mammals, including primates, never contain much sodium. Plants contain only trace amounts of Na+ and the consumption of large quantities of fruits, roots, leaves, and seeds did not contribute much sodium to the organism. For omnivorous and carnivorous species, occasional or regular absorption of meat increases sodium intake, but in limited proportions, because the meat consumed corresponds most of the time to the sodium poor intracellular medium and not to the sodium rich extracellular medium that is usually lost when meat is cooked. For example, a Yanomami native in the Amazon, who feed almost exclusively on plants, ingests between 1 and 10 mmol sodium per day. The diet of an Eskimo in Alaska, which contains more than 50% meat, contributes 15-35 mmol sodium day to the body.

The transition from hunting populations to modern societies has been accompanied by a reduction in potassium intake due to lower consumption of raw products rich in organic potassium salts. Thus, the average potassium intake of a Yanomami native is 230 -300 mmol/d, whereas a European is 70 - 80 mmol/d.

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This dietary change, unique in the human species, was rapid in evolutionary terms and is therefore unlikely to have been accompanied by a corresponding genetic adaptation.

Our proposal is that potassium in the diet is very important for health, that the population is exposed to a diet poor in potassium, and that decreasing sodium is neither sufficient nor feasible, at the recommended levels with contemporary nutrition.

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FOCUS ON LATIN AMERICA

Time to delve into the ground realities of hypertension

RAVEN VOORA, MAYRA AYALA AND CESAR ROMERO

My name is Mayra Ayala Alemán.
I am 37 years old and I am from Cochabamba, Bolivia. I am a Nephrologist, a wife, and a mother to a beautiful 8-month-old baby and a 3-year-old dog, who is like another child to me. I spent my early years in Cochabamba, and La Paz. I completed my MD degree at the Private University of the Valley (UNIVALLE) and then I moved to Buenos Aires, Argentina, to pursue my specialization at Cosme Argerich Hospital, where I became a member of staff after completing my specialization. We decided to return to Bolivia, where all our loved ones are, and it's here that our family began to grow. Currently, I work at Hospital Obrero N°2, the medical insurance provider for workers, in the Nephrology department.

My name is Raven Voora.
I am a clinical nephrologist with a specialized interest in hypertension. Currently, I am a Clinical Associate Professor of Medicine with the Division of Nephrology and Hypertension at the University of North Carolina in Chapel Hill. I currently reside in Chapel Hill with my husband and 2 children, who are aged 8 and 6. I completed my medical school training at the University of Maryland in 2002, Internal Medicine Residency at the University of North Carolina in 2005, and Nephrology Fellowship at the University of Pennsylvania in 2007.

Our repository of knowledge and guidelines in hypertension management is extensive, geared to address diverse clinical situations. However, despite this vast information, the global challenge of maintaining satisfactory blood pressure control endures. The key is no longer just understanding what needs to be done; it's effectively translating that knowledge into action, a realm known as implementation.

As the healthcare community prioritizes implementation, it's time to confront ground realities. Two eminent hypertension specialists shed light on challenges in high and low-income Americas settings. In both scenarios, inequalities emerge as a sobering constant. Notably, resource availability doesn't consistently translate to practical application. Most significantly, patient individuality and empowerment emerge as pivotal factors for success, diverging markedly from generalized global approaches.

Mayra and Raveen, can you describe the population you serve for hypertension?

Mayra (Bolivia): Most of my patients are retirees with multiple comorbidities. The primary patients seen in the Nephrology clinic are those with chronic kidney disease due to various factors, including diabetic kidney disease, hypertension, and glomerulopathies. Most of these patients belong to the lower-middle class, and their level of education averages up to high school.

Raveen (USA): In my current role, I see patients with chronic and end-stage kidney disease. In addition, I have a hypertension clinic where I see patients with routine and complex hypertension.

About 1/3 of my patients are self-described black, and about 10% are Hispanic. The number of Hispanic patients that I am seeing has increased in recent years. I see very few Asians. About 10% of my patients are unemployed, and about 15% are living below poverty. The average age of my patients is 50-55 years old. About 1/3 of my patients have completed high school or a GED, and about ½ of my patients have a higher education degree, including a bachelor's.

How much time are you typically available to discuss with your patients during appointments?

Raveen (USA): I feel very lucky that I am not pressured for time during office visits in an academic practice. I am allotted 30 minutes for a return visit and 60 minutes for a new patient. Patients oftentimes will comment and appreciate that I "spend a lot of time with them" as they have become accustomed to "quick visits" with community providers who are oftentimes pressured to see more patients in less time.

Mayra (Bolivia): The time allocated for consultations with them is not as ample as I would desire. I have only 2 hours to attend to 8 to 10 patients. Since many of them are new to the clinic, the initial interviews to get to know them tend to be more extensive and detailed.

Could you explain how you approach implementing non-pharmacological treatments for hypertension in your practice?

Mayra (Bolivia): For implementing non-pharmacological treatments, I strive to explain to the patients, using the simplest terms possible, and the results of their laboratory tests. For new patients, I conduct a comprehensive interview based on their habits, provide recommendations for improvement, and schedule a follow-up appointment a month later to assess their progress. Comparing previous results and pointing out improvements or deteriorations based on the measures being taken, whether medication or lifestyle changes, helps me consolidate or induce new changes.

Raveen (USA): Non-pharmacological treatment is the easiest thing to talk about but the most difficult to implement. For my patients, salt reduction is a focus. Many of my patients eat outside of the house several times a week. As a first step, I encourage them to eat more at home and to avoid canned and frozen prepared meals when eating at home. At our hypertension clinic, we are lucky to have a dietitian and lifestyle educator available to individualize the lifestyle counseling.

What is your experience with and opinion on using telemedicine for managing hypertension? How do you think it impacts patient care in this context?

Raveen (USA): I certainly think that much of hypertension care can be handled remotely. However, a successful telemedicine program is contingent on certain resources being accessible and available. For example, many of my patients do not own a smartphone or computer and, in some cases, a home BP monitor. For the patients who do have such capabilities, the clinical pharmacist in our Hypertension Clinic has been able to effectively follow up with patients by phone.

Mayra (Bolivia): Regarding telemedicine and hypertension, I haven't had any experience yet. However, if patients are educated about regular blood pressure monitoring, proper measurement techniques, and healthy lifestyles, along with access to telemedicine, it could be implemented. This approach would benefit the patients and enable us to monitor and guide them closely.

Do you have access to Ambulatory Blood Pressure Monitoring (ABPM) or home blood pressure monitoring in your practice?

Mayra (Bolivia): In the clinic, I currently have access to home blood pressure monitoring. We do not have ABPM.

Raveen (USA): We do have ABPM available. We don't widely use it for every patient, but there are certain circumstances where it can provide helpful information. On the other hand, I widely use home BP monitoring. For patients unable to purchase a home BP monitor, we try to provide a monitor at our Hypertension Clinic.

What are the typical first-line medications you prescribe when treating typical hypertensive patients in their 50s without comorbidities?

Raveen (USA): In terms of pharmacologic therapy, I widely use Angiotensin Receptor Blockers (ARBs) since they are mostly generic and have a low side effect profile.

Mayra (Bolivia): For new patients without comorbidities, I start with Angiotensin Receptor Antagonists (ARAs), and I also work on modifying their dyslipidemia, overweight, and habits before adding more medications.

What about patients with CKD?

Mayra (Bolivia): For chronic kidney disease patients, I primarily use ARAs as the initial treatment.

Raveen (USA): The first line is Ace-Inhibitors or ARBs. If the BP is still elevated and proteinuria is present, then I add mineralocorticoid receptor antagonists (MRAs). In addition, I prescribe SGLT2-inhibitors. I have not used non-steroidal MRAs due to cost.

Could you describe some of the common barriers to treatment adherence that you encounter in your patient population?

Raveen (USA): There are many. Many of my patients have various life stresses that interfere with self-management. As a result, patients will stop or pause taking medication or following a healthy lifestyle.

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Mayra (Bolivia): The main difficulties I encounter in patient adherence are various: Language: Some of my older patients have a limited understanding of Spanish and better comprehend Quechua, one of Bolivia's indigenous languages. I don't know Quechua. They often come with family members, but they sometimes need help to grasp the necessary changes we need to implement for them. Diet: rich in fats and carbohydrates among most patients with high consumption of sugary and carbonated drinks. Beliefs: The idea that being overweight indicates good health still circulates in my community, especially among older adults.

What would you add to your clinic to improve BP control or adherence?

Raveen (USA): I would like to have ways of more directly testing for adherence to identify those patients who need attention in this area. In addition, I wish there were more options for combination antihypertensive therapy that are affordable and comparable to monotherapy in cost.

Mayra (Bolivia): I primarily wish for more time with patients, especially new ones. Additionally, it would be ideal to have new and accurately calibrated blood pressure monitors and scales. Having different sizes of cuffs for blood pressure measurements would also be beneficial.

FOCUS ON LATIN AMERICA

The latest in our preparations for ISH2024 Congress in Cartagena, September 2024

DAGNOVAR ARISTIZABAL

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

We are continuing our diligent efforts to ensure that our 2024 congress in Cartagena becomes a memorable event. The chosen convention center is an iconic location situated by the Caribbean Sea, offering both pleasant spaces for academic activities and the enjoyment of an unbeatable view of colonial Cartagena.

So far, we have established a general structure for the content of the scientific program, and we have invited our ISH members to contribute their suggestions to help create an outstanding scientific program. We are working together to make this congress in Cartagena a remarkable and enriching experience for all participants.

Here's an overview of our recent activities, which have primarily focused on the proposed program structure and included some images from the convention center and the city. This lovely space can accommodate up to 2500 participants, featuring a beautiful theater with a

capacity for 1500 attendees. Additionally, there are entertainment areas with a view of the Caribbean Ocean, making it a perfect location for the opening reception, as it offers a glimpse of both the ocean and the charming old city.

As of now, the preliminary scientific program structure includes 26 scientific sessions, 4 keynote lectures, 10 inter-society sessions, 6 "How To" presentations, 3 Forum discussions, 6 Special Presentations, 6 "Need to know" sessions in basic and clinical hypertension and 2 Hot sessions on new hypertension guidelines. Additionally, the Pan American Health Organization (PAHO) and World Health Organization (WHO) will introduce the HEARTS project at the meeting, focusing on its relevance either for Latin America or worldwide. Furthermore, there will be 5 ISH Regional Advisory Group (RAG) meetings, a session on women in hypertension research, and young investigator activities with dedicated time slots along with the award ceremonies.

Our goal remains to receive 2500 attendees at the meeting, and we are diligently working toward achieving this target. The organizing committee is considering ways to enhance the participation of young researchers and the presentation of at least 400 research papers as oral or poster presentations.

As the field of hypertension is evolving, we see a significant opportunity to share the knowledge gained, not just for doctors. There's a new message emphasizing patient involvement and the active engagement of physicians in new systems of care. We anticipate that those new approaches will have a substantial impact on our practices and bring precision medicine into the realm of hypertension.

Furthermore, novel strategies for controlling hypertension are emerging, and those will be included in our scientific program as we firmly believe that these emerging areas of application and the utilization of modern technology will significantly influence our future approaches to hypertension diagnosis and therapy. Thus, we are considering having a track that combines basic and clinical hypertension with a focus on the application of these fundamental areas in patient care.

This scientific framework will make your visit to Cartagena memorable not only from the perspective of knowledge generation, learning, and professional relationships but also due to the charm of having visited the beauties of an enchanting colonial city in Latin America.

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THE ESH GUIDELINES

The 2023 European Society of Hypertension guidelines

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The 2023 hypertension guidelines of the European Society of Hypertension (ESH) were presented at the 2023 ESH annual meeting in Milan and published in the *Journal of Hypertension*.[1] The guidelines include several elements of novelties. The strength of the diagnostic and treatment recommendations is graded some what differently compared to previous ESH guidelines.[2] That is, while using (in a simplified fashion) the two previous criteria (class of recommendation and level of evidence), a novel approach to evaluate the study quality (including risk of bias, statistical precision, accuracy of measurements) has been added. Guidelines address in detail the advantages and limitations of the multiple approaches to blood pressure (BP) measurements, but they clearly consider the one measured in the office as the reference BP, because of its fundamental contribution to knowledge of the diagnostic and treatment aspects of hypertension. However, the important additional contribution of home and ambulatory BP is not forgotten,[3] and these measurements are recommended in each patient whenever they are feasible.

New important cardiovascular risk factors are mentioned and this is done also for measures of hypertension-related subclinical organ damage. Identification of subclinical organ damage continues to be regarded as fundamental for cardiovascular risk stratification and its search is extended to patient follow-up, because treatment-dependent changes of some organ damages have shown prognostic significance and may thus help physicians to decide whether initial treatment strategies should be continued or modified.

The 2023 guidelines confirm previous lifestyle interventions for hypertension management and provide novel aspects on specific interventions including the importance to dynamic strength exercise training, reduce sedentary time and novel recommendations for alcohol moderation. The classical BP threshold for drug use (systolic BP > 140 or diastolic BP > 90 mmHg) is confirmed, but mention is made that there are categories in which evidence is in favour of higher (e.g. isolated systolic hypertension or an age > 80 years) or lower (very high cardiovascular risk individuals) thresholds. This is the case also for target BP values, for which the ESH guidelines identify (i) a "must" BP target to aim at (< 140/80 mmHg), because of its association with a marked cardiovascular protection and a favourable balance between benefits and tolerability; and (ii) a SBP target of < 130 mmHg if treatment is well tolerated, due to its incremental benefit although with a clear increase in the risk of side effects.

As for BP threshold, mention is made that more conservative targets may be considered in some patients (isolated systolic hypertension, very old patients, and possibly patients with left ventricular hypertrophy) and recommend to never pursue a target of < 120/70 mmHg, due to a marked increase of serious side effects,[4] treatment discontinuation[5] and in some patients increased cardiovascular outcomes. The number of

antihypertensive drugs to be primarily considered for pharmacological treatment is expanded by the addition of beta-blockers to other major drug classes (ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics) based on the evidence of their protective effect in hypertensive patients, their safety in important comorbidities (obstructive lung disease, peripheral artery disease) for which they were regarded as unsafe, and their use in many cardiac, vascular and non-cardiovascular conditions frequently associated with hypertension. Initial treatment with a two drug, ideally in a single pill combination, is recommended, because evidence is now even stronger that this treatment strategy favours adherence to treatment and reduces treatment inertia, i.e. the main factors responsible for poor control of hypertension in real life.

However, although the importance of combinations of a blocker of the renin-angiotensin-system with a calcium channel blocker or a diuretic is confirmed, other combinations of drugs from all major classes are mentioned as therapeutically appropriate in several patient categories. To start with initial monotherapy is regarded as an exception and may be considered in old (very) frail patients, patients with high normal BP or patients with low risk and milder degrees of grade 1 hypertension. Possible advantages of other treatment strategies, e.g. very low dose four drug combinations with improved tolerability, are mentioned and use of the polypill is given the green light in both primary and secondary prevention because of the recent evidence of its favourable effects on adherence to treatment and cardiovascular risk.[6]

The definition of true resistant hypertension is emphasized in the new guidelines and addressed in detail, with a distinction between patients with and without advanced impairment of renal function and in the latter case use of spironolactone is recommended as the preferred drug.[7] Recommendations for the treatment of true resistant hypertension also extend to other drugs and include, as a final option, the application of renal denervation. The possibility to use new drugs, i.e. SGLT2is (in both heart failure with preserved [HFpEF] and reduced [HFrEF] ejection fraction and chronic kidney disease), valsartan/sacubitril in HFpEF, and the non-mineralocorticoid receptor antagonists finerenone in patients with chronic kidney disease associated with type 2 diabetes is also mentioned. Moreover, the impact of novel medications,e.g. GLP-1 receptor agonist or dual glucose-dependent insulinotropic polypeptide (GIP) plus GLP-1 receptor agonist, to lower BP in hypertensive patients with overweight or obesity is also addressed.

A final important aspect of the new ESH guidelines is that diagnostic and treatment recommendations are extended to conditions that have not been addressed – or only marginally addressed – in the past. A guidelines section is devoted to hypertension phenotypes identified by combined office and out-of-office BP measurements, isolated systolic or diastolic hypertension, and peripheral vs central BP elevations. Other sections deal with hypertension in different demographic conditions including children and adolescents, an extended section on sex and gender aspects in hypertension, as well as aspects related to ethnicity. Specific settings including hypertension disorders in pregnancy, hypertension emergencies and hypertension in the perioperative period are also addressed in more detail.

Furthermore, beyond the established cardiovascular comorbidities and non-cardiovascular comorbidities, such as diabetes, chronic kidney disease and obesity other diseases including respiratory diseases, rheumatic diseases, cancer, or infectious diseases are also addressed. In many of these conditions, treatment recommendations cannot count on the evidence provided by randomized controlled trials. Yet, available data allow us to deliver advice that may help physicians to appropriately follow and treat these patients, often in a way that differs from the recommendations issued for the general hypertensive population. Finally, the 2023 ESH guidelines address extensively the problems related to patients' follow-up, because of their fundamental importance for long-term successful treatment. In this area, trials or dedicated studies are rare. Nevertheless, the available evidence allows us to give physicians advice on issues such as the rate of visits, laboratory examinations, instrumental examinations (including out-of-office BP measurements) and assessment of non-adherence to treatment in the various follow-up phases and according to the patients' clinical conditions.[8]

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Women in Hypertension Research Lived Experiences

Women in Hypertension Research

Read the Lived Experiences of these women working in hypertension research on the WiHR webpage: https://ish-world.com/women-in-hypertension/

Anna Shalimova recently evacuated from Ukraine, and now practises in Poland.

Amela Jusic, Bosnia and Herzegovina, reflects on the challenges of performing research in a post-war country.

Lucia Davie Mbulaje Kaipa, Malawi, talks about the issues surrounding hypertension awareness, treatment and capacity building in Malawi.

Hind Beheiry, Sudan, discusses overcoming the challenges of performing research in an area with instability and poor infrastructure.

THE ESH GUIDELINES

Reflecting on the 2023 European Society of Hypertension guidelines

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Introduction

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) must be praised for executing an extraordinary task! The 2023 ESH guidelines, which have been published in June, is an exhaustive manuscript of 199 pages including 1,743 references, 27 tables, 21 figures, and 47 boxes. As both the authors of this article have contributed to the development of the 2023 ESH guidelines, we followed closely the intense efforts by the Task Force chairperson Giuseppe Mancia and his co-chair Reinhold Kreutz to orchestrate the writing teams and supervise numerous revisions and uncountable corrections, until the final paper was delivered.

The 2023 ESH guidelines provide a valuable source of updated information on all the aspects of clinical hypertension for in-depth training of doctors with special interest in hypertension. This document may also be useful to practicing doctors, who can focus on the execution guidance summarised in 47 boxes with Recommendations and Statements. Here we present some thoughts on key ESH recommendations from the International Society of Hypertension (ISH) perspective, which in 2020 published practice hypertension guidelines for global use.

Hypertension guidelines– Evidence, pragmatism, and implementation

The era of hypertension guidelines started in 1977 with the US JNC reports, followed by British, international, European, and other national guidelines. In the last decades there has been a major shift in guideline development, by abandoning inferential reasoning and speculation medicine, and implementing evidence-based medicine. Although this has been a major improvement in how the best practice of medicine is decided, evidence-based medicine is not a religion to be followed faithfully, as the evidence does not apply directly to many of our patients in clinical practice, and in many key areas evidence is lacking and practising doctors value the opinion of specialists who work in the field of hypertension. Moreover, pragmatism and feasibility are crucial if the guidelines are going to be implemented in primary care where most people with hypertension are managed.

Another issue to consider is the differences among recommendations provided by different organizations. Comparison of different guidelines has been a challenging intellectual exercise for hypertension experts, with differences among guidelines attributed to different interpretation of the same data, and also differences in geographic areas for which the guidelines are intended (e.g., in the epidemiology of hypertension and cardiovascular disease, healthcare systems

structure, financial resources, etc.). However, few conditions in medicine have such an enormous body of evidence from mega-trials addressing almost all the pragmatic research questions, as hypertension. This is clearly indicated by the considerable agreement in the key recommendations by recent guidelines, e.g., international, American, and European, which highlights the fact that we now have broad international consensus on how hypertension should be managed.

Hypertension diagnosis – still a trouble

The 2023 ESH guidelines put considerable emphasis on blood pressure (BP) measurement methods and hypertension diagnosis, with special sections on white coat and masked hypertension. The primary method for diagnosis of hypertension in the ESH guideline is office BP measurement, justified because this has been used in trials for defining the current diagnostic and treatment BP thresholds. However, office BP is often badly measured and is a weak cornerstone for decision making. Moreover, even with carefully taken measurements, one third of individuals with suspected or treated hypertension have different BP levels in their usual environment assessed by home or ambulatory monitoring (ABPM), with important diagnostic and prognostic implications.

It is time to acknowledge that the diagnosis of hypertension should not be made in the office, and that confirmation with out of office BP evaluation is necessary to achieve an accurate diagnosis. This should not apply only to resistant hypertension, but to all cases with hypertension, as there is no reason to believe that the diagnostic issues in patients on 1 or 2 drugs are less than in those on 3 drugs. The fact that in many settings many patients are still managed with office BP measurements alone, is not a reason for not recommending the best available methods which prevent overtreatment and undertreatment in many people, and also better engage patients in their treatment.

Moreover, the choice between ABPM and home monitoring should be guided by evidence but also realism. Although ABPM has been extensively studied and is used for almost 40 years, it is not available in most healthcare settings and user discomfort is common, particularly with repeated use. Thus, in its current form repeated ABPM measurements will never be a solution for most people with elevated BP around the world. On the other hand, home BP monitoring is being widely used by patients in many countries, more so after the pandemic, and is suitable and advantageous for long-term monitoring. With some technological advancements in home-BP telemonitoring (and hopefully cuffless BP technologies), this method will soon become the basis for hypertension management, with office measurement used for screening and ABPM in selected cases and settings.

Optimizing the prediction of risk

The assessment of total cardiovascular risk has been a major contribution of previous and current ESH guidelines, as it has been an efficient tool for the practicing doctors to stratify their patients more accurately. In its 2023 guidelines ESH presents a list of markers (tests) with their special characteristics, advantages, and limitations. However, practising clinicians need to decide which tests should be done in routine practice, dependent on which are well documented, widely available, and easily applicable (e.g., LVH, eGFR, albuminuria). Other tests such as pulse wave velocity, renal resistant index, and retinal imaging, are not routinely used or ready for widespread clinical use.

The 3 primary goals of treatment

Here the 2023 ESH guidelines gave a clear and strong message – the primary goal of treatment is to reduce BP. This is important as the practicing doctors are often confused by debates and discussions on which is the best drug, which however is less important that the BP lowering per se in most patients. The second strong message is consistent with the ESC-ESH 2018 guidelines, i.e. that the first goal is to reduce BP <140/90 mmHg which will offer most of the cardiovascular protection. Of course, some additional benefit will be achieved in many patients with even lower BP levels, i.e. <130/80 mmHg, if it can be achieved without adverse effects. The third message is to aim for optimal control within 3 months. With more than 50% of treated patients having uncontrolled BP in most countries, the above 3 messages must become the focus for treating hypertension. Of course, treatment goals should be individualized, according to the treatment tolerance, cardiovascular risk, and frailty.

New lifestyle interventions

The readers of the 2023 ESH guidelines should be very interested to look at the new recommendation for several lifestyle interventions, as new data have changed our beliefs on several of them, including dynamic strength exercise training, alcohol consumption, and other. This is an important component of therapy for all our patients, and the ISH has just published an extensive position paper on lifestyle management of hypertension and cardiovascular disease, with novel recommendations on nutrition, physical activity, stress, sleep, and more.

An efficient treatment plan

The core treatment strategy presented by the ESH is practically the same as in previous guidelines, with (i) treatment initiation with dual therapy in most patients (ii) preference to fixed-dose combinations in single morning administration, and (iii) a stepwise treatment plan. This is a simple and easy to memorize protocol, which aims at improving long-term adherence and can achieve BP control in 90% of patients within 2-3 months. Of course, this should be individualized according to the presence of other conditions and treatment tolerance. Emphasis was put on using b-blockers at any stage, if there is any of many compelling or other indications for their use. The main difference here is that all other guidelines emphasise that b-blockers should be used when there is a guideline directed indication for their use, recognizing that when there is no such indication, the regular treatment algorithm would apply.

A recent retrospective analysis of 1.4 million patients with hypertension in primary care in England who were qualified for dual BP therapy according to the 2018 ESC-ESH guidelines and had follow-up data for 15 years showed than about 50% received monotherapy and had 33% mortality. These data suggest that prior recommendation for dual therapy initiation of treatment is not getting through and supports the continued strong recommendation by ESH for treatment initiation with combination therapy in most patients.

First indications for renal denervation

Following recent recommendations on renal denervation by the European Society of Cardiology (ESC) Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI), the ESH presented for the first time indications for hypertension. After investigating renal denervation for longer than a decade, we now know that the procedure is generally safe and can lower BP as much as one antihypertensive drug. It is important to protect the method from being misused in clinical practice, and to be applied in the right patients and in experienced centers, and gain more data on the optimal patient selection and the long-term effects of the method.

Perspectives

The ESH provided a valuable contribution to the hypertension community and to our patients by developing an excellent and extensive review of the current evidence on hypertension management. It is unfortunate that this time the ESC was not a partner to this project, and has announced that will publish separate guidelines in 2024. Having different guidelines by two prestigious organizations is not a good service to European doctors and their patients.

Hypertension research has generated an enormous amount of data and has adequately addressed most of the practical management issues. We are now reaching the point of guideline overload as is evidenced by the fact that little has changed between 2018 and 2023. Now is the time to focus on implementation, by approaching and training our patients and inventing tools to make them partners in our mutual mission, which is to make progress in achieving optimal and long-term BP control.

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THE ESH GUIDELINES

Research opportunities from the ESH clinical guidelines and tips for new investigators - summarizing unanswered questions

SUBMISSION BY NEUSA JESSEN, JOSE PATRICIO LOPEZ AND DEAN PICONE
on behalf of the New Investigator Committee

The most recent version of the European Society of Hypertension clinical guidelines was published in June 2023.[1] The large team of experts exhaustively reviewed evidence on all aspects of clinical hypertension management. Like past guidelines, the 2023 version includes a section on gaps in evidence (section 22, pages 150-51). This section provides an excellent overview of critical evidence gaps and emerging methods or topics relevant to clinical hypertension management. New Investigators may find it valuable to review these evidence gaps to identify potential areas of clinical research that will both excite them and provide impactful new evidence for the field. Here we provide an overview of the gaps in the evidence section of the guidelines with a focus on the opportunities for New Investigators and some tips on how to get started answering a research question.

Themes emerging from gaps in evidence identified in the ESH guidelines

Randomized controlled trials (RCTs) have been the main evidence source for recommendations in hypertension guidelines. Nevertheless, RCTs have several limitations. They are costly, time and resource consuming and, because they are usually performed in a well-controlled environment with strictly selected participants, their results may not be directly transferable to clinical practice. As such, many important hypertension questions remain unanswered.

The need for implementation

There is a great body of RCT data on the efficacy of medications that lower BP and that explore optimal management strategies. These knowledge and tools mean that we could expect control of high BP to be very good. However, in many countries in the world, control rates are low. This strongly suggests a disconnect between the evidence and real-world practice. For this reason, real-world implementation of clinical practice guidelines, supported by high-quality research that tracks and evaluates the work, is urgently needed.[2]

Leveraging big data and register RCTs

Nowadays several countries have databases of routine health information, including BP, that has been collected frequently over long periods. Retrospective analysis of such rich databases brings the advantage of capturing the normal heterogeneity of the population observed in everyday clinical practice. Importantly, this includes the most vulnerable groups, for example, those at extreme ages and/or with several comorbidities

that are usually excluded from RCTs. Nationwide or regional administrative and clinical databases can be used to perform register-based RCTs, a pragmatic method of collecting data, randomizing and following-up, based on case registries. There are no formal guidelines for reporting registry-based RCTs and it is important that new investigators appreciate that there are major challenges that have to be considered related to data quality, ethical issues and methodological aspects.[3] However, the importance of real-world studies has been shown[4] and they are particularly well suited to answer questions related to drug therapies, including prognostic aspects and issues related to medical practice. The utility of real-world studies to complement controlled.[4] Furthermore, for big and complex real-world datasets, machine learning may be used to automatically process the data using sophisticated statistics.[5]

Measurement strategies compared to standard office BP

Another gap identified in the ESH guidelines is the need to examine the role of ambulatory BP monitoring or home BP monitoring compared to usual office BP measurement in diagnosis, management guidance, and prognosis in patients with hypertension. One example of these questions is: does home BP-guided or ambulatory BP guided therapy significantly reduce morbidity and mortality compared to office BP-guided treatment? This question is currently being evaluated in the MASked-unconTrolled hypERtension management

Figure 1. Steps for answering your research question.

Identify the research question	• From daily practice, previous reading or conversations with mentors*, colleagues and collaborators *if you do not have a mentor, contact the Mentoring and Training Committee of the ISH!
Thoroughly review the literature	• Understand the magnitude of the problem • Previous studies: methods used and results
Refine the question	• Narrow the scope of the study to ensure it is feasible. • Use the PICO(T) structure, especially for clinical questions (https://tees.ac.uk/lis/learninghub/cinahl/pico.pdf) • Helps to minimize confusion or misunderstanding
Develop the study protocol and submit for relevant approvals	• Consider this a road map for the study: specify who / when / how / where: required sample size, data collection and management, data analysis process, study closeout • Submit for ethical and governance approvals
Perform the research, analyse and share the results	• Follow your protocol for all steps of your research • Disseminate your results at meetings* and through a peer-reviewed publication *ISH2024 is coming fast, and is a great opportunity to share your research with the global hypertension community

based on office BP or ambulatory BP measurement (MASTER) study.[6] The MASTER study will examine the impact of masked-uncontrolled hypertension management, based on ambulatory or office BP monitoring, on intermediate cardiovascular and renal outcomes. Aside from cuff BP research, there are also many emerging questions about cuffless BP monitoring.

Laboratory science

We want to highlight that many new investigators within ISH work in laboratory/discovery/basic research. This is an incredibly important branch of hypertension research that we have not focused on in this article because of the emphasis on the ESH clinical guidelines. Nevertheless, without continued efforts in the lab, major breakthroughs that completely transform our understanding of- and treatments for- hypertension may not be achieved.

Tips to get started

To answer your research question, a scientific process must be followed. It is crucial to dedicate time and effort to plan how you want to answer the question, so that reliable conclusions can be made. Having a good idea and a good research question is critical!

This research process should systematically follow interlinked steps in an objective way (see Figure). Every study needs to have the methods documented sufficiently so that the study can be replicated by a different investigator team. Take your time to deeply plan your approach to answering the research question – this will set you up for success in the long run! Having a mentor (or mentors) and/or being embedded in a supportive research group will give you the opportunity to share your ideas, learn from others and refine your research questions so that they can be answered in the best possible way. If you need funding for your study, this planning process will also help you when formulating your grant proposals by showing you have thoroughly reviewed the literature and have a strong methodological protocol for answering the question.

In summary, the 2023 ESH guideline document has concisely summarized many of the current clinical evidence gaps that require additional research. Some themes that we identified include the need for implementation research, to leverage big data and advanced analytics and more evidence on the role of out-of-office BP. We have also provided some tips to get started on answering a research question and we hope these are useful for new investigators!

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ISH REPORTS

Update on ISH Global Health Partnerships

TAZEEN H. JAFAR
Chair, ISH Global Health Partnerships

I am honored to take on the role of Chair for the new ISH-Global Health Partnerships (GHP) initiative. In this capacity, I will work closely alongside ISH President Professor Bryan Williams and the members of the ISH Council with the aim of achieving our shared aspirations of eliminating global disparities in BP control and improving vascular health for all.

The ISH-GHP represents a key initiative that aligns with ISH's overarching mission to enhance global BP control. True to its name, the main purpose of ISH-GHP is to cultivate meaningful relationships and robust collaborations, both internally within ISH Regional Advisory Groups (RAGs) and externally with reputable organizations such as the World Health Organization, Global Coalition for Circulatory Health, World Hypertension League, and Resolve to Save Lives.

These partnerships and collaborations with external organizations will be mutually beneficial in leveraging each other's strengths, resources, and expertise. We will be able to address complex health challenges more effectively and advocate more strongly for BP control on a global scale and create a larger impact.

Among the key priority areas for ISH-GHP, one of the most important goals is to widely share and promote ISH's hypertension treatment guidelines and evidence-based strategies for controlling blood pressure (BP). This goal is particularly crucial in low- and middle-income countries (LMICs) where the rates of BP control are notably lower. This lack of success can be attributed, in part, to a complex interplay of social and environmental factors that hinder effective hypertension management.

To achieve this objective, ISH-GHP plan to intensify our efforts, with a focus on LMICs. The strategy involves conducting regional webinars, hosting policy forums, and engaging with local governments and non-governmental organizations. The aim of these activities is to facilitate the exchange of knowledge and experiences across different regions. By comparing and contrasting experiences, the initiative aims to find practical and tailored solutions for implementing evidence-based strategies for hypertension care that align with the local cultural, health system, and policy contexts.

Simultaneously, ISH-GHP is committed to organizing various seminars and leveraging social media platforms to disseminate key position papers jointly with our partners that have direct implications for global BP control.

In the same vein, ISH-GHP is committed to advancing applied knowledge base with practical solutions to improve hypertension management across resource-constrained settings. This entails an ambitious plan to conduct a major systematic review of quality improvement studies on BP control including non-traditional models of hypertension care and multisectoral approaches, as well as community engagement studies. The intended outcome of this extensive program is to establish an enduring resource that can be continuously updated. This resource will serve as a valuable tool, aiding in the implementation of practical strategies based on the ISH 2020 Global Hypertension Practice Guidelines, ultimately advancing the quality of care in a variety of healthcare delivery channels.

One particularly exciting facet of ISH-GHP is its emphasis on amplifying tools, training, and capacity-building for non-physician healthcare workers (NPHWs) in hypertension care. A wealth of evidence underscores the effectiveness of engaging trained NPHWs, operating under physician supervision, to achieve BP control in the contexts of many low- and middle-income countries. Our objective is to provide them with the necessary skills for precise BP measurement, diagnosing hypertension, effectively communicating to encourage healthier lifestyles, and making suitable referrals when needed.

The objectives mentioned were discussed in detail at the ISH Council meeting in July 2023, which took place in Singapore. The initiative received unanimous support from all members, who also mentioned their own favorable experiences with potential external partners at the regional level. These experiences are seen as valuable resources to be utilized and expanded upon. The specific action plan will continue to evolve as our journey continues towards the mutual aims of enhancing population BP control and reducing hypertension-related CVD mortality especially in LMICs, and thereby achieving UN Sustainable Development Goals around non-communicable diseases.

I encourage ISH members to contact me with ideas aligned with ISH-GHP's objectives. I will also attend RAG meetings and seek feedback from external partners.

Together, we look forward to making a tangible impact on combating hypertension!

Tazeen Jafar - tazeen.jafar@duke-nus.edu.sg

ISH REPORTS

Mentorship and Training Committee Report

AUGUSTO MONTEZANO
Chair ISH Mentorship and Training Committee on behalf of the MTC

It is with great pleasure and excitement that I write our first Mentorship and Training Committee (MTC) report. First, let me introduce to you the members of our MTC! As the chair of the MTC, I have the pleasure to work with an outstanding team of hypertension researchers from all over the globe including Drs Lebo Gafane-Matemane (South Africa), Zhiyi Ma (China), Karla Neves (UK), Hamdi Jama (Australia), Mariane Bertagnolli (Canada) and, Rodrigo Maranon (Argentina). We have been very busy for the past few months, re-shaping the current activities of the MTC and planning new endeavours to bring to everyone the benefits of mentorship and career skills training.

ISH MTC Podcast

Our successful podcast is coming back for a second season starting in October. In our first episode you will have the opportunity to get to know more

Mentorship and Training Committee

Augusto Montezano
Chair / Canada

Zhiyi Ma
China

Lebo Gafane-Matemane
South Africa

Hamdi Jama
Australia

Francine Marques
Australia

Rodrigo Maranon
Argentina

Karla Neves
UK

Mariane Bertagnolli
Canada

about our MTC members and the new podcast hosts! They will share their experiences, and you will not want to miss this episode! In addition, a new roster of exciting guests will join us during the new season! But this is not all, as we will also introduce a new podcast format that will facilitate the discussion of career development hot topics, amplifying shared experiences and opportunities for listeners to learn a trick or two on how to move forward in their scientific careers! The best part is that some of these podcasts will be live recordings, where you will have the opportunity to interact with us and our guests, enriching the exchange and gaining the opportunity to be heard and network with you peers. Stay tuned for our future announcements in the many ISH news outlets!

Thanks to MTC Past Chair – Francine Marques

We also say farewell to our past chair and my co-host of the ISH podcast Associate Professor Francine Marques (Australia). A heartfelt thank you to you Francine! You have been a strong influence on our work and have constantly advocated for a better professional career for all of us. Your work ethic inspires us to be our best every day. The MTC look forward to keeping in touch!

Podcast archive

If you would like to have a blast from the past catch up on our previous episodes.

Mentorship Program

The MTC is also updating our mentorship program and if you have never heard of it, this is what you have been missing out on! In our mentoring web page, you will find a registration link for new mentees and mentors to apply to join the program. Those, interested in enrolling in our program will need to answer a few specific questions related to their needs or expertise, so our team can match a mentee with an international mentor with the objective of fostering a lasting supportive relationship for the mentee's professional growth. We are now working on expanding this program to be an even more dynamic experience where group mentorship and networking will be a focus of our mandate. It is also an ambition of the MTC to create a library of resources for the benefit of our registered ISH mentees. Those registered will be able to access webinar recordings, examples of important documents, masterclasses on transferable career skills, references to interesting

readings/websites/career blogs and this will be a space for interaction. We are so excited to bring this to project to life and work closely with other ISH committees, such as the New Investigator Committee (NIC) and the Women in Hypertension Research (WiHRC) amongst others.

How to find out more about our activities?

Lastly, we will increase our social media and newsletter/e-bulletin presence, working with the ISH communications team, to bring to you a bit more of our "mentoshare" experience. We will create the "ISH Inspire", where researchers will share their experiences in diverse themes related to career development and progress and how they accomplished a milestone or overcame a hurdle; as well as the "ISH Mentoshare Tips", where short questions on different mentorship and career progress/development themes will be asked and different researchers will share their answers/ advice.

We hope you are as excited as we are after reading our MTC report. As you can see, we are very ambitious and to achieve all the above-mentioned, we will need your help! If you feel inspired by our work and want to spread the word regarding the benefits of mentorship in the many shapes described here and be part of the MTC community, please consider joining us by sending an email. The MTC would love to extend our family and increase its representation in the international community of ISH researchers.

Thank you for reading our report and wishing you all the best!

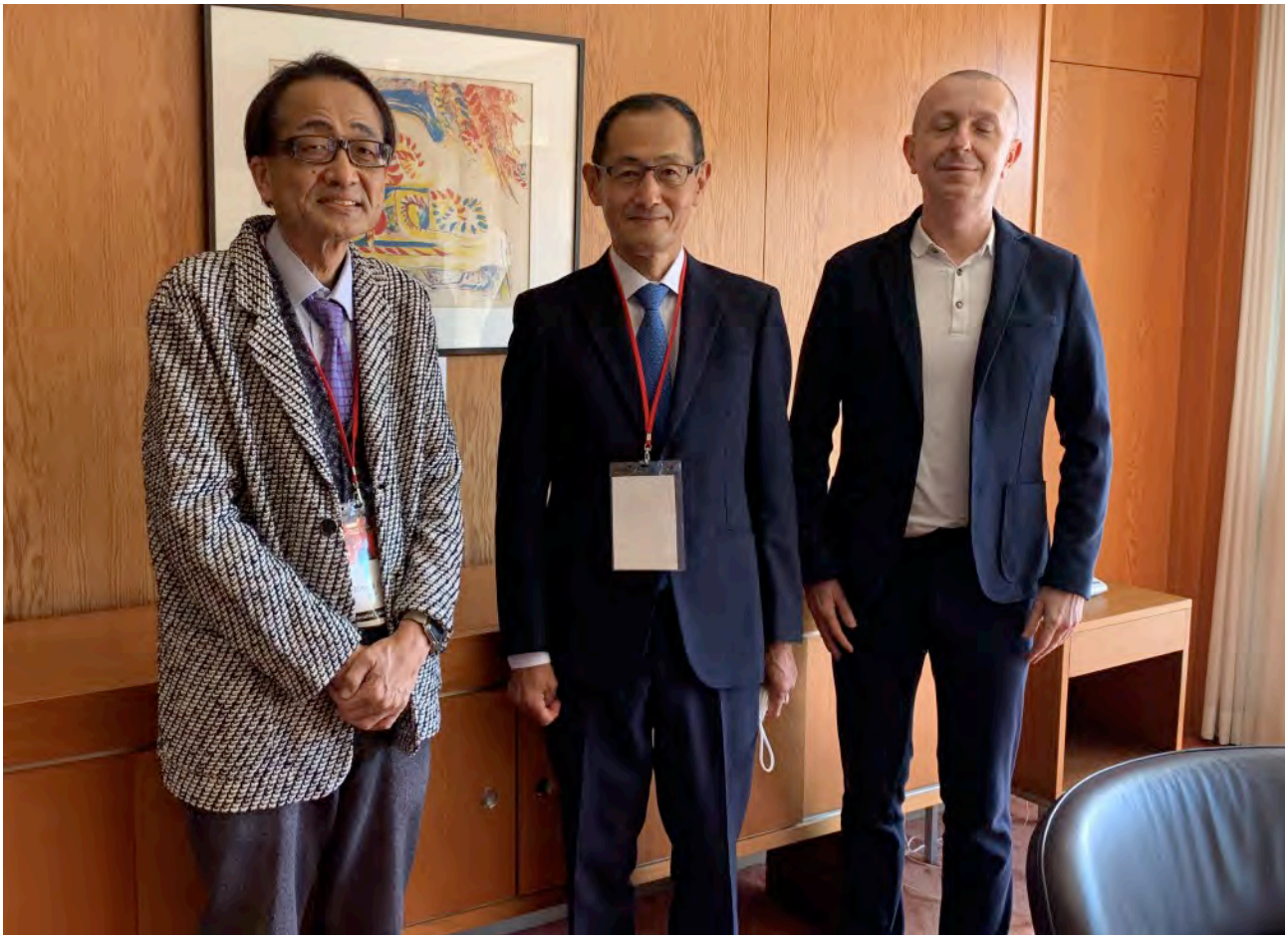
Augusto Montezano - secretariat@ish-world.com

Professor Hiroshi Itoh: a giant of medicine

MACIEJ TOMASZEWSKI
University of Manchester, Manchester, UK
Immediate Past President of International Society of Hypertension

When I received an invitation to contribute to a project commemorating Prof. Hiroshi Itoh's retirement, I was of course delighted. However, at the same time, I was saddened to learn that the International Society of Hypertension (ISH), the Japanese Society of Hypertension, and medicine in general may lose Professor Itoh's full-time contribution to research and clinical initiatives and undertakings.

It is very difficult to reflect upon and recollect all of the many achievements, accomplishments, honours, contributions, publications, awards, and leadership positions of Professor Itoh in one or two pages. He is one of the most recognised faces of cardiovascular, endocrine and metabolic research globally, with his scientific portfolio spanning molecular biology of hypertension,



Professor Hiroshi Itoh - chair of ISH2022 Kyoto with Professor Yamanaka (Nobel Prize winner) and Professor Maciej Tomaszewski (then: ISH President) - picture taken at the time of the 29th Scientific Meeting of the International Society of Hypertension.

atherosclerosis, vascular remodelling, metabolic aging, clinical hypertension, and nephrology. His papers and lectures delivered at international meetings always teach us something new; I am constantly impressed by the way Professor Itoh explains complex molecular biology and connects it with clinical medicine and points to important practical applications. Professor Itoh's discoveries are an inspiration to me and my team here at the University of Manchester – we have spent long hours discussing Professor Itoh's work on NAD supplementation, "greedy organ" hypothesis, and his recent studies on urinary cells. I should stress though that Professor Itoh's work in cardiovascular, endocrine and metabolic medicine and nephrology has been relevant not only to us practicing hypertension, but also - to many others working in disciplines that are not directly associated with hypertension. Indeed, both Professor Itoh and his research are both renowned within and outside of his specialities, and, therefore, he and his research are truly transcendent – something that is very unique within clinical research with its increasing focusing on narrow specialties.

Professor Itoh has made magnificent contributions to the ISH over the years. At the beginning of my ISH presidency (2020-2022), Professor Itoh kindly agreed to take up the position of ISH Vice-President, and the support he showed to me, my Executive Committee, and the Society's mission has been second to none. I vividly remember times and moments when his words of wisdom, support, and advice were instrumental to overcoming major difficulties in the Society and led the ISH to the successful position that it is in today.

Maciej Tomaszewski - pastpresident@ish-world.com

Professor Itoh was an outstanding chair for both the ISH2022 Kyoto Biennial Meeting and the ISH2022 Kyoto Programme Committee. Leading the Local Organising Committee, he has worked, under the most difficult circumstances of COVID-19 and immediate post COVID-19 realities with grace, dedication, and passion to ensure ISH2022 Kyoto became a truly outstanding congress. It would be impossible to list the many highlights of ISH2022 Kyoto within the space constraints of this contribution. To me personally, Professor Itoh's Chairman's speech illuminated the early origins of hypertension, the Opening Ceremony graced by the presence of their Imperial Highnesses Crown Prince and Crown Princess Akishino, as well as many inspirational figures of Japanese science invited by Professor Itoh (including Nobel Laureate Professor Shinya Yamanaka – here pictured with Professor Itoh prior the plenary lecture in Kyoto) along with the very special hospitality will stay in my memory forever.

I remain inspired by Professor Itoh's diversity of passions, both within and outside of science and medicine. Professor Itoh is an artist whose beautiful paintings have graced ISH publications and have also inspired attendees of ISH2022 Kyoto. He is truly a man of many talents and interests, and we are very fortunate that he has been sharing those with us over the years.

I am privileged to be able to continue to see and interact with Professor Itoh over the next two years, during the ISH Executive Committee meetings under the new ISH presidency (Professor Itoh has very kindly agreed to remain in post as ISH Vice-President). I am also confident that that those who have benefitted from Professor Itoh's wisdom including his colleagues, students, and patients will continue to be educated, inspired and nurtured by his wisdom long after his retirement.

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)

Myeong-Chan Cho
(South Korea)

Tazeen Jafar
(Singapore)

Kazuomi Kario
(Japan)

Prabhakaran Dorairaj
(India)

Cesar Romero
(USA)

Ulrike (Muscha) Steckelings
(Denmark/Germany)

Augustine Odlili
(Co-opted Council Attendee, Nigeria)

ISH CORPORATE MEMBERS

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