HYPERTENSION NEWS

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Air pollution and hypertension

The need to improve air quality to improve cardiovascular health

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INTRODUCTION FROM THE PRESIDENT

BRYAN WILLIAMS
President, International Society of Hypertension

This will be my last introductory piece for *Hypertension News* as President of the ISH. My two-year term as President will soon come to an end at the close of our ISH Congress in Cartagena Colombia in September. Time really does fly by and it is at times like this one reflects on what we have achieved as a leadership team of the ISH during my term as President. Firstly, I have had the advantage of working with some wonderfully committed and supportive people as part of our Executive committee and wider Council. I was also fortunate to have been secretary of ISH during the presidency of my predecessor, Maciej Tomaszewski. He took over the Society leadership at a challenging time for us all, in the midst of the Covid Pandemic. We set about rebooting and modernising the ISH. Reflecting the fact that the way academic clinical societies are supported and function had to change or risk becoming irrelevant in a fast-changing world. Much of this early work is unglamorous and happens behind the scenes but is important. A key issue for me has always been robust governance and clarity of purpose. One of the early challenges was recognising that our constitution and Charity status was out of date with modern requirements. We had to rewrite our constitution to be compatible with ISH becoming an incorporated Charity by the Charity commission. This kind of thing sounds dull. It was dull and tedious but vital to limit the future liabilities of the ISH and its officers. This process began during Maciej's Presidency and has now been completed during my term.

It was also important to modernise and professionalise our communications and extend its reach into multiple Platforms. Our appointment of Matt Chorley, a media and communications professional, that I had worked with in my role as Director of the Biomedical Research Centre at University College London (UCL) Hospitals and UCL, was an inspired move. It has transformed our web presence, social media outputs and rapid professional response to media enquiries. I also wanted to bring *Hypertension News* back into the heart of the ISH as the centre piece of the ISH outputs. I hope you will agree, *Hypertension News* has been transformed and is an outstanding source of contemporary information about global research and clinical activities in hypertension. That transformation is in large part down to the work of Matt and Helen, supported by our Executive committee and the many authors who have been remarkable in supporting *Hypertension News* with their expert articles and viewpoints. In addition, our monthly ISH e-bulletin serves a different function to Hypertension News, but an equally important one, by providing up to the minute news about ISH activities, as well as events and happenings in hypertension and the work of our partner societies across the world.

To improve our communications with the membership and our membership portal, we also sourced a new provider for our web presence and we were delighted to appoint Canica from Argentina who have professionalised our web presence including the membership portal, but this is just a start and there will be so much more to come. A major impetus to improve our web presence was to refresh our membership. This has been a major mission I set for the ISH. This presented a number of challenges, not least, the complexity of our previous membership tiers and cost of membership, which was prohibitive for many potential members in lower income regions of the world. This meant they were not able to join our global society and benefit from the outputs of the ISH and the opportunity to interact with the wider ISH community. As an International Society, I

concluded the model was flawed. We had to allow people interested in hypertension, from wherever they reside, to become members. So, under the expert leadership of Débora Colombari from Brazil, we have transformed our membership fee structure. This also includes a new category of Associate Membership, that is free and allows anybody with an interest in hypertension, including patients and the public, to join the ISH, from wherever they are in the world. Our Member category does involve a fee for some countries but a lower fee than before and this category of membership is free currently for those based in Ecuador, Sudan and Ukraine and trainees, and allows our Members to be actively involved the Society and stand for office and vote for officers and in various constitutional matters. The purpose is simple, to enable anybody with an interest in hypertension to join the ISH. The mission is for the ISH to become the largest hypertension society in the world, which it should be as a global Society. At the outset of my Presidency, I set the Society a goal to achieve this ambition and we are well on our way, with over 500 new members joining since we launched the new membership portal in April this year. There is no reason why this shouldn't grow to many thousands in the years to come.

Another key mission I outlined in my aims as President was to play a much greater role in on-line global education for hypertension. Producing high quality, trusted and respected educational outputs on all aspects of hypertension at different levels, from basic knowledge to specialist insights. This has been superbly led by Erika Jones from South Africa, and her team. We have built this from scratch and having reviewed some of the early production, I am confident this will be a terrific resource for our membership. It is only the beginning and we will need to continue to support this in the years to come. It is possible that this could eventually be used for credentialing of expertise in Hypertension clinical practice and will also be an excellent platform for future symposia.

A third mission was to build on the excellent position paper initiative started under Maciej's Presidency and develop specialist focus groups from the ISH membership, to generate detailed outputs on contemporary topics of interest. The outstanding ISH position paper on Lifestyle interventions for hypertension, expertly led by Fadi Charchar from Australia, the ISH Treasurer, was published in 2023. Another excellent position paper on "innovations in blood pressure measurement" led by Kazu Kario from Japan will soon be published in the Journal of Hypertension. These are examples of how our global membership community can work together to generate high quality and impactful research outputs of immediate relevance to clinical practice.

A fourth mission was something I am personally passionate about, notably "empowering our patients" to improve the detection and treatment of hypertension. Despite endless numbers of guidelines across the world, some of which I have had the privilege to lead and/or contribute to, we have to concede, that guidelines have not worked. By that I mean, they haven't worked in dramatically improving the poor detection, treatment and control rates for hypertension, which have remained stubbornly and depressingly poor in many countries, including those with well developed health care systems. They have of course worked in boosting citations and as centre pieces of scientific congresses but surely that cannot be their principal purpose. I am not sure we need any more of the conventional guideline outputs which have been largely targeted at health care professionals and have had too little focus on implementation and patients. So, we need to produce an output for patients, that explains to patients why controlling blood pressure is so important, what should be happening to them if they are suspected of having hypertension, what their doctor or health care professional should be doing to assess the severity and impact of their blood pressure, what treatment they should be receiving as optimal therapy and what good blood pressure control looks like. Empowering patients in this way will give them more control over their treatment, will help overcome clinical inertia, should improve adherence to treatment, and shift the epicentre of control of blood pressure to a patient-centred partnership. The opportunities afforded by digital and remote technology, data science and AI and better patient engagement, provide an outstanding opportunity to empower

our patients to improve the treatment of blood pressure through new systems and models of care. Under my leadership, the ISH is leading a programme of work in this area, which will soon generate a different type of guideline, a guideline for patients, that can be adapted to local treatment capabilities across the world.

There are many other aspects of the work of the ISH we have modernised. We established a new Hypertension awards committee which is Chaired by the ISH secretary and involves adjudication of our awards by all members of the ISH Council. We have new leadership of many of our committees and regional advisory groups which has invigorated their work and I am deeply grateful to all of them.

A key function of the ISH leadership is oversight of the biennial ISH congress. I took over as President at the end of the last ISH Congress in Kyoto in October 2022. During the past 2 years, we have completed the expressions of interest process and awarded the 2026 ISH Congress to Dubai, which is another new venue for the ISH Congress. Alongside and foremost in our minds has been the development of the forthcoming ISH congress in Cartagena, Colombia, in September. Those who have participated in the leadership, development and hosting of a major congress will know what a major undertaking this is and the huge amount of work it involves. This has been a thread that has been at the forefront of all of our efforts throughout my Presidency but we are all especially indebted to the incredible devotion and hard work of Dagnovar Aristizabal the Executive President of the ISH Congress 2024 and Cesar Romero the programme Chair. It promises to be an outstanding meeting in a wonderful location and I look forward to seeing many of you there. It is at the end of that meeting that we will also launch the Cartagena Declaration encouraging the world to focus on improving medication adherence as a key unmet need for the better control of blood pressure world-wide.

Sadly, two longstanding friends and colleagues, George Bakris and Henry Black, of huge influence on me and many in the field of hypertension, will not be with us in Cartagena. I had great affection for them both and their recent deaths will be felt by many as a huge loss to us all in the global hypertension community. We have included heartfelt obituaries in this issue of *Hypertension News* and send our condolences to their family and friends. May they rest in peace.

Finally, it has been an honour to serve as President of the ISH. In so doing, my overarching ambition was to modernise the ISH and make the ISH more representative of, and accessible to, the global hypertension community, and leave the Society in a stronger position than when I started. Others will judge whether that has been achieved. I couldn't have achieved anything without the dedication and support of the ISH senior officers, my executive committee colleagues, our Council, the many leaders and members of our various committees, the impressive work of Matt Chorley in communications and the outstanding support and institutional memory of our executive assistant Helen Horsfield. I am also fortunate that at the close of the Cartagena meeting, I will be able to hand over the reins to our next President George Stergiou, who I have worked closely with as ISH Secretary for the past two years and will continue to support as Immediate Past President for the next two years. In closing, a special mention to three senior ISH officers and executive committee members who have served the ISH with distinction and dedication for at least 8 years and who will leave the council in September; Maciej Tomaszewski (Past President), Fadi Charchar (Treasurer) and Nadia Khan (Officer at Large). From us all, thank you.

Bryan Williams - president@ish-world.com

OBITUARIES

Professor George Bakris

We are hugely saddened to hear of the death of our friend and colleague Professor George Bakris.

George was a superb clinician, investigator and communicator. He was a true giant in cardiovascular medicine at a global level.

George leaves a remarkable legacy in research and patient care. He published prodigiously in hypertension and kidney disease, played a huge role in guideline and policy development, and was an outstanding leader while at the helm of societies including the American Society of Hypertension and the American Society of Nephrology.

George supported and inspired many scientists around the world. He was able to convey the excitement of research in hypertension and nephrology to younger scientists, and spurred them on with his enthusiasm and passion for his work.

He was known to many of us connected with the ISH – not only as a brilliant scientist, but as a close friend, and someone who was always enjoyable to spend time with.

His death is a huge loss for the international medical community and for all of us.

We would like to express our sincere condolences to George's family and loved ones, and everyone who knew him.

We have lost one of the greats, and we will miss him.

Prof. Bryan Williams
ISH President

Prof. George Stergiou
ISH Secretary and President-Elect

Professor Henry Black

The ISH was very saddened to hear of the death of Professor Henry Black. Professor Black was a significant figure in the field of hypertension, publishing almost 400 papers and authoring several textbooks on hypertension. He was formerly President of the American Society of Hypertension, and was known for the time he dedicated to mentorship of students in the field.

Read an online obituary of Professor Black.

FROM THE NEWS DESK

Addressing social determinants of health could reduce racial disparities in hypertension

Addressing social determinants of health could reduce racial disparities in hypertension and reduce excess cardiovascular disease among Black adults, researchers in a new study have concluded.

A research team from the United States looked at the association between social determinants of health - such as education and income levels - and incident apparent treatment-resistant hypertension (aTRH).

The team analysed data from 2774 White and 2257 Black adults taking antihypertensive medication from across the US. Participants were from a study called REGARDS (Reasons for Geographic and Racial Differences in Stroke).

Over a median follow up of 9.5 years, 24% of Black adults, compared with 15.9% of White adults, developed incident apparent treatment-resistant hypertension.

The research team found that social determinants of health contributed to a higher risk of incident aTRH among Black compared with White adults.

Social determinants of health included lower education levels, lower income, not seeing a friend or relative in the past month, lack of health insurance, living in a disadvantaged neighbourhood, and a lack of public health infrastructure.

Authors of the paper, published in the Journal of the American Heart Association, noted examples of interventions addressing social determinants of health that have successfully improved BP control among Black adults: for example, team-based care delivered at barbershops serving mainly low-income Black men has been linked with a decrease in systolic blood pressure.

Read the full paper:

Akinyelure, O. P., Jaeger, B. C., Safford, M. M., Oparil, S., Carson, A. P., Sims, A., Hannon, L., Howard, G., Muntner, P., & Hardy, S. T. (2024). Social Determinants of Health and Incident Apparent Treatment-Resistant Hypertension among White and Black US adults: the REGARDS Study. Journal of the American Heart Association. Cardiovascular and Cerebrovascular Disease. https://doi.org/10.1161/jaha.123.031695

Using real-world data to identify effective hypertension drugs

A team in the United States will use data routinely collected in health care settings to identify the most effective hypertension drugs.

Researchers from Yale University will analyze data from more than 100 million patients held in five electronic health record databases in the US to compare the effectiveness of second antihypertensive drugs on major cardiovascular events, as well as their comparative risk on potential drug-related adverse events.

The project – 'Real-World Evidence to Inform Decisions for Hypertension Treatment Escalation' - will also look at the effectiveness and safety of each second antihypertensive agent in different patient subgroups based on age, sex, race, ethnicity and comorbidities – with the aim of addressing disparities for patients with hypertension.

The team said it is the first study of its kind using real-world data and reproducible methods to comprehensively evaluate the safety and effectiveness of second anti-hypertensive drugs added after monotherapy.

Yuan Lu, ScD, assistant professor of medicine (cardiology) and assistant professor of biomedical informatics and data science and of epidemiology (chronic disease) at Yale, recently received funding from the National Institutes of Health in the US for the project.

In a news release from Yale School of Medicine, she said: "The question is: when the first drug is not enough, what is the optimal second drug to add?

"There are more than 50 drugs across five major classes available for treating hypertension. Conducting clinical trials to compare every possible drug and combination thereof is impractical; it would be incredibly time-consuming and costly."

Lu said her team would combine the power of computing, data science and clinical knowledge to generate new evidence around effective antihypertensive treatment.

"We hope our research will inform the prioritization of future clinical trials, assisting investigators in selecting the most promising drug combinations for testing," she said.

The team also hopes the research will inform the development of clinical guidelines.

Eventually, the team plan to develop a clinical decision support tool that would incorporate the knowledge gained from their project. The tool would help doctors quickly and easily see recommendations about the types of combination therapies that may work best for their individual patients.

Visit the Yale website to find out more: https://medicine.yale.edu/news-article/research-real-world-data-effective-hypertension-drugs/

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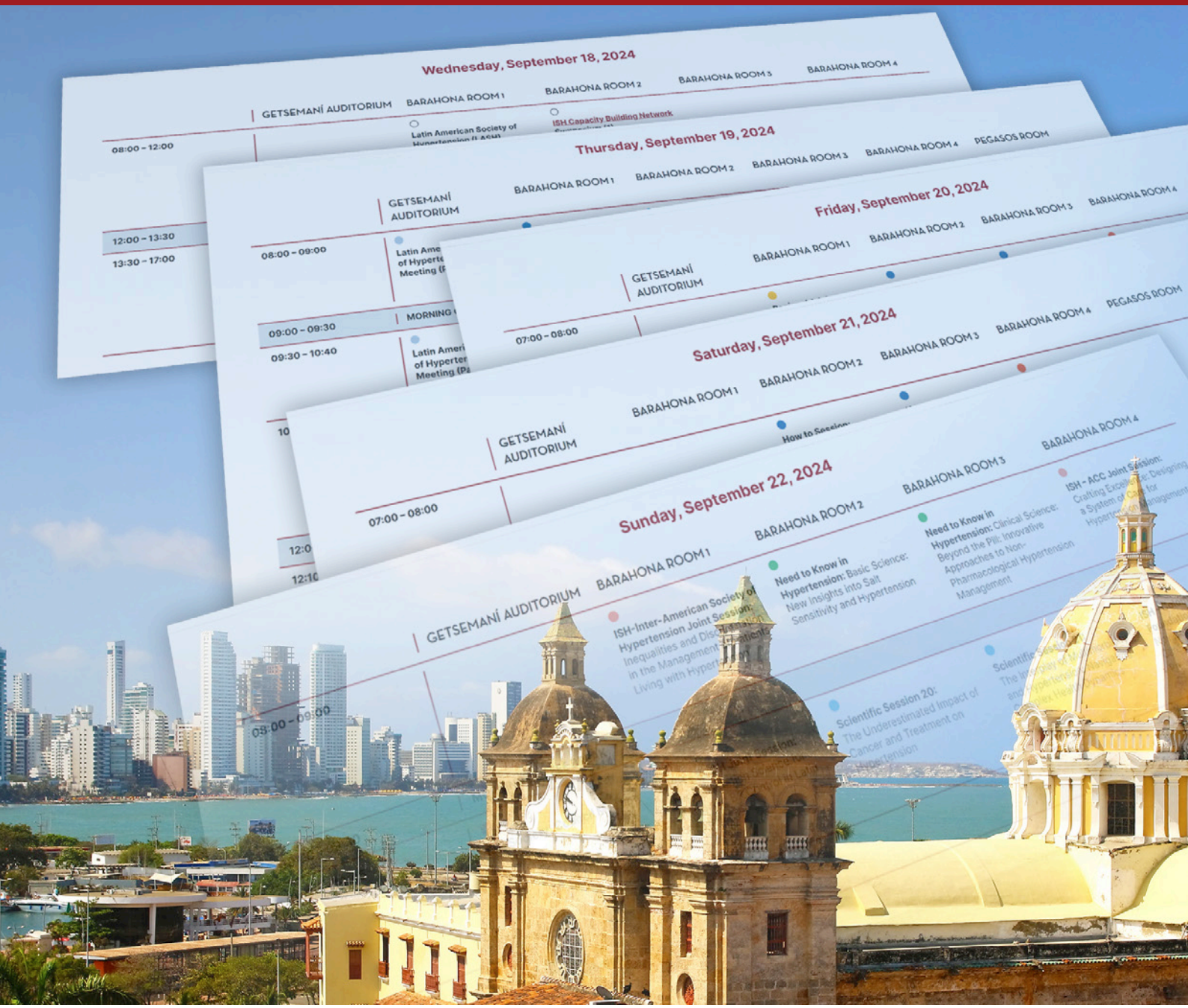

PERSPECTIVES IN HYPERTENSION

Nighttime blood pressure measurement: Why, what, and how?

GEORGE STERGIOU AND ANASTASIOS KOLLIAS

Hypertension Center STRIDE-7, National and Kapodistrian University of Athens, School of Medicine, Third Department of Medicine, Sotiria Hospital, Athens, Greece

The "non-dipper" and "night-time blood pressure" concepts

In 1988, Eoin O'Brien introduced the concept of non-dippers.[1] At that time, he highlighted than non-dippers "may be at higher risk of cerebrovascular complications" and that "we need to determine the prognostic and therapeutic implications of this finding".[1] In 1999, Jan Staessen et al. reported results from the Systolic Hypertension in Europe (Syst-Eur) trial and showed that an increase in night-to-day systolic ambulatory blood pressure (ABP) ratio was associated with increased risk of cardiovascular disease (CVD) endpoints independently of average 24h ABP.[2]

Outcome studies showed nighttime blood pressure (BP) to be the most important aspect of the BP profile.[3,4] In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study in Italy,[3] nighttime systolic ABP presented the strongest association with the risk of total mortality, compared to office, home, and daytime ABP. In the same line, a recent analysis of the Spanish ABP registry including 59,124 patients followed for an average of 9.7 years showed nighttime BP to be more closely associated with all-cause and CVD mortality than office, daytime, or 24h ABP.[4] Interestingly, even isolated nighttime hypertension (normal office and daytime ABP) appears to predict independently CVD outcome.[5]

Today we know that the non-dipping pattern is much more common - and probably more important - in high-risk patients, e.g., patients with diabetes, chronic kidney disease, CVD, etc.[6] However, it is amazing that 36 years after the landmark observation by Eoin O'Brien, we confirmed his finding regarding the prognostic relevance of non-dipping, but we are still uncertain about its pathophysiology[7] and in answering the important question he posed regarding its therapeutic implications.[1]

Non-dipping versus night-time hypertension

As discussed above, both non-dipping and nighttime hypertension are associated with an adverse CVD prognosis. However, the relative prognostic contribution of each of these nocturnal BP phenotypes remains uncertain. In general, the evidence on the prognostic role of nighttime hypertension appears to be more consistent than of the dipping status.[8] Several studies have shown that the prognostic ability of the non-dipping pattern is attenuated or even lost if adjusted for the average nighttime BP levels. Non-dipping depends on daytime BP and presents only moderate reproducibility.[8] Moreover, the prognostic value of the dipping status depends on the population characteristics, i.e. a U-shaped relationship between nocturnal dipping and adverse outcome is present in individuals older than 70 years.[9] The recent Japan ABP Monitoring Prospective (JAMP) study showed that higher nighttime systolic BP was associated with higher CVD risk than the dipping status.[10] However, for endpoints such as coronary artery disease and

heart failure, the risk was highest in individuals with a riser pattern and higher nighttime systolic ABP.[10] Data from the Spanish ABP monitoring registry also showed higher CVD mortality hazard ratios with abnormal nighttime systolic BP than with abnormal dipping, but highest when both abnormalities were present.[11]

Non-dipping and night-time BP assessed by home monitors

ABP monitoring is the reference method for the evaluation of the nighttime BP and dipping. In the last few years, low-cost devices for self-home BP monitoring have been developed, allowing automated nighttime BP measurements during sleep.[12] Studies comparing with reference nighttime ABP monitoring suggested that nighttime home BP monitoring is feasible, and these methods present similar BP values, have reasonable agreement in detecting nighttime hypertension and non-dipping, as well as comparable relationship with indices of preclinical organ damage.[13] More importantly, recent prospective outcome data in Japan showed that nighttime systolic BP and uncontrolled nighttime hypertension detected by home monitors independently predict CVD.[14,15] A different schedule for nighttime BP evaluation is used by home monitors, and 3 hourly measurements per night for 3 consequent nights appears to be the minimum reliable schedule.[16]

What for now and in the future

Undoubtfully, nighttime hypertension and non-dipping are important for prognosis. Why nighttime BP is so important is not clear. Maybe the daytime measurements are polluted by variability in behaviour, mental and physical activity, whereas nighttime BP, despite obtaining fewer measurements, is standardised in terms of body position and activity, revealing thereby the true BP level of the individual.

However, the evaluation of nighttime hypertension and the dipping pattern in individual patients in clinical practice is problematic. First, the availability of devices for nighttime BP monitoring (ABP or home monitors) is limited. Second, the reproducibility of these diagnoses is far from perfect, and more than a single 24h ABP recording is required. Third, there is no evidence that targeting nighttime BP with bedtime dosing of drugs would be beneficial in improving prognosis.[6]

At the present time elevated nighttime BP should alarm the clinician to consider (i) poor sleep quality, (ii) obstructive sleep apnea, (iii) uncontrolled 24h BP, (iv) increased CVD risk. Although the diagnostic and prognostic consequences of this information are clear, its therapeutic implications for clinical practice remain uncertain. A reasonable consensus at the present time might be that optimal control of BP should be achieved, which can be best assessed by employing complementary measurement methods, in the office, at home and with 24h ABP monitoring.

In the future, if and when accurate cuffless wearable BP monitors become available, they are expected to obtain 24h BP information for days, weeks or months, providing thereby complete and accurate information on the individual's BP profile and behaviour. Moreover, prospective outcome studies in patients with nocturnal hypertension and/or non-dipping are needed to verify whether targeting selectively nighttime BP can improve prognosis further to standard care.

References

1. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. Lancet. 1988;2(8607):397.

2. Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. JAMA. 1999;282:539-46.

3. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation. 2005;111:1777-83.

4. Staplin N, de la Sierra A, Ruilope LM, et al. Relationship between clinic and ambulatory blood pressure and mortality: an observational cohort study in 59 124 patients. Lancet. 2023;401:2041-50.

5. Fan HQ, Li Y, Thijs L, et al; International Database on Ambulatory Blood Pressure In Relation to Cardiovascular Outcomes Investigators. Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. J Hypertens. 2010;28:2036-45

6. Stergiou G, Brunström M, MacDonald T, et al. Bedtime dosing of antihypertensive medications: systematic review and consensus statement: International Society of Hypertension Position Paper. J Hypertens. 2022;40:1847-58

7. Huart J, Persu A, Lengelé JP, et al. Pathophysiology of the nondipping blood pressure pattern. Hypertension 2023;80:719-29.

8. Tang A, Yang E, Ebinger JE. Non-dipping blood pressure or nocturnal hypertension: does one matter more? Curr Hypertens Rep. 2024;26:21-30.

9. Palatini P, Verdecchia P, Beilin LJ, et al. Association of extreme nocturnal dipping with cardiovascular events strongly depends on age. Hypertension. 2020;75:324-30.

10. Kario K, Hoshide S, Mizuno H, et al; JAMP study group. Nighttime blood pressure phenotype and cardiovascular prognosis: practitioner-based nationwide JAMP Study. Circulation. 2020;142:1810-20.

11. de la Sierra A, Staplin N, Ruilope LM, et al. A blunted nocturnal blood pressure decline is associated with all-cause and cardiovascular mortality. J Hypertens. 2024;42:1197-202.

12. Asayama K, Fujiwara T, Hoshide S, et al. International Expert Group of Nocturnal Home Blood Pressure. Nocturnal blood pressure measured by home devices: evidence and perspective for clinical application. J Hypertens. 2019;37:905-16.

13. Kollias A, Ntineri A, Stergiou GS. Association of night-time home blood pressure with night-time ambulatory blood pressure and target-organ damage: a systematic review and meta-analysis. J Hypertens. 2017;35:442-52.

14. Mokwatsi GG, Hoshide S, Kanegae H, et al. Direct comparison of home versus ambulatory defined nocturnal hypertension for predicting cardiovascular events: The Japan Morning Surge-Home Blood Pressure (J-HOP) Study. Hypertension. 2020;76:554-61.

15. Tabara Y, Matsumoto T, Murase K, et al. Sleep blood pressure measured using a home blood pressure monitor was independently associated with cardiovascular disease incidence: the Nagahama study. J Hypertens. 2024. Online ahead of print.

16. Kollias A, Andreadis E, Agaliotis G, et al. The optimal night-time home blood pressure monitoring schedule: agreement with ambulatory blood pressure and association with organ damage. J Hypertens. 2018;36:243-49.

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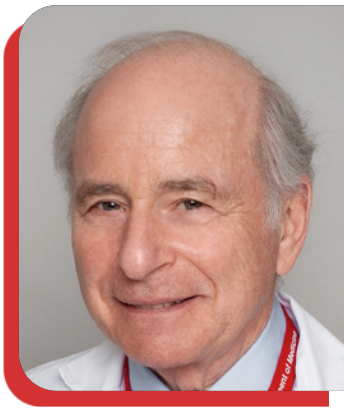
PERSPECTIVES IN HYPERTENSION

Immunological insights into hypertension



ERNESTO SCHIFFRIN

Director, Hypertension and Vascular Research Unit,
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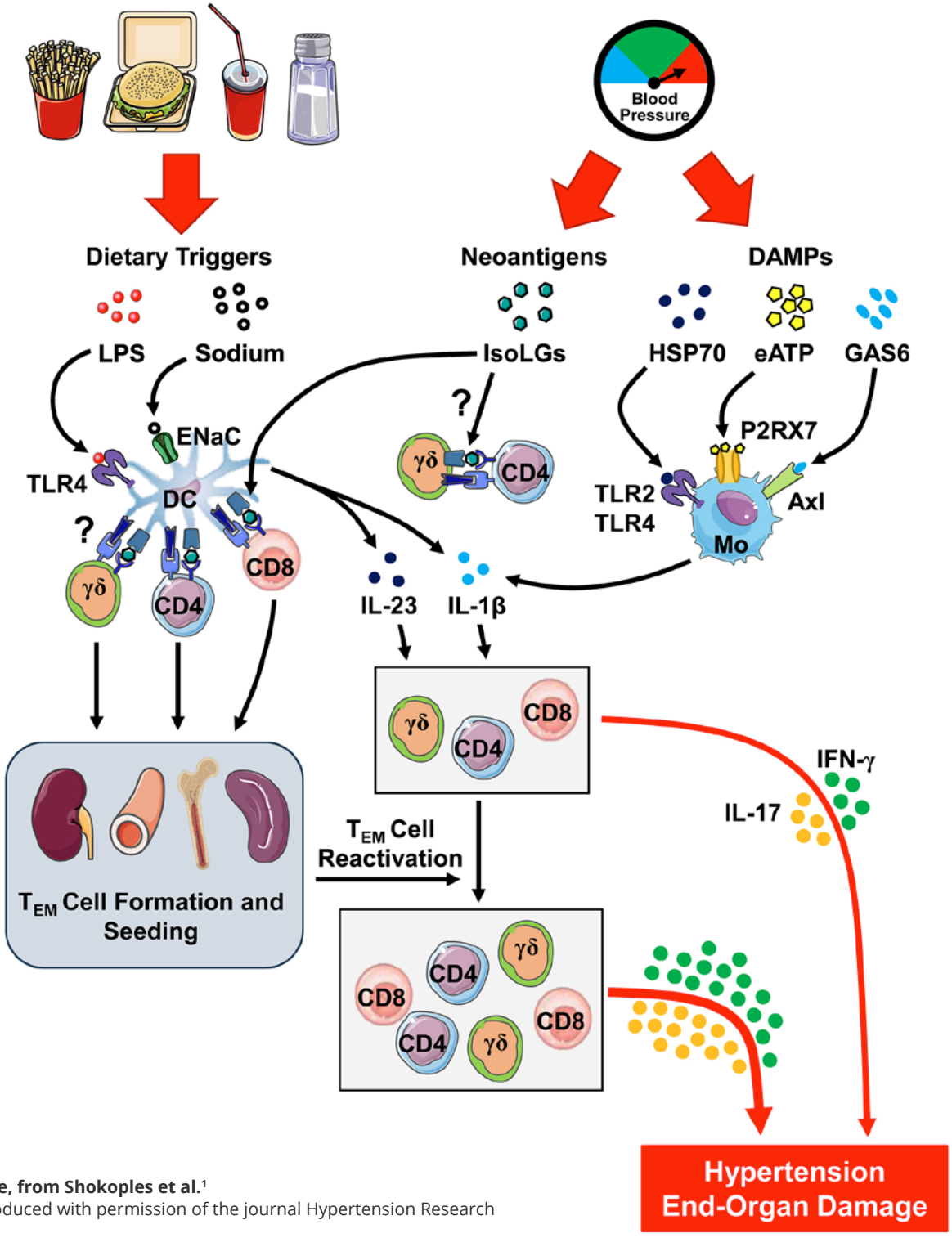
The first author of the paper "Immunological insights into hypertension: unraveling triggers and potential therapeutic avenues",[1] was Brandon Shokoples. Brandon recently obtained his PhD at McGill University working in my lab, and is now an MD student in Calgary, AB, Canada. The manuscript was commissioned as part of the Japanese Society of Hypertension (JSH) 14th Hypertension Research Award, which was awarded for the paper Shokoples B. et al Hypertension Res. 2023; 46(1):40-49.[2]

Hypertension remains the leading cause of morbidity and mortality worldwide. Despite its prevalence, the development of novel antihypertensive therapies has only recently picked up, with a number of novel agents which are not yet available commercially. This, despite the fact that a substantial proportion of individuals do not respond or are non-adherent to existing treatments.

In this paper,[1] we reviewed some of the history of the immune hypothesis of hypertension and its mechanisms, as well as the potential for novel immune treatments of the "silent killer". Although several investigators noted the presence of abundant immune cells around blood vessels in different target tissues in experimental hypertension, it was not until 2002-2005 that we identified for the first time the involvement of the innate immune system and specific immune cells, macrophages/monocytes, in angiotensin II-induced hypertension,[3,4] and 2007, that David Harrison's group showed the role of adaptive immunity and T cells in similar models of hypertension.[5]

Since then, an increasingly abundant literature has demonstrated that chronic low-grade inflammation participates to an important degree in the triggering and sustained elevation of blood pressure in both experimental animals and in humans.[6] Salt and pathogen-associated as well as damage-associated molecular patterns (PAMPs and DAMPs) play roles in activating the immune system. Diets rich in fat or sodium promote inflammation by favoring passage of toxins and bacteria through the intestinal barrier and by triggering salt-sensitive receptors in dendritic cells and T cells. DAMPs, such as extracellular adenosine triphosphate and heat-shock protein (HSP) 70 released secondary to tissue injury during episodes of increased blood pressure, contribute to immune cell activation and inflammation. We have shown how unconventional lymphocytes such as the innate-like γδ T cells participate in the initiation and maintenance of an immune response through involvement in experimental and human hypertension in antigen presentation and regulating cytokine-mediated responses.[7,8] Immunological memory resulting from generation of effector memory T cells after exposure to hypertensive insults maintains the immune response in hypertension.[9] These memory cells can be activated, and then participate in the mechanisms of elevated blood pressure and target organ damage. Recent evidence from human hypertension agrees with distinct immune pathways in human hypertension,[10] creating an opportunity for targeted immune interventions. Reduction in anti-inflammatory T regulatory lymphocytes (Treg) may favor the persistent state of low grade inflammation.[11-14] Small elevations of blood pressure induced by salt in susceptible individuals lead to

microbiome-dependent intestinal wall immune cell activation and through microbiome-derived short chain fatty acids to hemodynamic changes and endothelial and kidney damage, generation of neoantigens and DAMPs, and together with other insults such as lipopolysaccharides (LPS), sodium, heat-shock protein (HSP)70, extracellular adenosine triphosphate (ATP), and growth arrest-specific 6 (GAS6), activate the innate immune system, including dendritic cells (DCs) and monocytes through their respective receptors (toll-like receptor [TLR]4, amiloride-sensitive epithelial sodium channel, TLR2/4, P2X7 receptor [P2RX7],[15] and Axl). This leads to costimulatory



Figure, from Shokoples et al.[1]
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molecule expression and interleukin (IL)-1β and IL-23 production.[2] The neoantigens HSP70 and isolevuglandins[16] generated within antigen presenting cells activate T effector cells by DCs and possibly γδ T cells, resulting in production of cytokines IL-17[17] and interferon (IFN)-γ,[2] and formation of T effector memory (T_{EM}) cells in the kidney, perivascular adipose tissue, bone marrow, and spleen. Exposure of T_{EM} cells to their cognate antigen or previous activating stimuli causes these cells' rapid expansion and activation. This inflammatory condition thus contributes to blood pressure elevation and target organ injury. The process of activation of the immune system and target organ damage is depicted in the figure. Target organ injury feeds back into immune activation leading to further tissue injury and blood pressure elevation.

References

1. Shokoples BG, Paradis P, Schiffrin EL. Immunological Insights into Hypertension: Unraveling Triggers and Potential Therapeutic Avenues. Immunological insights into hypertension: unraveling triggers and potential therapeutic avenues. Hypertens Res. 2024; doi:10.1038/s41440-024-01731-6.

2. Shokoples BG, Comeau K, Higaki A, Ferreira NS, Caillon A, Berillo O, Oukka M, Paradis P, Schiffrin EL. Angiotensin II induced a steeper blood pressure elevation in IL-23 receptor-deficient mice: Role of interferon-γγ-producing T cells. Hypertension Res. 2023; 46(1):40 49.

3. Tostes R, Touyz RM, He G, Chen X, Schiffrin EL. Contribution of endothelin-1 to renal activator protein-I activation and macrophage infiltration in aldosterone-induced hypertension. Clin Sci 2002;103(Suppl 48):25S-30S. DOI: 10.1042/CS103S025S.

4. De Ciuceis C, Amiri F, Brassard P, Endemann DH, Touyz RM, Schiffrin EL. Reduced vascular remodeling, endothelial dysfunction and oxidative stress in resistance arteries of angiotensin II-infused macrophage colony-stimulating factor-deficient mice: evidence for a role in inflammation in angiotensin-induced vascular injury. Arterioscl Thromb Vasc Biol 2005;25:2106-2113.

5. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, Goronzy J, Weyand C, Harrison DG. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J Exp Med. 2007;204:2449-2460.

6. Caillon A, Paradis P, Schiffrin EL. Role of immune cells in hypertension. Brit J Pharmacol. 2019;176:1818-1828.

7. Caillon A, Mian MOR, Fraulob Aquino JC, Huo K G, Barhoumi T, Ouerd S, Sinnaeve PR, Paradis P, Schiffrin EL. Gamma Delta T Cells Mediate Angiotensin II-Induced Hypertension and Vascular Injury. Circulation. 2017;135:2155 2162.

8. Berillo O, Comeau K, Caillon A, Leclerc S, Shokoples BG, Mahmoud AUM, Andelfinger G, Paradis P, Schiffrin EL. Similar CD28 expressing δ T cell subtypes in perivascular tissue of angiotensin II-infused male mice and subcutaneous tissue of obese humans. J Hypertens. 2024;42:1256 1268. Comeau

9. Comeau K, Shokoples BG, Caillon A, Paradis P, Schiffrin EL. Angiotensin II-induced memory gamma/delta T cells sensitize mice to a mild hypertensive stimulus. Amer J Hypertens. 2023;36:619–628.

10. Schiffrin EL. Regarding immune mechanisms driving hypertension in REGARDS. Invited Editorial. Hypertension. 2024;81:1254–1256.

11. Viel EC, Lemarié CA, Benkirane K, Paradis P, Schiffrin EL. Immune regulation and vascular inflammation in genetic hypertension. Amer J Physiol Heart Circ Physiol. 2010;298:H938-H944.

12. Barhoumi T, Kasal DAB, Li MW, Shbat L, Laurant P, Fritsch Neves M, Paradis P, Schiffrin EL. T regulatory lymphocytes prevent angiotensin II-induced hypertension and vascular injury. Hypertension. 2011;57: 469-476.

13. Kasal DAB, Barhoumi T, Li MW, Fritsch Neves M, Laurant P, Paradis P, Schiffrin EL. T regulatory lymphocytes prevent aldosterone-induced vascular injury. Hypertension 2012;59:324-330.

14. Mian MOR, Barhoumi T, Briet M, Paradis P, Schiffrin EL. Deficiency of T regulatory cells exaggerates angiotensin II-induced microvascular injury by enhancing immune responses. J Hypertens 2016, 34:97–108.

15. Shokoples BG, Berillo O, Comeau K, Chen YH, Higaki A, Caillon A, Ferreira NS, Engert, JC, Thanassoulis G, Paradis P, Schiffrin EL. P2RX7 gene knockout or antagonism reduces angiotensin II-induced hypertension, vascular injury and immune cell activation. J Hypertens. 2023;41:1701–1712.

16. Elijovich F, Laffer CL, Sahinoz M, Pitzer A, Ferguson JF, Kirabo A. The Gut Microbiome, Inflammation, and Salt-Sensitive Hypertension. Curr Hypertens Rep. 2020;22:79. doi: 10.1007/s11906-020-01091-9.

17. Dixon KB, Davies SS, Kirabo A. Dendritic cells and isolevuglandins in immunity, inflammation, and hypertension. Am J Physiol Heart Circ Physiol. 2017;312:H368-H374.

18. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik TJ, Harrison DG. Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. Hypertension. 2010;55:500-507.

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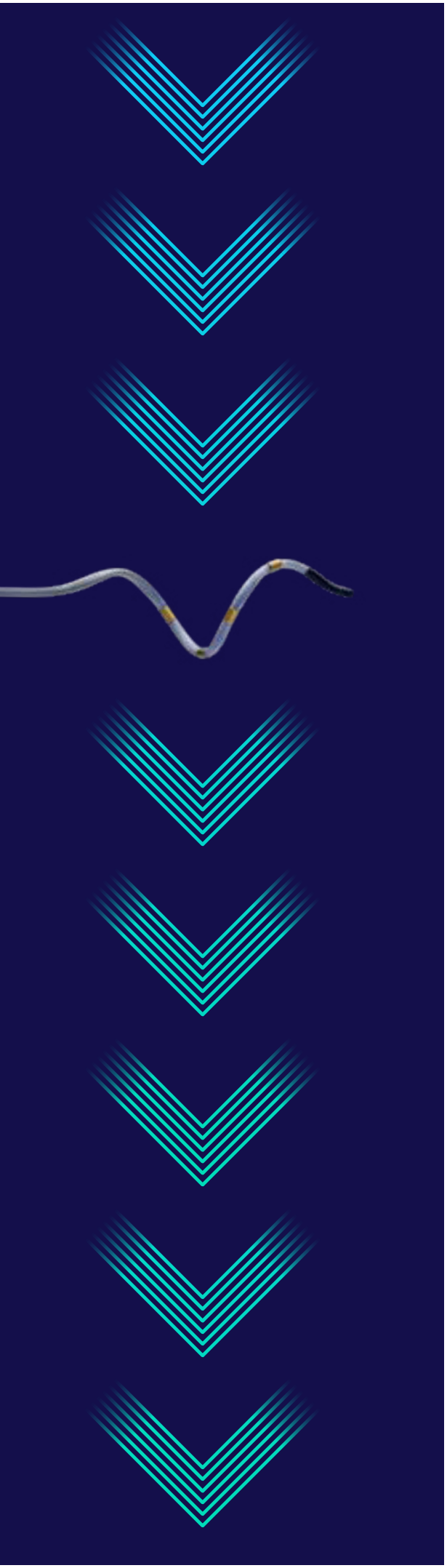

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PERSPECTIVES IN HYPERTENSION

Hypertension in sub-Saharan Africa: the current profile, recent advances, gaps, and priorities

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The African continent continues to be a hot topic when it comes to the global burden of hypertension and its subsequent impact on cardiovascular morbidity and mortality. This is justifiable as the unmet need for adequate care for hypertension and diabetes threatens to reverse the 10-year gain in healthy life expectancy in the African region between 2000 and 2019.[1] Almost all papers calling for action to address hypertension in sub-Saharan Africa (SSA) underline the rising blood pressure (BP) levels, poor detection, and sub-optimal treatment and control rates. Recent roadmaps and major manuscripts led by teams of global experts in the field of hypertension have repeatedly called for urgent contextualised interventions throughout the African continent to reduce the health and economic consequences of raised high BP.

Similar to other work done before by our group in 2017[2], we tried in our recent review[3] to present a comprehensive state of hypertension in SSA. We discussed both public health matters and biomarker investigations that should be prioritised for research and innovation targeting hypertension risk factors, and the provision of care for all people living with hypertension in the region. Based on our review of studies published between 2017 and 2023, nationwide representative studies and multi-national studies employing standardised methods remain scarce, given the population sizes of SSA countries. This is especially the case for large-scale observational and prospective studies led by local researchers, which is essential for context and sustainability. Indeed, we cannot deny the invaluable impact of global initiatives as seen with the May Measure Month (MMM) global screening campaign, which remains the main source of recent data as we highlighted in our review paper.

The main risk factors for the publication period were unhealthy diet, sedentary lifestyle, increased adiposity and underweight, ageing, level of education, and/or income as well as psychosocial factors, while the role of smoking and alcohol use remained unclear. Socioeconomic inequality was a major driver for risk factors not only in adults but also in children, affecting the development and detection of hypertension in children. Therefore, significant health and economic benefits can be derived by addressing social determinants of health during the early stages of life. This is clear when looking at the pathway of exposure to risk factors in utero, infancy and childhood to early adulthood, leading to poorer cardiovascular health (**Figure 1**).

Hypertension phenotypes in populations of African ancestry remain relevant for primary prevention and therapeutic interventions. Advances to understand the mechanistic aspects of hypertension development such as the renin angiotensin aldosterone system, salt handling, particularly the growing interest in the role of dietary potassium and endothelial function using prospective studies and across the lifespan is limited to certain regions in SSA. Although these new data are relevant in improving the understanding of hypertension development,

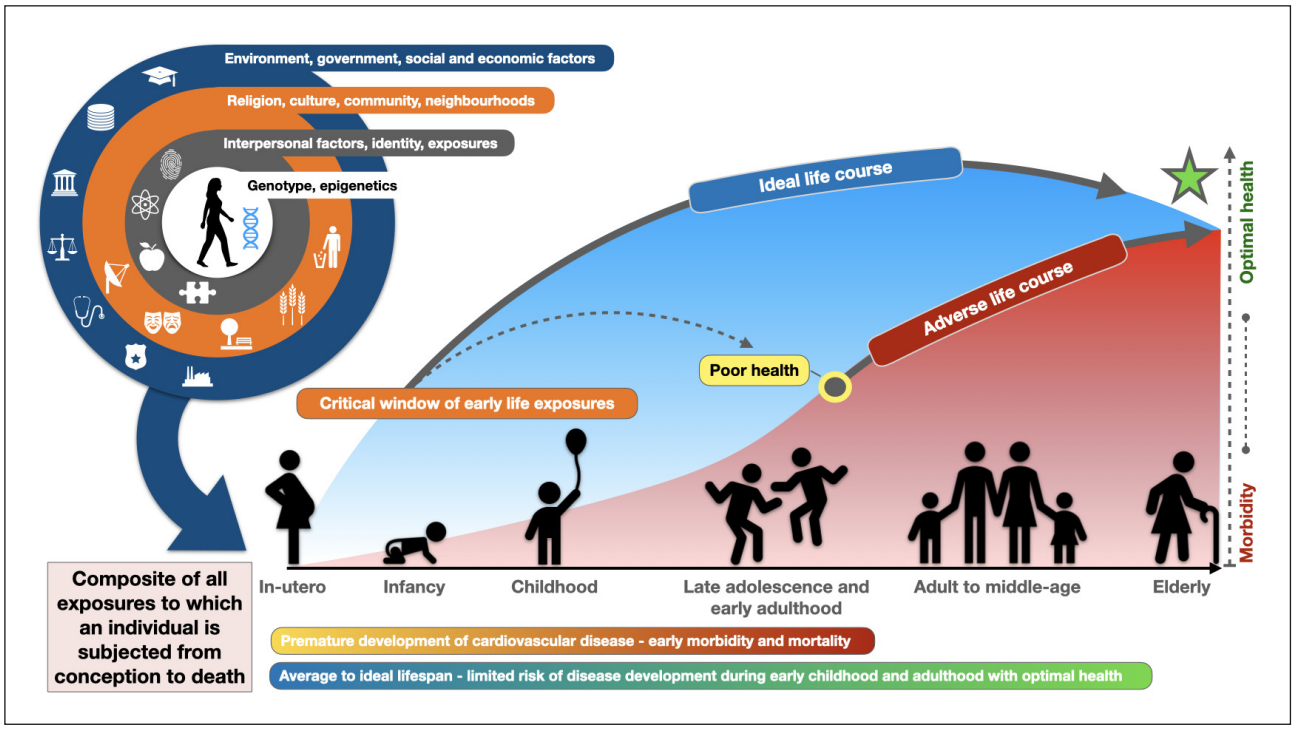

Figure 1: Risk factors exposome of hypertension across the lifespan.

the rate at which knowledge is translated into tangible solutions in clinical practice and public health is concerning. On the other hand, HIV/AIDS remains a major public health concern in SSA. Despite lower BP levels and lower odds of having hypertension in people living with HIV as compared to those without HIV,[4-6] the association between HIV, antiretroviral therapy, and cardiovascular disease drives the continued need to monitor hypertension risk factors, prevalence, and management in individuals living with HIV.

Other than funding challenges due to competing health priorities (communicable versus noncommunicable diseases), perhaps one of the most important aspects of tackling hypertension in SSA, is the vast diversity in social determinants of health, between and within countries. These factors which include education level, rural versus urban dwellings, rates of employment as well as cultural and religious beliefs not only impact risk and prevalence, but also management of hypertension. When comparing, for example, interventions for the management of hypertension in South Africa and other sites within the same study, socioeconomic and demographic factors such as residing in a rural area, low education, and literacy levels in patients, and the high unemployment rate as well as health system-related barriers are some of the factors determining the failure or success of interventions.[7]

To conclude, even though the burden of hypertension in SSA is on a crisis trajectory, collaborative efforts and improved stakeholder engagement (patient populations, governments and traditional leaders) show promise. It is without doubt that targeting modifiable risk factors has the greatest potential to prevent hypertension in SSA. There are several initiatives including multi-country strategies,[8] and randomised control trials, some ongoing and others in the formative phase. The expectation, perhaps too ambitious, is for the manuscripts in the next decade to present the tangible impact current actions have had on mitigating hypertension risk factors and reducing hypertension-mediated target organ damage through improved detection, treatment and control. In addition to global efforts, more collaboration is needed between local researchers to develop regional initiatives and improve working relationships with government despite the known challenges to ensure equitable, culturally acceptable, and sustainable interventions.

References

1. World Health Organisation. Tracking Universal Health Coverage in the WHO African Region, 2022. https://www.afro.who.int/publications/tracking-universal-health-coverage-who-african-region-2022.

2. Schutte AE, Botha S, Fourie CM, Gafane-Matemane LF, Kruger R, Lammertyn L, et al. Recent advances in understanding hypertension development in sub-Saharan Africa. J Hum Hypertens. 2017;31:491–500.

3. Gafane-Matemane LF, Craig A, Kruger R, Alaofin OS, Ware LJ, Jones ESW, et al. (2024). Hypertension in sub-Saharan Africa: the current profile, recent advances, gaps, and priorities. J Hum Hypertens (2024). https://doi.org/10.1038/s41371-024-00913-6.

4. Houle B, Kabudula CW, Tilstra AM, Mojola SA, Schatz E, Clark SJ, et al. Twin epidemics: the effects of HIV and systolic blood pressure on mortality risk in rural South Africa, 2010-2019. BMC Public Health. 2022;22:387.

5. Niwaha AJ, Wosu AC, Kayongo A, Batte C, Siddharthan T, Kalyesubula R, et al. Association between blood pressure and HIV status in rural Uganda: results of cross-sectional analysis. Glob Heart. 2021;16:12.

6. Phalane E, Fourie CM, Mels CM, Schutte AE. A comparative analysis of blood pressure in HIV-infected patients versus uninfected controls residing in sub-Saharan Africa: a narrative review. J Hum Hypertens. 2020;34:692–708.

7. Flor L, Wilson S, Bhatt P, Bryant M, Burnett A, Camarda J, et al. Community-based interventions for detection and management of diabetes and hypertension in underserved communities: a mixed-methods evaluation in Brazil, India, South Africa and the USA. BMJ Glob Health. 2020;5:e001959.

8. Owolabi M, Olowoyo P, Mocumbi A, Ogah OS, Odili A, Wahab K, et al. African Control of hypertension through innovative epidemiology and a vibrant ecosystem (ACHIEVE): novel strategies for accelerating hypertension control in Africa. J Hum Hypertens. 2023; https://doi.org/10.1038/s41371-023-00828-8.

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PERSPECTIVES IN HYPERTENSION

Sex differences in obesity and potential consequences for cardiovascular risk

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Hypertension in Women

Hypertension remains a key risk factor for cardiovascular disease (CVD) and premature death in women globally.[1] Around 600 million women worldwide are hypertensive, including hypertension during pregnancy, a leading contributor to maternal death.[1-3] However, hypertension in women (and in men) is underdiagnosed and undertreated, with control rates as low as 23% among women with hypertension.[1,3]

Thus, better prevention, detection, and treatment of hypertension in women are critical healthcare challenges. Established risk factors for hypertension, including unhealthy diet and lifestyle, obesity, and aging, are common among both men and women and are well-recognized in practice guidelines for clinical care.

However, women or female-specific factors remain understudied in basic, clinical, and population research. These risk factors are not only related to menarche, reproduction, menopause, and (pharmacological use of) sex hormones, but also to the (strength of the) association between established risk factors such as obesity and hypertension and CVD, with often a stronger association between risk factor burden and adverse effects in women than in men.[1,4,5] Furthermore, recent sex-specific analyses have suggested that blood pressure increases more rapidly with aging among premenopausal women than among age-matched men. In addition, blood pressure treatment thresholds and efficacy of interventions to lower blood pressure and cardiovascular disease risk may differ between sexes (Box 1).[1,4,5] Recent papers relevant to this topic are discussed below.[6,7]

Box 1. Hypertension in women[1]

- The rise in blood pressure during the life course of women is steeper than in men
- Women-specific risk factors for hypertension and CVD include gynecological disorders, complicated pregnancies, and early menopause
- Evidence indicates that hypertension control declines with aging in women
- The association of blood pressure with poor outcomes seems stronger in women
- Women and gender-specific aspects of hypertension treatment are understudied

Increasing Obesity Among Women

The NCD Risk Factor Collaboration (NCD-RisC), a network of health scientists around the world who collaborate to collect and analyze data on major risk factors for non-communicable diseases, published a paper on worldwide trends in underweight and obesity from 1990 to 2022, with data from 3663 population-representative studies including 222 million children, adolescents, and adults residing in 200 countries and territories.[6]

Pooled data from population-based studies with height and weight measurements in samples of the general population were analyzed using a Bayesian hierarchical meta-regression model. The primary outcome was the individual and combined prevalence of underweight (adults; age ≥20 years)

or thinness (school-aged children and adolescents; age 5–19 years) and obesity. Underweight was defined as a body mass index (BMI) of less than 18.5 kg/m2 and thinness as a BMI less than two SD below the median of the WHO growth reference. Obesity was defined as a BMI of 30 kg/m2 or higher for adults and a BMI of more than two SD above the median of the WHO growth reference for children and adolescents. The data and details of the statistical methods are available at https://ncdrisc.org/.

The main conclusion from this analysis, which covers more than 99% of the world's population, was that obesity has starkly increased in recent years, and that this rise affects children and young adults increasingly. The global age-standardised prevalence of obesity increased from 8.8% (95% credible interval, 8.5–9.1) in 1990 to 18.5% (17.9–19.1) in 2022 in adult women and from 4.8% (4.6–5.0) to 14.0% (13.4–14.6) in adult men. The number of women and men with obesity in 2022 was 504 million (489–520) and 374 million (358–391), respectively, which was an increase of 377 million (360–393) and 307 million (290–324), respectively, from 1990. The countries with the largest absolute numbers of adults with obesity in 2022 were the USA, China, and India.

Over the same period, the age-standardized prevalence of obesity increased in girls in 186 countries (93%) and in boys in 195 countries (98%). In most countries, obesity in children more than doubled. The global age-standardised prevalence of obesity in school-aged children and adolescents increased from 1.7% (1.5–2.0) in 1990 to 6.9% (6.3–7.6) in 2022 in girls and from 2.1% (1.9–2.3) to 9.3% (8.5–10.2) in boys. The number of girls and boys with obesity in 2022 was 65.1 million (59.4–71.7) and 94.2 million (85.3–103.0), respectively, an increase of 51.2 million (45.2–57.8) and 76.7 million (67.6–85.7), respectively, from 1990. In almost all countries, there was an increase in obesity and a decline in underweight or thinness among school-aged children, adolescents, and adults. Visualisations per country can be viewed on the NCD-RisC website.

Obesity, Hypertension, and Cardiovascular Disease Risk

A different paper by this group concerned the rise in blood pressure during this period.[3] In that paper, hypertension was defined as having systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or taking medication for hypertension. Controlled hypertension was defined as taking medication for hypertension and having systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg. These analyses were restricted to men and women aged 30–79 years.

The data indicated that the number of people with hypertension doubled from 1990 to 2019, from 331 (95% credible interval, 306–359) million women and 317 (292–344) million men in 1990 to 626 (584–668) million women and 652 (604–698) million men in 2019, despite the stable global age-standardised prevalence. Globally, 47% (43–51) of women and 38% (35–41) of men were treated. Control rates among people with hypertension in 2019 were 23% (20–27) for women and 18% (16–21) for men.

In 2019, the global age-standardised prevalence of hypertension in adults aged 30–79 years was 32% (30–34) in women and 34% (32–37) in men, similar to 1990 levels of 32% (30–35) in women and 32% (30–35) in men. The stable global prevalence was a net effect of a decreased prevalence in high-income countries and an increase in low-income and middle-income countries.

However, it is important to note that there are data indicating that a threshold of 140/90, as used in most parts of the world, or even 130/80, might be too high for women, as recent studies show that these thresholds for treatment might not adequately reduce cardiovascular risk in women.[4,5,7,8] A recent Women's Health Initiative analysis suggested that optimal systolic blood pressure levels in women might be around 100 at age 65.[7] In addition, different pathways seem to link obesity with hypertension and cardiovascular disease more detrimentally in women compared to men. This includes perturbations in the regulation of sex hormones, insulin resistance, sodium sensitivity, inflammatory responses, sympathetic nervous system activation, endothelial and neuroendocrine dysfunction, skeletal muscle characteristics, and gynecological disorders.[1,9-13]

Obesity, sodium sensitivity, and hypertension are strongly associated in women, and the prevalence of uncontrolled hypertension is higher in obese than in non-obese women.[1,9] Higher lipoprotein lipase activity, greater lipolysis in response to lipolytic stimuli, and greater suppression of lipolysis by insulin in the fed state create stronger

drivers of obesity in females compared to males.[10] Furthermore, the neuroendocrine hormone leptin and the renin-angiotensin system may contribute to obesity-associated hypertension via sex-specific mechanisms.[1,9-13]

Leptin is thought to have a key role in obesity in women, regulating food intake, metabolism, and fat distribution. Leptin may affect blood pressure independent of obesity through sympathetic activation.[1,9,11] Plasma leptin levels are higher in women than in men at any given measure of obesity, consistent with a state of relative leptin resistance.[1,9,11] Progesterone is thought to promote leptin-mediated endothelial dysfunction in obese premenopausal women through aldosterone and endothelial mineralocorticoid receptors,[9] and leptin has also been implied in the high prevalence of obesity in women with gynecological disorders.[13,14]

Conclusion

In summary, obesity in women may affect hypertension risk and cardiovascular disease through sex-dimorphic pathways. Therefore, the consequences for hypertension and cardiovascular risk of the large increase in the global prevalence of obesity among women recently reported need to be critically assessed, taking sex-specific mechanisms in the development of hypertension and cardiovascular disease into account.

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References

1. Chapman N, Ching SM, Konradi AO, Nuyt AM, Khan T, Twumasi-Ankrah B, Cho EJ, Schutte AE, Touyz RM, Steckelings UM, Brewster LM. Arterial Hypertension in Women: State of the Art and Knowledge Gaps. Hypertension. 2023 Jun;80(6):1140-1149. doi: 10.1161/HYPERTENSIONAHA.122.20448. Epub 2023 Mar 15. PMID: 36919603.

2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396:1204-1222. doi:10.1016/S0140-6736(20)30925-9

3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398:957-980. doi:10.1016/S0140-6736(21)01330-1

4. Wang X, Carcel C, Woodward M, Schutte AE. Blood Pressure and stroke: a review of sex- and ethnic/racial-specific attributes to the epidemiology, pathophysiology, and management of raised blood pressure. Stroke. 2022;53:1114-1133. doi:10.1161/STROKEAHA.121.035852

5. Ji H, Niiranen TJ, Rader F, Henglin M, Kim A, Ebinger JE, Claggett B, Merz CNB, Cheng S. Sex Differences in Blood Pressure Associations With Cardiovascular Outcomes. Circulation. 2021;143:761-763. doi:10.1161/CIRCULATIONAHA.120.049360

6. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. Lancet. 2024 Mar 16;403(10431):1027-1050. doi: 10.1016/S0140-6736(23)02750-2.

7. Haring B, Andrews CA, Hovey K, Shadyab AH, LaCroix A, Martin LW, Rosal MC, Kuller LH, Salmoirago-Blotcher E, Saquib N, Koo P, Laddu D, Stefanick ML, Manson JE, Wassertheil-Smoller S, LaMonte MJ. Systolic Blood Pressure and Survival to Very Old Age. Results from the Women's Health Initiative. medRxiv [Preprint]. 2023 Jun 29:2023.06.22.23291783. doi: 10.1101/2023.06.22.23291783.

8. Brewster LM, Perrotta ID, van Montfrans GA. Should women have lower thresholds for hypertension diagnosis and treatment? J Hum Hypertens. 2023 Aug;37(8):753-754. doi: 10.1038/s41371-023-00838-6.

9. Faulkner JL, Belin de Chantemèle EJ. Sex differences in mechanisms of hypertension associated with obesity. Hypertension. 2018;71:15-21. doi:10.1161/HYPERTENSIONAHA.117.09980

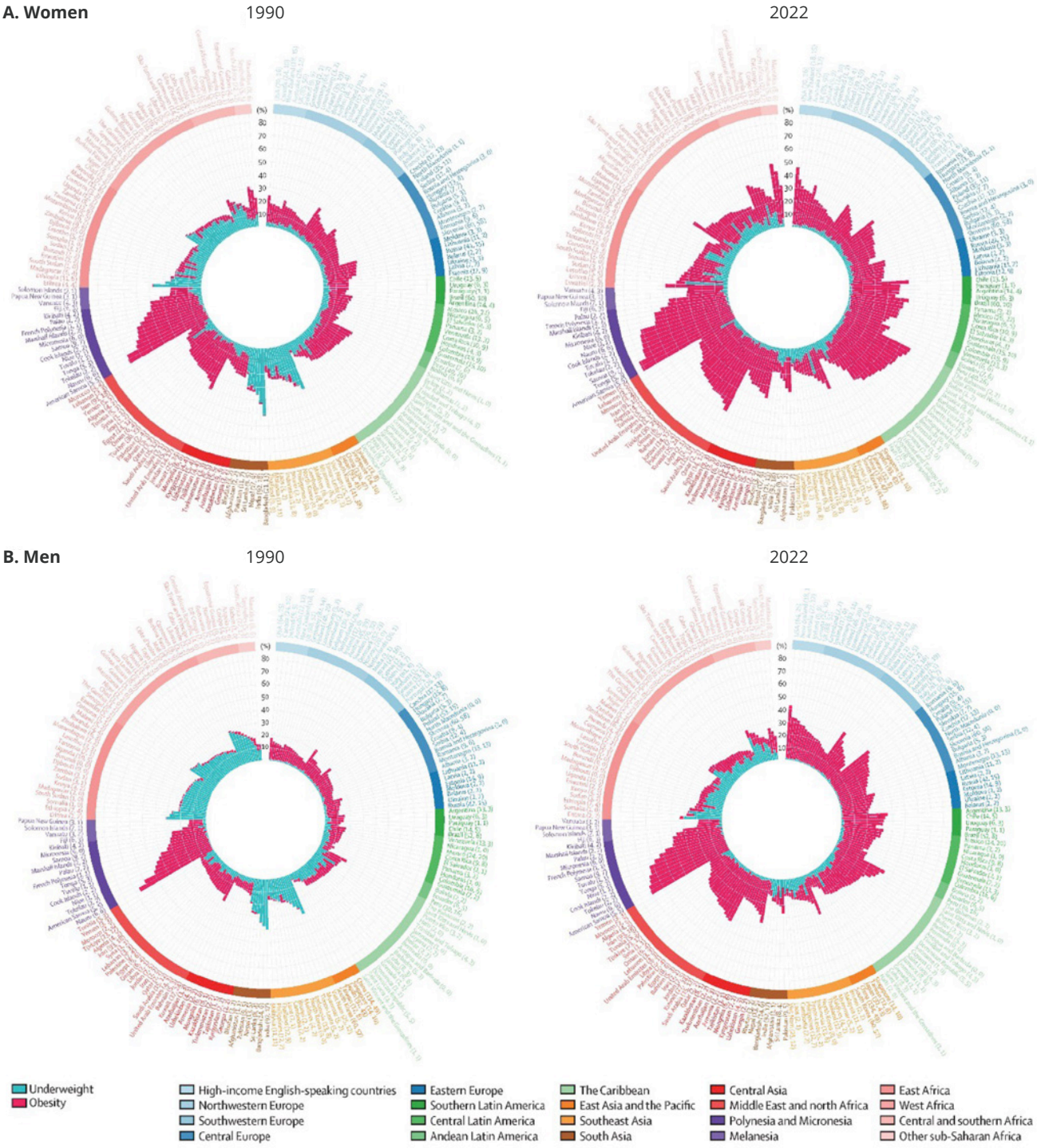
10. Palmisano BT, Zhu L, Eckel RH, Stafford JM. Sex differences in lipid and lipoprotein metabolism. Mol Metab. 2018;15:45-55. doi:10.1016/j.molmet.2018.05.008

11. Ma D, Feitosa MF, Wilk JB, Laramie JM, Yu K, Leiendecker-Foster C, Myers RH, Province MA, Borecki IB. Leptin is associated with blood pressure and hypertension in women from the National Heart, Lung, and Blood Institute Family Heart Study. Hypertension. 2009;53:473-479. doi:10.1161/HYPERTENSIONAHA.108.118133

12. Soave I, Marci R. From obesity to uterine fibroids: an intricate network. Curr Med Res Opin. 2018;34:1877-1879. doi:10.1080/03007995.2018.1505606

13. Kumawat M, Choudhary P, Aggarwal S. Association of serum leptin with anthropometric indices of obesity, blood lipids, steroidal hormones, and insulin resistance in polycystic ovarian syndrome. J Hum Reprod Sci. 2021;14:228-233. doi:10.4103/jhrs.jhrs_35_21

Figure 1 Increase in age-standardised combined prevalence of underweight and obesity between 1990 and 2022, by country, for adults (age ≥20 years), indicating a greater increase in women.[6] A. Women, B. Men. The circular bar plots show the burden of underweight and obesity in 1990 and 2022. The lengths of the bars show the age-standardised prevalence of underweight (blue) and obesity (red), and their sum shows the age-standardised combined prevalence, indicating a higher prevalence of obesity in women. Country names are coloured by region. The numbers in brackets after each country's name show the total number of data sources and the number of nationally representative data sources, respectively. The maps show the change in combined prevalence of underweight and obesity from 1990 to 2022, and its level in 2022. NCD Risk Factor Collaboration.[6] Published with permission of the NCD Risk Factor Collaboration and Elsevier Publishers under CC-BY license.



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PERSPECTIVES IN HYPERTENSION

Are nanobodies the future of tissue-specific angiotensin AT_1-receptor blockers?

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Angiotensin AT_1 receptor blockers (ARBs) are among the most frequently prescribed anti-hypertensive drugs. They combine high therapeutic efficacy with very good tolerability. Approved ARBs such as Losartan, Valsartan, Olmesartan, Candesartan, Irbesartan or Telmisartan are fully synthetic small molecules. While small molecule antagonists of G-protein coupled receptors (GPCRs) usually have the advantage of a high affinity for their target, they also have limitations such as undesired passage through the placental barrier due to their small size and chemical properties. Regarding ARBs, placental passage constitutes a significant problem since ARBs are fetotoxic, because intact AT_1 receptor (AT_1R) signalling is required for normal kidney development. Another problem of GPCR ligands is the often-limited selectivity for other receptors or receptor subtypes or tissues.

Antibodies generally possess much better selectivity than small molecule drugs. This could also apply to antibodies binding to receptors, because – unlike small molecule agonists or antagonists, which solely interact with structures within the receptor binding pocket - antibodies could be designed to additionally recognize epitopes outside of the orthosteric pocket in order to increase selectivity.[1] Pharmacologically, such antibodies could act as competitive or allosteric antagonists, or, in principle, agonists.

While there are several good reasons to develop therapeutic, GPCR-targeting antibodies, this type of antibody is still a rare exception with presently only two FDA-approved drugs of that kind.[2]

The groups of Andrew C. Kruse and Robert J. Lefkowitz have developed a method for discovery of GPCR-targeting antibodies and as one of the first targets they selected the angiotensin AT_1 receptor.[1,3] These AT_1R-targeting antibodies are of a special type, called nanobodies (Fig. 1).[4] Nanobodies consist of a single variable domain heavy chain derived from heavy-chain only antibodies (Fig. 1), the latter being endogenously present in very few species like for example in camelids (camels, dromedars, lamas, alpacas – nanobodies derived from camelids are called VHH nanobodies) or in sharks (so-called VNAR nanobodies). The prevailing type of nanobody in drug development projects is camelid VHH nanobodies. Such nanobodies can be generated by immunisation of camelids or of transgenic mice, which have been generated to produce heavy-chain-only antibodies. Alternatively, there are also techniques for fully synthetic production of nanobodies by cDNA recombinant technologies, i.e. not requiring in vivo immunisation. Large-scale production and amplification of nanobodies for therapeutic use in humans can be processed in microbial expression systems, whereas conventional antibodies are usually produced in mammalian cell cultures, the latter being more costly, yielding lower amounts and requiring more complex purification steps.[4,5] Nevertheless, for regulatory reasons and because of large production capacities based on mammalian cell cultures worldwide, mammalian expression systems are currently still often preferred for nanobodies. Nanobodies have a number of advantages over conventional antibodies such as extreme stability (potentially allowing oral

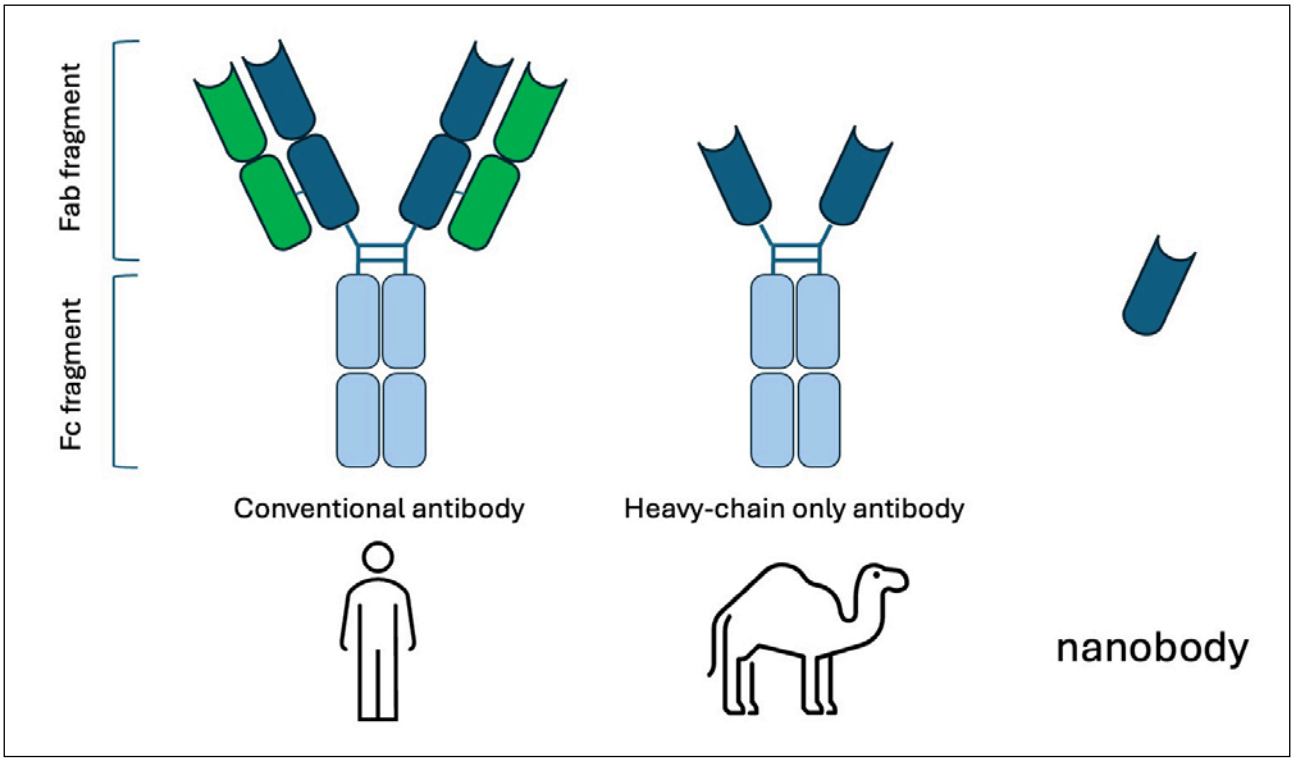

Figure 1: Conventional IgG antibody (left), camelid heavy-chain-only antibody (middle), nanobody (right). Dark blue: heavy chain, Green: light chain

application), low immunogenicity (especially when humanised), less posttranslational modifications and a much smaller size, which enables fast distribution and deep tissue penetration.[4,5]

Despite their small size, nanobodies retain high specificity and possess a higher antigen binding affinity for their target antigens than conventional antibodies. The first nanobody-based drug (Caplacizumab), a bivalent nanobody for the treatment of acquired thrombotic thrombocytopenic purpura, was approved by the FDA in 2018.[6] Currently (July 2024), there are three more nanobody-based drugs approved and in clinical use, two of them approved by FDA (Caplacizumab, Ciltacabtagene), one approved in China (Envafolimab) and one approved in Japan (Ozoralizumab) (https://www.biochempeg.com/article/375.html). At least 20 more of such drugs are in clinical development.

The AT_1R-targeting antibody developed by the Lefkowitz/Kruse groups is derived from a yeast-displayed library of fully synthetic nanobodies, i.e. it does not require animal immunisation. The initial lead, the AT118 nanobody, was selected based on its ability to compete with angiotensin II and the ARB Olmesartan for binding into the AT_1R binding pocket.[3] Modification of AT118 resulted in the higher affinity nanobody AT118-A, which was further modified to yield a humanised variant termed AT118-H. The Kruse group took these modifications further, starting with the generation of AT118-H variants with reduced non-specific binding (AT118-L).[1] Next steps served to reduce renal filtration and increase plasma half-life by fusion of the nanobody to a human IgG1 Fc and by dimerising this fusion-protein. In a final step, the Fc's neonatal Fc receptor (FcRn) binding site was mutated to prevent transport of the antibody across the placental barrier into the foetal circulation. Various tests revealed that concentrations of the fused nanobody were indeed minimal in the foetal circulation in a mouse model, while its ability to antagonise AT_1R-mediated Gαq signalling and lower Ang II-induced hypertension in mice was retained thus making this nanobody a potential candidate for treating maternal hypertension in pregnancy by AT_1R blockade without the teratogenic risk.

Interestingly, extensive additional cryo-electron microscopy studies revealed that the interaction of the nanobodies with the AT_1R differs from

that of small molecule AT_1R antagonist: like AT_1R antagonists, they "freeze" the intracellular pocket in an inactive state that does not allow receptor signalling, whereas – unlike AT_1R antagonists - the extracellular domain is stabilised in an active-like state.[1]

Collectively, these studies by the Kruse and Lefkowitz groups introduced a new modality for AT_1R-targeting drugs. While (modified) nanobodies will with high certainty not replace the well-established small molecule AT_1R antagonists as treatment for "conventional" hypertension, they may open up new possibilities for treating hypertension under conditions which require a tissue specific effect such as AT_1R blockade in maternal but not foetal tissue during pregnancy.

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References:

1. Skiba MA, Sterling SM, Rawson S, Zhang S, Xu H, Jiang H, et al. Antibodies expand the scope of angiotensin receptor pharmacology. Nat Chem Biol. 2024 May 14;

2. CUSABIO [Internet]. [cited 2024 Jul 11]. The Collection of Progress of Anti-GPCR Antibody Drugs. Available from: https://www.cusabio.com/c-21061.html

3. McMahon C, Staus DP, Wingler LM, Wang J, Skiba MA, Elgeti M, et al. Synthetic nanobodies as angiotensin receptor blockers. Proc Natl Acad Sci U S A. 2020 Aug 18;117(33):20284–91.

4. Jin BK, Odongo S, Radwanska M, Magez S. NANOBODIES®: A Review of Diagnostic and Therapeutic Applications. Int J Mol Sci. 2023 Mar 22;24(6):5994.

5. Kunz S, Durandy M, Seguin L, Feral CC. NANOBODY® Molecule, a Giga Medical Tool in Nanodimensions. Int J Mol Sci. 2023 Aug 25;24(17):13229.

6. Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, et al. Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. N Engl J Med. 2019 Jan 24;380(4):335–46.

PERSPECTIVES IN HYPERTENSION

The ESPRIT trial

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Lowering blood pressure (BP) is one of the most effective treatments to prevent cardiovascular events. Uncertainty exists about whether targeting standard office systolic blood pressure (SBP) <120 mm Hg is better than <140 mm Hg due to limited and conflicting evidence from randomized controlled trials. The Systolic Blood Pressure Intervention Trial (SPRINT) is the only trial that proved targeting SBP <120 mm Hg prevents more major vascular events than <140 mm Hg in patients with high cardiovascular risk but without diabetes or stroke.[1] In contrast, The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial compared the two SBP targets in patients with diabetes and the Recurrent Stroke Prevention Clinical Outcome (RESPECT) trial in those with history of stroke, and both obtained nonsignificant results.[2,3] The differences in results among these trials might be due to the statistical underpower of ACCORD and RESPECT, the confounding effect of factorial design, the interactions by diabetes status and history of stroke, or different BP measurements. Therefore, given the above uncertain benefit and potential harm, most current clinical guidelines do not recommend lowering SBP to less than 120 mm Hg.[4-7] To provide more evidence on comparing the efficacy and safety of the two SBP targets, we conducted the Effects of Intensive Systolic Blood Pressure Lowering Treatment in Reducing Risk of Vascular Events (ESPRIT) trial.[8]

ESPRIT is an open-label, blinded-outcome, randomized controlled trial conducted at 116 sites (103 hospitals and 13 community medical centres) in China. All data in the trial were processed electronically. We used an online system and a minimized randomization program to randomly allocate participants to either intensive treatment (targeting standard office SBP <120 mm Hg) or standard treatment (targeting standard office SBP <140 mm Hg) in a 1:1 ratio. Then we followed up the participants regularly. At each clinic visit, a trained investigator used an electronic BP monitor to measure the standard office BP. We titrated participants' antihypertensive medications to achieve the set SBP target or the lowest tolerable BP. The COVID-19 pandemic caused a 3-month delay for the intensive treatment group to reach the target SBP, so we extended the follow-up by 3 months.9 The primary outcome was major vascular events, i.e., a composite of myocardial infarction, coronary or non-coronary revascularization, hospitalization/emergency room visit for heart failure, stroke, or death from cardiovascular causes.

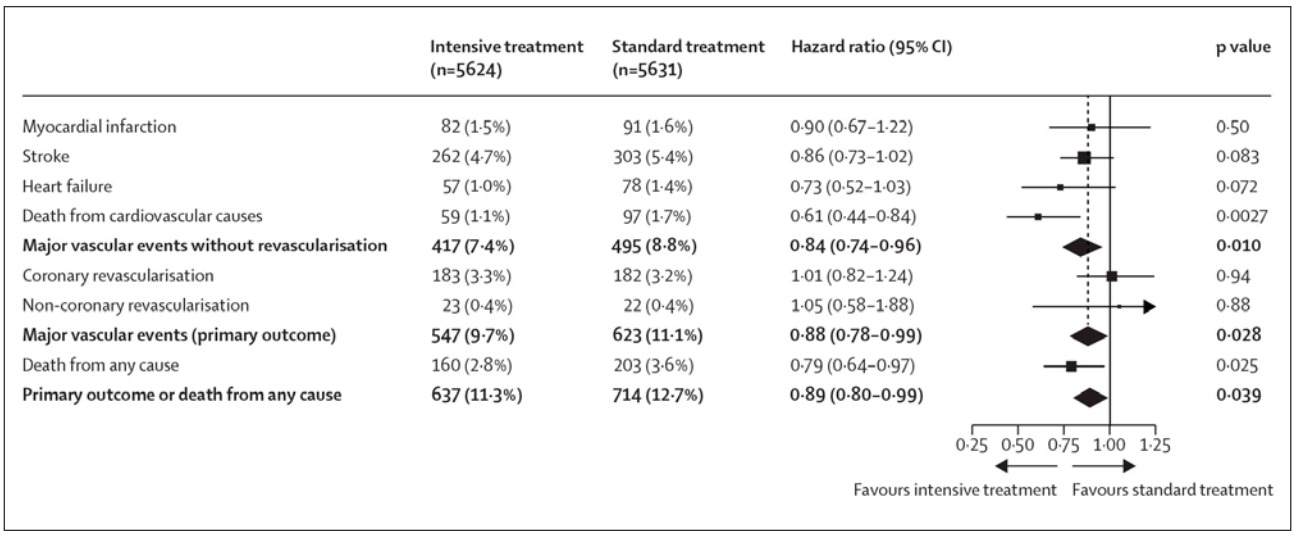
We enrolled 11,255 participants with high cardiovascular risk and with or without diabetes or previous stroke during 2019-2020. Mean age was 64.6 years, 41.3% were women and 58.7% were men, and a history of diabetes was reported by 38.7% of the participants and stroke by 26.9%. The mean baseline SBP in the intensive and standard treatment groups were 146.8±10.5 mm Hg and 147.0±10.7 mm Hg, respectively. Throughout the follow-up (except the first 3 months for titration), we achieved a mean SBP of 119.1±11.1 mm Hg in the intensive treatment group, and 134.8±10.5 mm Hg in the standard treatment group.

During a median of 3.4 years of follow-up, the primary outcome event occurred in 547 (9.7%) participants in the intensive treatment group and 623 (11.1%) in the standard treatment group. The intensive treatment reduced 12% risk of major vascular events. There was no heterogeneity of

effects by diabetes status, duration of diabetes, or history of stroke. To prevent a primary outcome event and a cardiovascular death, 75 and 148 patients need to be treated for 3 years, respectively. The individual components of primary outcome showed differential effects. Death from cardiovascular causes occurred in 59 participants (1.1%) from Intensive Group and in 97 (1.7%) from Standard Group (HR 0.61; 95% CI 0.44-0.84). The between-group differences of myocardial infarction, heart failure, and stroke were similar with the primary outcome but not statistically significant. However, the rates of coronary revascularization and non-coronary revascularization were almost the same between groups. The risks of death from any cause (HR 0.79; 95% CI 0.64-0.97) and composite of primary outcome or death from any cause (HR 0.89; 95% CI 0.80-0.99) were lower in Intensive Group (Figure).

Consistent with SPRINT, we observed that the intensive treatment increased risk of sustained renal function decline.[1] However, few participants developed end-stage renal disease. Serious adverse events of syncope occurred more frequently in the intensive treatment group (0.4%) than in standard treatment group (0.1%). There was no significant between-group difference in the serious adverse events of hypotension, electrolyte abnormality, injurious fall, or acute kidney injury. Moreover, the intensive treatment group experienced much fewer of these serious adverse events in our trial than previous trials. The better safety might be attributed to the nature of the study population or treatment.

Our trial has a number of strengths to facilitate reliable assessments of moderate but important treatment effects, including a large sample size, high adherence to intervention, few participants lost to follow-up, and a large number of clinical outcomes. Our study was conducted at both hospital and community settings in diverse economic–geographic regions. Our trial shows that treatment on a regular follow-up basis, with committed personnel, and common,



Primary outcome and secondary outcomes

The primary outcome is a composite cardiovascular outcome of myocardial infarction, coronary or non-coronary revascularisation, hospitalisation or emergency room visit for new-onset heart failure or acute decompensated heart failure, stroke, or death from cardiovascular causes. Heart failure is defined as hospitalisation or emergency room visit for new-onset heart failure or acute decompensated heart failure. The prespecified secondary outcomes included components of the primary composite outcome, death from any cause, a composite of the primary outcome or death from any cause. The analysis for the outcome of major vascular events without revascularisation was a post-hoc analysis. A single patient can have multiple events and therefore can contribute information to more than one row. The size of each square for hazard ratio is proportional to the precision of the estimates (with larger boxes indicating a greater degree of precision), the horizontal lines represent 95% CIs, and the dashed vertical line indicates the overall hazard ratio for the effect of intensive treatment on the first major vascular event. For composite outcomes, hazard ratios and their corresponding 95% CIs are represented by bold text and diamonds.

accessible, and affordable drugs is feasible to benefit hypertensive patients with high risk of cardiovascular disease.

In conclusion, targeting SBP of less than 120 mm Hg, as compared with that of less than 140 mm Hg, prevents major vascular events and death with minor excess risk in patients with hypertension at high cardiovascular risk, regardless of the status of diabetes or history of stroke.

References

1. Group SR, Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015;373:2103-2116. doi: 10.1056/NEJMoa1511939

2. Cushman WC, Evans GW, Byington RP, Goff DC, Jr., Grimm RH, Jr., Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575-1585. doi: 10.1056/NEJMoa1001286

3. Kitagawa K, Yamamoto Y, Arima H, Maeda T, Sunami N, Kanzawa T, Eguchi K, Kamiyama K, Minematsu K, Ueda S, et al. Effect of Standard vs Intensive Blood Pressure Control on the Risk of Recurrent Stroke. JAMA Neurology. 2019;76. doi: 10.1001/jamaneurol.2019.2167

4. Jones NR, McCormack T, Constanti M, McManus RJ. Diagnosis and management of hypertension in adults: NICE guideline update 2019. Br J Gen Pract. 2020;70:90-91. doi: 10.3399/bjgp20X708053

5. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, Muiesan ML, Tsioufis K, Agabiti-Rosei E, Algharably EAE, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41:1874-2071. doi: 10.1097/hjh.0000000000003480

6. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;138:e426-e483. doi: 10.1161/cir.0000000000000597

7. 2018 Chinese Guidelines for Prevention and Treatment of Hypertension-A report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. J Geriatr Cardiol. 2019;16:182-241. doi: 10.11909/j.issn.1671-5411.2019.03.014

8. Liu J, Li Y, Ge J, Yan X, Zhang H, Zheng X, Lu J, Li X, Gao Y, Lei L, et al. Lowering systolic blood pressure to less than 120 mm Hg versus less than 140 mm Hg in patients with high cardiovascular risk with and without diabetes or previous stroke: an open-label, blinded-outcome, randomised trial. Lancet. 2024. doi: 10.1016/s0140-6736(24)01028-6

9. Liu J, Wang B, Li Y, Yan X, Ge J, Li J. Rationale and design of the Effects of intensive Systolic blood Pressure lowering treatment in reducing RIsk of vascular evenTs (ESPRIT): A multicenter open-label randomized controlled trial. American Heart Journal. 2023;257:93-102. doi: 10.1016/j.ahj.2022.12.003

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PERSPECTIVES IN HYPERTENSION

Orthostatic hypertension and frailty in elderly hypertensives

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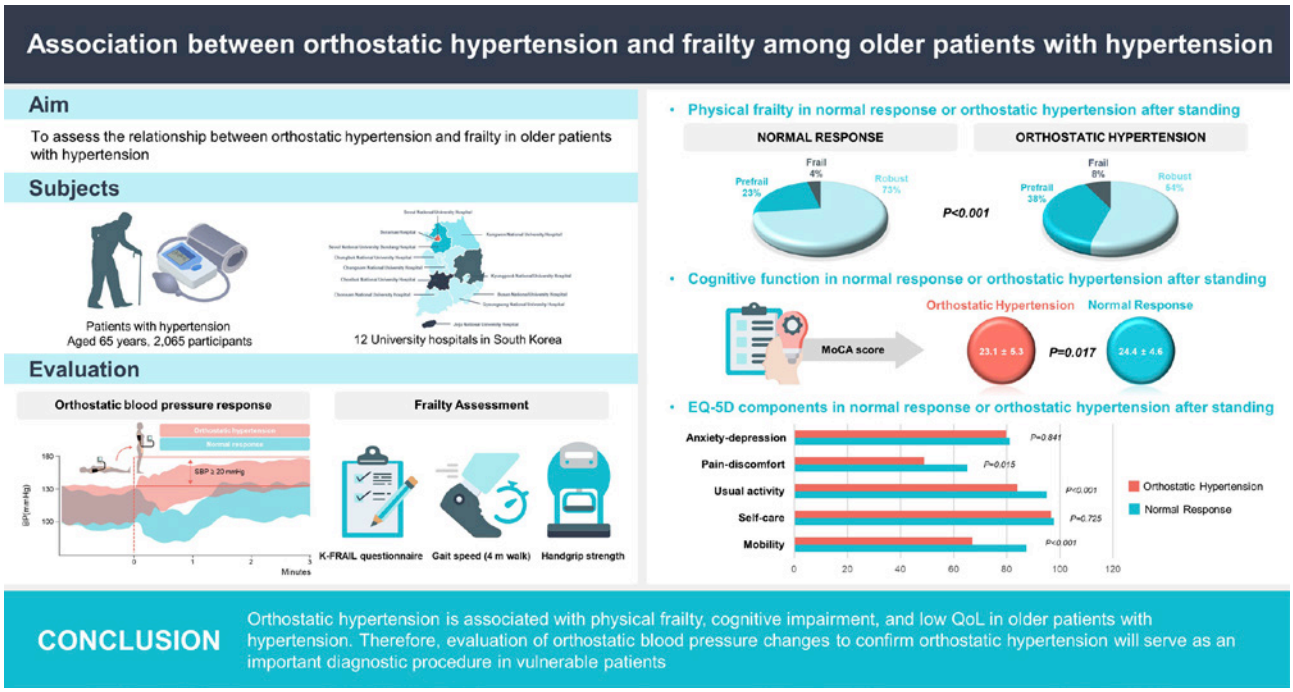
Hypertension is a very common chronic condition, with its prevalence continuously increasing due to rapid population aging. It is one of the most significant socioeconomic burdens and a leading cause of premature cardiovascular complication and death worldwide. Trends show that individuals aged ≥80 years will be the fastest-growing segment of the population in the near future. In managing hypertension among the oldest-older patients, several specific factors should be considered including frailty, multiple comorbidities, polypharmacy, cognitive impairment, depression, disability, dizziness, syncope and falls.[1] Assessing frailty, physical function, activity of daily living and cognitive function is described as an essential component to determine intensity of treatment and autonomy of older hypertensive patients in national and international guidelines (European Society of Hypertension 2023 guideline).[2] In people with orthostatic hypertension, blood pressure rises despite those processes. Recent proposals suggest that orthostatic hypertension could be defined as an increase in systolic blood pressure greater than or equal to 20 millimeters of mercury (mm Hg) and upright systolic blood pressure of ≥140 mm Hg when going from lying down to standing.[3] In a recent paper published in Hypertension, we reviewed the association between orthostatic hypertension and frailty, cognitive function and quality of life.[4] We hope this will drive future discussions to include comprehensive geriatric assessment for older hypertensive patients in hypertension guidelines.

This is an analysis of the study participants of the HOWOLD-BP trial (How to Optimize Elderly Systolic Blood Pressure), which was a prospective, multicenter, open-label randomized clinical trial to compare the optimal target blood pressure for older Korean patients with hypertension.[5] In older patients, frailty and hypertension often coexist. To investigate the relationship between frailty and orthostatic hypertension in older hypertensive patients in Korea, we measured blood pressure in both supine and standing positions and assessed the degree of physical frailty, cognitive function and quality of life in 2,065 patients recruited from 12 university hospitals. As a result of the orthostatic blood pressure test, 91.3% showed normal responses, while 4.6% of the patients were observed to have orthostatic hypertension and 4.1% of the elderly hypertensive patients were observed to have orthostatic hypotension. In the group with normal orthostatic blood pressure response, 23% were pre-frail and 4% were frail. In contrast, among the patients with orthostatic hypertension, 38% were pre-frail and 8% were frail ($p < 0.001$). Patients with orthostatic hypertension had significantly lower scores on the Montreal Cognitive Assessment compared to the normal group, 23.1±5.3 versus 24.4±4.6; $p = 0.017$) indicating cognitive decline. A higher proportion of these patients also had slower gait speed and weaker grip strength. (25.5% vs. 15.1%, $p = 0.024$) Additionally, their health-related quality of life, as measured by the EQ-5D index (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), was found to be significantly reduced. (0.89±0.11 vs. 0.94±0.09, $p < 0.001$)

Orthostatic hypertension is associated with exaggerated sympathetic response, leading to excessive vasoconstriction and increased peripheral vascular resistance. Previous studies demonstrated orthostatic hypertension is associated with increased cardiovascular



risk, silent cerebral infarctions and advanced white matter lesions, and ultimately, increased mortality.[6-8] In our present study, frail older hypertensive patients were more likely to have impaired autonomic function, consistent with previous studies.[9] Measuring orthostatic blood pressure, including both orthostatic hypotension and orthostatic hypertension, will serve as an important diagnostic procedure for identifying vulnerable older hypertensive patients. To our knowledge, this is the first study to report the association between orthostatic hypertension and frailty. Further studies are needed to obtaining generalizability and identifying the clinical significance of orthostatic hypertension in frail older hypertensive patients.

References

1. Lee JH, Kim KI, Cho MC. Current status and therapeutic considerations of hypertension in the elderly. Korean J Intern Med. 2019;34(4):687-95.

2. Mancia G, Kreutz R, Brunstrom M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874-2071.

3. Jordan J, Biaggioni I, Kotsis V, Nilsson P, Grassi G, Fedorowski A, Kario K. Consensus statement on the definition of orthostatic hypertension endorsed by the American Autonomic Society and the Japanese Society of Hypertension. Clin Auton Res. 2023;33(1):69-73.

4. Choi JY, Ryu DR, Lee HY, Lee JH, Hong Y, Park SK, et al. Association Between Orthostatic Hypertension and Frailty Among Older Patients With Hypertension. Hypertension. 2024;81(6):1383-90.

5. Lee DH, Lee JH, Kim SY, Lee HY, Choi JY, Hong Y, et al. Optimal blood pressure target in the elderly: rationale and design of the HOW to Optimize eLDerly systolic Blood Pressure (HOWOLD-BP) trial. Korean J Intern Med. 2022;37(5):1070-81.

6. Yatsuya H, Folsom AR, Alonso A, Gottesman RF, Rose KM, Investigators AS. Postural changes in blood pressure and incidence of ischemic stroke subtypes: the ARIC study. Hypertension. 2011;57(2):167-73.

7. Kario K, Eguchi K, Hoshide S, Hoshide Y, Umeda Y, Mitsuhashi T, Shimada K. U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: orthostatic hypertension as a new cardiovascular risk factor. J Am Coll Cardiol. 2002;40(1):133-41.

8. Pasdar Z, De Paola L, Carter B, Pana TA, Potter JF, Myint PK. Orthostatic hypertension and major adverse events: a systematic review and meta-analysis. Eur J Prev Cardiol. 2023;30(10):1028-38.

9. Debain A, Loosveldt FA, Knoop V, Costenoble A, Lieten S, Petrovic M, et al. Frail older adults are more likely to have autonomic dysfunction: A systematic review and meta-analysis. Ageing Res Rev. 2023;87:101925.

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PERSPECTIVES IN HYPERTENSION

The gut microbiome in hypertension: The devil is in the details

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The association between the gut microbiome and hypertension is increasingly accepted. Over the past decade, our group and many others have sought to determine the role of the gut microbiome in hypertension using various approaches.[1] Our collective aim is to shift the field from association toward causation. Animal studies have shown that the gut microbiome mediates critical factors of blood pressure control, including dietary components, medication response, and immune activation.[2-4] Our team had previously shown that the protective effects of a high-fibre diet are mediated by the gut microbiome through the production of short-chain fatty acids (SCFAs) in mice. In a recent clinical study, we showed that supplementation with SCFAs reduced 24-hour systolic blood pressure in untreated hypertensive patients.[5]

Focusing on causation would allow us to target specific microbes or groups of microbes and their metabolites. This approach has been fruitful in conditions such as atherosclerosis.[6] However, current studies in hypertension do not consistently identify the same microbes. Functionally, we observe a depletion of beneficial, fibre-utilising microbes, which is not unique to hypertension. So, what are we missing? One common mistake is not considering factors that influence the gut microbiome. The gut microbiome in both humans and experimental animals is influenced by diet, living environment, sex, and genetics, amongst others, requiring careful experimental planning and adjustment. Failing to consider these intrinsic and extrinsic factors leads to confounded findings that are not replicable nor-biologically relevant findings.

In a recent study published in *Cardiovascular Research*, we investigated factors influencing the gut microbiome in the angiotensin II experimental hypertension mouse model.[7] Previous small-scale studies found that angiotensin II induced significant gut microbiome variations. Our aim was to validate these findings using a large, heterogeneous cohort of mice to quantify the extent to which angiotensin II and other experimental factors—such as diet, animal housing, sex, genotype, age, sampling site, and sequencing batch—affected gut bacterial variations.[7] We analysed 538 microbiome samples from 303 mice of different genotypes, diets, housing conditions, and age groups.[7] We confirmed that angiotensin II does induce gut microbiome variations, but it explained only 0.4% of the observed variations.[7] Factors like diet and sampling site had a more significant impact, explaining 6-6.8% of the variations.[7] We identified *Clostridium leptum* as differentially abundant between the groups.[7] Using publicly available data, we demonstrated that *Clostridium leptum* abundance was inversely associated with systolic blood pressure in both mice and hypertensive patients and positively correlated with plasma butyric acid levels (a short-chain fatty acid).[7]

This study serves as a cautionary tale, urging researchers to pay careful attention to study design, methods, and results. Moving forward, it

is essential to ensure that we consider all relevant factors to produce biologically meaningful data. Our group and others have proposed guidelines to ensure the robust design of gut microbiome studies.[8-10] We also need to accept that our understanding of the gut microbiome is still in its infancy, and as the field rapidly develops, the methods we use to study the gut microbiome will evolve accordingly.

References

1. Durgan DJ, Zubcevic J, Vijay-Kumar M, Yang T, Manandhar I, Aryal S, Muralitharan RR, Li H-B, Li Y, Abais-Battad JM, Pluznick JL, Muller DN, Marques FZ, Joe B. Prospects for leveraging the microbiota as medicine for hypertension. Hypertension. 2024;81:951-963

2. Xu C, Marques FZ. How dietary fibre, acting via the gut microbiome, lowers blood pressure. Curr Hypertens Rep. 2022;24:509-521

3. Yang T, Mei X, Tackie-Yarboi E, Akere MT, Kyoung J, Mell B, Yeo JY, Cheng X, Zubcevic J, Richards EM, Pepine CJ, Raizada MK, Schiefer IT, Joe B. Identification of a gut commensal that compromises the blood pressure-lowering effect of ester angiotensin-converting enzyme inhibitors. Hypertension. 2022;79:1591-1601

4. Saleem M, Masenga SK, Ishimwe JA, Demirci M, Ahmad T, Jamison S, Albritton CF, Mwesigwa N, Porcia Haynes A, White J, Neikirk K, Vue Z, Hinton A, Arshad S, Desta S, Kirabo A. Recent advances in understanding peripheral and gut immune cell-mediated salt-sensitive hypertension and nephropathy. Hypertension. 2024;81:436-446

5. Jama HA, Rhys-Jones D, Nakai M, Yao CK, Climie RE, Sata Y, Anderson D, Creek DJ, Head GA, Kaye DM, Mackay CR, Muir J, Marques FZ. Prebiotic intervention with hamsab in untreated essential hypertensive patients assessed in a phase ii randomized trial. Nature Cardiovascular Research. 2023;2:35-43

6. Wang Z, Roberts Adam B, Buffa Jennifer A, Levison Bruce S, Zhu W, Org E, Gu X, Huang Y, Zamanian-Daryoush M, Culley Miranda K, DiDonato Anthony J, Fu X, Hazen Jennie E, Krajcik D, DiDonato Joseph A, Lusis Aldons J, Hazen Stanley L. Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. Cell. 2015;163:1585-1595

7. R Muralitharan R, Nakai ME, Snelson M, Zheng T, Dinakis E, Xie L, Jama H, Paterson M, Shihata W, Wassef F, Vinh A, Drummond GR, Kaye DM, Mackay CR, Marques FZ. Influence of angiotensin ii on the gut microbiome: Modest effects in comparison to experimental factors. Cardiovascular Research. 2024

8. Muralitharan RR, Snelson M, Meric G, Coughlan MT, Marques FZ. Guidelines for microbiome studies in renal physiology. American Journal of Physiology-Renal Physiology. 2023;325:F345-F362

9. Marques FZ, Jama HA, Tsyganov K, Gill PA, Rhys-Jones D, Muralitharan RR, Muir J, Holmes A, Mackay CR. Guidelines for transparency on gut microbiome studies in essential and experimental hypertension. Hypertension. 2019;74:1279-1293

10. Mirzayi C, Renson A, Furlanello C, Sansone S-A, Zohra F, Elsafoury S, Geistlinger L, Kasselman LJ, Eckenrode K, van de Wijgert J, Loughman A, Marques FZ, MacIntyre DA, Arumugam M, Azhar R, Beghini F, Bergstrom K, Bhatt A, Bisanz JE, Braun J, Bravo HC, Buck GA, Bushman F, Casero D, Clarke G, Collado MC, Cotter PD, Cryan JF, Demmer RT, Devkota S, Elinav E, Escobar JS, Fettweis J, Finn RD, Fodor AA, Forslund S, Franke A, Furlanello C, Gilbert J, Grice E, Haibe-Kains B, Handley S, Herd P, Holmes S, Jacobs JP, Karstens L, Knight R, Knights D, Koren O, Kwon DS, Langille M, Lindsay B, McGovern D, McHardy AC, McWeeney S, Mueller NT, Nezi L, Olm M, Palm N, Pasolli E, Raes J, Redinbo MR, Rühlemann M, Balfour Sartor R, Schloss PD, Schriml L, Segal E, Shardell M, Sharpton T, Smirnova E, Sokol H, Sonnenburg JL, Srinivasan S, Thingholm LB, Turnbaugh PJ, Upadhyay V, Walls RL, Wilmes P, Yamada T, Zeller G, Zhang M, Zhao N, Zhao L, Bao W, Culhane A, Devanarayan V, Dopazo J, Fan X, Fischer M, Jones W, Kusko R, Mason CE, Mercer TR, Sansone S-A, Scherer A, Shi L, Thakkar S, Tong W, Wolfinger R, Hunter C, Segata N, Huttenhower C, Dowd JB, Jones HE, Waldron L, Genomic Standards C, Massive A, Quality Control S. Reporting guidelines for human microbiome research: The storms checklist. Nature Medicine. 2021;27:1885-1892

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PERSPECTIVES IN HYPERTENSION

A randomised trial of a hypertension certification program for pharmacists: The RxPATH Study

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As you know, uptake and implementation of practice guidelines is challenging. We created a novel educational program, the Hypertension Canada Professional Certification Program (HC-PCP) for primary care providers. The HC-PCP is based upon the Hypertension Canada guidelines and constructed around core competencies developed by hypertension experts and primary care providers (1). The HC-PCP is a 4 module self-directed online program which covers correct BP measurement technique (assessed via video) and submission of 3 patient cases reviewed by hypertension experts (see https://hypertension.ca/professional-certification-program).

We took the opportunity to evaluate the impact of the HC-PCP taken by primary care providers on patient outcomes in the RxPATH study (2). Pharmacists were the group selected because of their interest in the program. We used a stepped wedge cluster randomised design, with the pharmacy as the unit of randomization. Pharmacists enrolled their patients with poorly controlled hypertension.

- During the Control period, pharmacists were given a copy of the Hypertension Canada Guidelines and provided usual care to their patients.
- During the Intervention period, pharmacists completed the HC-PCP, then provided an enhanced level of care as outlined in the program to their patients.

Uniquely, we evaluated the HC-PCP at the level of the pharmacists' patients. We enrolled 890 patients from 59 pharmacies (104 pharmacists). We found that the intervention (pharmacists completing the HC-PCP and delivering care accordingly to their patients) was associated with a 4.76mmHg greater systolic BP reduction at 3 months, compared to control (95% confidence interval 2.02 to 7.50, $p<0.0001$) (Figure). Patient satisfaction with pharmacist care was high at 75.9 (/90) using the Consultation Satisfaction Questionnaire.

We think the implications and unique aspects of the RxPATH study are:

- The HC-PCP is a novel approach to the implementation of the Hypertension Canada Guidelines
- A patient-level evaluation of a professional education program aimed at primary care providers
- Demonstrates a clinically important reduction in BP
- Adds further evidence to the almost 100 randomised trials of pharmacist care in hypertension
- The HC-PCP is easily scalable within primary care

References

1. Watson KE, Tsuyuki RT, Beahm NP, Sedore R, Bell A. Assessment of the educational competencies for the Hypertension Canada Professional Certification Program (HC-PCP) designed for implementation of hypertension guidelines into primary care. Can Pharm J (Ott) 2021; 154: 271-277.

2. Watson KE, Chan JCH, Pan B, Al Hamarneh YN, Tsuyuki RT. Enhancing hypertension detection and control through a hypertension certification program for pharmacists: A cluster randomized trial (The RxPATH Study). Can Pharm J (Ott); 157: online ahead of print. DOI:10.1177/17151635241254089

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Hypertension & DOHaD (Developmental Origins of Health and Disease)

- Emaciation in Women
- Pregnant Women's Health
- Dietary Education, Taste Flavor etc.

NEW DIMENSION SERIES

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

CATEGORY B: HYPERTENSION AND DIVERSITY

When in Rome, do as the Romans do: respect to regional traditional arts for coping with diseases

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Sustainable development goals (SDGs) focus upon the reduction of regional disparities of income, education quality, food availability, clear water/energy supply or living circumstances. Food availability/choice and eating behaviors are crucial in SDGs and well-being, which are the themes of this *Hypertension News* Series. In a Gallup World Poll on the joy of eating, healthy eating, food choices, and subjective well-being, conducted in over 140 countries or regions in 2022[1], =87% of the survey participants answered that they enjoyed their meals during the last 7 days, although social situations differ greatly in different countries. 82% of them thought that they eat healthy food and 63% felt that they are offered several choices of food. There are significant positive links between dietary diversity and happiness. Surprisingly, the analysis shows that the contributing power to subjective well-being of enjoying meals is comparable to that of income. Many people in the world, thus, enjoy their meals in their respective regions by their respective ways, which usually serves for the promotion of their health.

Japan is now the No.1 country for longevity in the world, partly due to Japanese traditional food, which was designated as being on UNESCO list of Intangible Cultural Heritage in 2013. It contains a variety of dishes including fermented food and raw fish. Mediterranean diets also show their effectiveness for prevention of cardiovascular diseases in a similar fashion.

It is clearly demonstrated that calorie restrictions, intermitting fasting or time-restricted eating exert prolongation of healthy life span up to the primates. In this issue, Dr. Boobes reports on the effectiveness of Ramadan fasting (RF) for the patients with hypertension (see next article), chronic kidney disease or cardiovascular diseases. Safe and favorable effects of RF can be expected, depending on the extent of the disease state in each patient.

Regional traditional or religious arts should be respected. I believe that these “habits” contain meaning, since they have been inherited through a long period of history for the maintenance of society and of the health of people living in that society. Diversity, in this sense, is significant for SDGs.

Darwin's concept of "survival of the fittest" posits that advantageous traits, conferring stronger survival abilities, are selected for survival. Individuals possessing beneficial genetic mutations for overcoming competition and surviving can prevail. The theory of “natural selection”, which emerged around 1920, is rooted in this idea, suggesting that survival of the strongest is "natural" and inevitable. This concept, however, sounds somewhat discordant to me. Intuitively, relying solely on the survival of the strongest in competition seems unsustainable for the world. Diversity is crucial for ensuring robustness in biological societies. The famous Japanese

geneticist, Motoo Kimura (1924-1994), advocated the "neutral theory (principle) of molecular evolution", suggesting that observed genetic variations survive by chance rather than solely through advantageous traits. Genetic mutations passed to the next generation were due not only to their survival advantages but also various factors (such as bottleneck effects and genetic drift), ultimately attributing their survival to fortunate circumstances (equilibrium selection theory) in contrast to "survival of the fittest" in natural selection theory. In addition, Kinji Imanishi (1902-1992), an ecologist at Kyoto University, proposed the "Theory of Habitat Segregation" regarding species evolution. Through observing variously shaped mayflies in the Kamo River in Kyoto, Imanishi developed his unique perspective. He thought that mayflies, which gradually assumed different forms due to random genetic mutations, came to inhabit parts of the river that matched their bodies and, as a result, survived there. In other words, the organisms actively sensed their environment, found the right place to live, and achieved a peaceful life and survival. Darwin's idea that the natural environment selects the species is entirely opposite to Imanishi's idea that species choose their environment.

I believe that all people in various regions of the world have been surviving in their respective regions, by making efforts to modify their living habits and maximally adjust themselves to their environments in order to achieve a maximal health condition.

"When in Rome, do as the Romans do", I think is really a true saying.

References

1. Recipes for Wellbeing Report - Ando Foundation/Nissin Food Products (ando-zaidan.jp) https://www.gallup.com/analytics/512390/eating-behavior-wellbeing.aspx

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NEW DIMENSION SERIES

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

CATEGORY B: HYPERTENSION AND DIVERSITY

Ramadan fasting and its relationship with cardiovascular and renal diseases

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An international task force of expert physicians established the Ramadan and Kidney Disease working group (RaK Initiative) to provide recommendations for chronic kidney disease (CKD) patients considering fasting during Ramadan.[1] This group aims to integrate existing evidence with expert insights, in collaboration with the Diabetes and Ramadan (DaR) International Alliance, to offer empirical guidelines for CKD patients.

Effect of Ramadan Fasting on Blood Pressure Control in Non-Renal Patients

Numerous studies have examined the impact of Ramadan fasting (RF) on blood pressure (BP) control among hypertensive patients. The consensus across these studies is that patients with controlled hypertension can safely fast during Ramadan, with many studies documenting improved BP control due to fasting.[1-4]

Hypertension in CKD patients who fast during Ramadan:

The available literature is limited. Overall, the effects of RF on BP control in CKD patients appear to be generally favorable or neutral. However, the impact on kidney function remains inconclusive, necessitating further research.[1, 5, 6]

Ramadan Fasting for Patients with Cardiovascular Diseases

Most stable cardiac patients, including those with heart failure, ischemic heart disease, and cardiac arrhythmia, generally tolerate fasting during Ramadan well. However, for CKD patients with cardiovascular diseases, the available data are limited, making it challenging to establish concrete recommendations. A thorough evaluation by both nephrologists and cardiologists is strongly recommended to determine the safety of Ramadan fasting for these patients.[1,7]

Effect of RF on CKD Patients:

Several studies have investigated the impact of RF on patients with CKD. The majority did not identify significant differences in kidney function parameters between fasters and non-fasters during Ramadan or when patients were compared with themselves before and after RF. Some studies have suggested that RF might lead to moderate improvement in kidney function. However, a limited number of studies have reported worsening renal function in some patients with moderate to severe CKD during RF. The available data suggest a progressive increase in the risk of acute kidney injury (AKI) with CKD severity: Stages 1 and 2 show a low risk, stage 3 exhibits a moderate risk, while stages 4 and 5 pose a high risk.[1, 8-10]

Assessment

We recommend that all CKD patients contemplating RF consult their healthcare provider to evaluate personal risks and make decisions tailored to their unique medical conditions. Pre-Ramadan medical evaluations for CKD patients should encompass a detailed history, including past RF experiences, a physical exam, and a targeted lab panel. Based on the assessment, patients' risk of RF will be classified as low, moderate, or high, as outlined in the reference.[1]

Conclusion

Studies in non-renal hypertensive patients generally indicate improved BP control due to Ramadan fasting, though some studies show no statistical difference. Favorable effects on cardiovascular risk factors were noted, and RF is considered safe for patients with mild to severe controlled hypertension. While RF appears safe for many patients with cardiovascular and renal diseases, individualized evaluation and careful monitoring are essential to ensure patient safety and well-being.

Acknowledgments

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References

1. Boobes Y, Afandi B, AlKindi F, et al. Consensus recommendations on fasting during Ramadan for patients with kidney disease: review of available evidence and a call for action (RaK Initiative). BMC Nephrol. 2024 Mar 6;25(1):84.

2. Perk G, Ghanem J, Aamar S, Ben-Ishay D, Bursztyn M. The effect of the fast of Ramadan on ambulatory blood pressure in treated hypertensives. J Hum Hypertens. 2001;15(10):723-725. doi: 10.1038/sj.jhh.1001262.

3. Aktürk IF, Biyik I, Koşaş C, Yalçın AA, Ertürk M, Uzun F. Effects of Ramadan fasting on blood pressure control, lipid profile, brain natriuretic peptide, renal functions and electrolyte levels in hypertensive patients taking combination therapy. Nobel Medicus. 2013;9:43–46.

4. Al-Jafar R, Zografou Themeli M, Zaman S, Akbar S, Lhoste V, Khamliche A, et al. Effect of Religious Fasting in Ramadan on Blood Pressure: Results From LORANS (London Ramadan Study) and a Meta-Analysis. J Am Heart Assoc. 2021 Oct 19;10(20):e021560.

5. Baloglu I, Turkmen K, Kocyigit I, et al. The effect of Ramadan fasting on kidney function in patients with chronic kidney disease. Int Urol Nephrol. 2020;52(7):1337-1343.

6. Bakhit AA, Kurdi AM, Wadera JJ, Alsuwaida AO. Effects of Ramadan fasting on moderate to severe chronic kidney disease. A prospective observational study. Saudi Med J. 2017;38(1):48-52.

7. Ben Ahmed H, Allouche E, Bouzid K, Zrelli S, Hmaidi W, Molahedh Y, et al. Impact of Ramadan fasting on lipid profile and cardiovascular risk factors in patients with stable coronary artery disease. Ann Cardiol Angeiol (Paris). 2022;71(1):36-40.

8. Bernieh B, Al Hakim MR, Boobes Y, Abu Zidan FM. Fasting Ramadan in chronic kidney disease patients: clinical and biochemical effects. Saudi J Kidney Dis Transpl. 2010;21:898–902.

9. Karatas A, Canakci E, Arici YK, Kaya M, Sayim B. The effect of Fasting during Ramadan on the Kidney functions of Stage III-IV Chronic Kidney Disease Patients. Pak J Med Sci. 2021;37(4):972-978. doi: 10.12669/pjms.37.4.3661.

10. Bakhit AA, Kurdi AM, Wadera JJ, Alsuwaida AO. Effects of Ramadan fasting on moderate to severe chronic kidney disease. A prospective observational study. Saudi Med J. 2017;38(1):48-52. doi: 10.15537/smj.2017.1.17566.

NEW DIMENSION SERIES

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

CATEGORY A: HYPERTENSION AND LIFE ENVIRONMENT

Air pollution: A proven risk factor of hypertension and cardiovascular diseases

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Air pollution is considered to be the world's greatest environmental health threat, with 99% of the world's population living in areas where air quality does not meet the World Health Organization (WHO)'s Air Quality Guidelines (AQG).[1] Addressing this issue is an urgent matter as it contributes to the death of approximately 7 million individuals, 3.1 million premature deaths, and 3.2% of the global disease burden,[2] with vulnerable groups being disproportionately affected. Contrary to what the public might think, air pollution does not only cause respiratory adverse health outcomes. It is linked to five main outcomes: strokes, heart disease, lung cancer and both chronic and acute respiratory diseases, including asthma.

This report aims to highlight the association between air pollution and cardiovascular (CV) health effects. According to the US Environmental Protection Agency (EPA), both short- and long-term exposure to air pollution (Particulate Matter 2.5 or PM2.5) cause adverse cardiovascular health outcomes.[3] There is a growing body of evidence that air pollution is an environmental risk factor for hypertension and a determining factor for its prognosis.[4] Numerous studies have been conducted to elucidate the pathophysiological mechanisms of blood pressure (BP) elevation and increased CV risk due to pollution.[5]

The global air quality situation, like in the Eastern Mediterranean Region (EMR), is characterized by a deteriorating air quality due to several factors like the emissions coming from transportation, production, waste burning, cooking, heating, etc.[6] in addition to the arid nature of our region coupled with dust storms, excessive heat, and harsh geography.[7] Air quality monitoring shows that air quality management in the EMR region faces challenges such as poor commitment, duplication of effort, lack of coordination, and weak health surveillance systems. In Lebanon several studies were conducted focusing on air pollution and its impacts on the human health. Since 2012, the Beirut Air pollution and Health Effects (BAPHE) study documented high levels of air pollution and significant health effects. At the time, Lebanon lacked a national strategy, and the air pollution was greatly visible to the naked eye with Particulate Matter (PM) and Nitrogen dioxide (NO_2) levels exceeding the WHO standards at the time. Our study aimed at researching the association between high levels of air pollution and daily emergency hospital admissions for specific causes: respiratory, cardiovascular, cerebrovascular and skin diseases. Descriptive results of the short-term relationships between CVD and PM air pollution in 2012 showed an annual average of 51 µg/m3 (151% above the WHO levels) of Particulate Matter

10 (PM10) level and an annual average of 30 µg/m3 (200% above the WHO levels) of PM2.5. These numbers were accompanied by hospital admission data from 2012 for cardiopulmonary conditions with a total of 10,811 admissions. In addition, we found a significant association between the increase in air pollution levels and cardiovascular admissions among several age groups. The study has also found an association from 2012 to 2014, between levels of PM10 and PM2.5 and admissions for cardiovascular conditions, after recording environmental data for three years and collecting the admissions data.

Air pollution is considered to be one of the modifiable cardiovascular risk factors. Improving air quality needs the involvement of several stakeholders. Knowing that hypertension results from both genetic predisposition and environmental factors and that air pollution is proven to be a modifiable cardiovascular factor, physicians have an important role in preventing hypertension. We cannot modify our genes, but we are able to address modifiable and controllable factors such as sedentary lifestyles, weight gain, sodium intake, unhealthy diets, and exposure to pro-hypertensive substances. Cardiologists should raise awareness about the impact of the environment on human health, educate their patients, and advocate for cleaner environments to improve cardiovascular health.[8] The long-term goal would be integrating environmental exposure assessment in the diagnosis of cardiovascular diseases.

References

1. World Health Organization (WHO). WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide, and sulfur dioxide: global update 2005. 2006. https:// www.who.int/airpollution/publications/aqg2005/en/. Accessed 10 May 2021.

2. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, Balakrishnan K, Brunekreef B, Dandona L, Dandona R, Feigin V, Freedman G, Hubbell B, Jobling A, Kan H, Knibbs L, Liu Y, Martin R, Morawska L, Pope CA 3rd, Shin H, Straif K, Shaddick G, Thomas M, van Dingenen R, van Donkelaar A, Vos T, Murray CJL, Forouzanfar MH. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet. 2017. https:// doi.org/ 10. 1016/ S0140- 6736(17) 30505-6

3. U.S. EPA. Supplement to the 2019 Integrated Science Assessment for Particulate Matter (Final Report, 2022). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-22/028, 2022.

4. The effect of pollution on hypertension and on the total risk score in hypertensive patients. Susanna Tykhonova; Vasyl Shtanko; Olena Khyzhnyak, Nataliia Tofan. European Society of Cardiology, e-Journal of Cardiology Practice, Vol. 22, N° 17 - 29 Jun 2022.

5. Münzel T, Sørensen M, Gori T, Schmidt FP, Rao X, Brook FR, Chen LC, Brook RD, Rajagopalan S. Environmental stressors and cardio-metabolic disease: part II-mechanistic insights. Eur Heart J. 2017;38:557-64.

6. Malkawi M, Al-Yousfi B, Mandil A. Air quality and health impacts in the Eastern Mediterranean Region: an eye on COVID-19. East. Mediterr Health J, 2021.https://doi.org/10.26719/2021. 27.1.3

7. Klepac, P, Locatelli, I, Korošec, S, Kunzli, N, Kukec, A. Ambient air pollution and pregnancy outcomes: a comprehensive review and identification of environmental public health challenges, Environ. Res. 2018. https:// doi.org/ 10. 1016/j. envres. 2018. 07. 008

8. Sanjay Rajagopalan, MD, Chair, Michael Brauer, ScD, Aruni Bhatnagar, MD, Deepak L. Bhatt, MD, MPH, Jeffrey R. Brook, PhD, Wei Huang, ScD, Thomas Münzel, MD, PhD, David Newby, MD, PhD, Jeffrey Siegel, PhD, Robert D. Brook, MD, Vice Chair, On behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Stroke Council Volume 142, Issue 23, 8 December 2020; Pages e411-e431 https://doi.org/10.1161/CIR.0000000000000931

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A quality improvement approach for better chronic care

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We are excited to share updates on the HEARTS in the Americas initiative. Did you know that in the Americas up to 40% of adults are affected by hypertension, and cardiovascular diseases (CVDs) contribute to approximately 2 million deaths each year?

As you might remember, HEARTS in the Americas is the regional adaptation of the World Health Organization's Global HEARTS Initiative. It uses hypertension control improvement as the entry point to enhance primary healthcare and comprehensively address the prevention and treatment of CVDs. It is guided by regional health ministries and supported by the Pan American Health Organization (PAHO). Our program has made significant strides in recent years thanks to a fruitful collaboration between PAHO and Resolve to Save Lives.

Recent Highlights and Progress

HEARTS in the Americas is being implemented in over 6,000 PHC facilities across 33 countries, with 4.5 million patients enrolled. Impressively, 27 countries have approved the national use of a HEARTS clinical pathway, and 8 countries have scaled up the program in over 80% of their PHC facilities. El Salvador is leading the charge by

scaling up HEARTS in 100% of its public primary healthcare facilities.

For 2024, HEARTS in the Americas has defined the following programmatic priorities:

1. Scale up HEARTS implementation in more than 60% of the region's PHC facilities.
2. Institutionalize the HEARTS clinical pathway in all PHC networks.
3. Implement the HEARTS quality improvement approach in at least 30% of the PHC facilities implementing the program.
4. Improve data quality and reporting on HEARTS implementation in more than 90% of the implementing PHC facilities.

What's New with HEARTS in the Americas?

Our program is now fully focused on quality improvement to accelerate HEARTS implementation, improve hypertension control, and reduce human suffering from avoidable cardiovascular illness and death. At the heart of this approach are eight clinical and managerial processes known as the Key Drivers for Hypertension Control.

One of our major priorities for 2024 is the widespread adoption of the HEARTS quality improvement approach. We've developed a technical document to guide its implementation in PHC facilities entitled HEARTS in the Americas. Quality Improvement for Primary Health Care Centers.

HEARTS Quality Improvement Workshops in Latin America

In the first half of this year, we conducted HEARTS quality improvement workshops in Belize (April), El Salvador (May), and Mexico (June) using a 'train the trainer' methodology. These workshops successfully trained around 200 national leaders.

In Mexico, our workshop [Taller HEARTS para la mejora de calidad de la atención primaria de salud] featured international hypertension experts like Don DiPette (South Carolina University, USA), Andrew Moran (Resolve to Save Lives), Dean Picone (University of Sydney, Australia), and Taskeen Khan (WHO, Geneva). A panel led by Deputy Minister of Health Dr. Ruy López Ridaura emphasized HEARTS in the Americas as an 'innovative process for primary healthcare' and stressed the importance of advancing its implementation as part of Mexico's ongoing healthcare reform.

Future Plans

Looking ahead to the second half of the year, we're excited to launch a comprehensive virtual course on the HEARTS quality improvement approach for PHC teams. Additionally, we'll be rolling out a series of quality improvement workshops in selected countries. Stay tuned for more updates on our webpage: PAHO HEARTS in the Americas.

Thank you for your interest in our work. Together, we can make a significant impact on cardiovascular health in the Americas and worldwide.

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Learning from HEARTS in the Americas

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The Global HEARTS initiative was launched in 2016 by the World Health Organization and United States CDC to improve the heart health of people globally. The HEARTS technical package is a central initiative that guides implementation of standardised cardiovascular disease risk reduction strategies in primary care.[1]

HEARTS in the Americas is a large regional adaptation of the Global HEARTS initiative that is supported by the Pan American Health Organization.

In June I had the privilege of joining the HEARTS in Mexico and HEARTS in the Americas teams for a two-day quality improvement workshop in Merida, Yucatan, and visits to three primary care centres. Because my expertise is largely blood pressure measurement, I was excited to see how the primary care centres have implemented the use of validated automated blood pressure devices and standardized measurement processes – as recommended by the HEARTS in the Americas clinical pathway.[2] But I was also keen to learn about aspects of the HEARTS program that I was less familiar with, and to gain firsthand understanding of the importance of local context for adapting HEARTS to ensure it is effective on the ground.

So, what did I learn? Much more than anticipated!

From the quality improvement workshop, it was a unique insight into the critical need for effort at a grassroots level for successful implementation. Everyone in the room was highly motivated to improve health outcomes for their community, it was very uplifting and positive. The workshop was designed to 'train-the-trainer' and had a mix of standardized lectures and practical learning activities.

A highlight was the overview of the experience of HEARTS in Yucatan state presented by Mtra. Ileana Fajardo – showing their major progress to implement HEARTS. In 2020, 13 primary care units had implemented HEARTS, and by 2023, this had risen to 140 units, which is all primary care units in the state. The presentation showed a substantial, coordinated effort and team work to achieve this goal. Critically, they are closely tracking the maturity of the implementation of HEARTS to monitor and report on success and identify units which need more support. To support their local implementation efforts, Yucatan have taken the standardized HEARTS in the Americas clinical pathway and renamed it "Cuida tu Corazon" or 'Take Care of Your Heart' and importantly, developed resources in both Spanish and the local Mayan language.[3]

During the primary care centre visits, I was on the lookout for validated, automated blood pressure devices....and they were everywhere we went! The centre nurses were responsible for undertaking the measurement and the clinical pathway document, including the steps to achieve standardized, accurate readings was displayed prominently. But I learned much more beyond observing the blood pressure measurement process.

The HEARTS in the Americas clinical pathway is clear, if high blood pressure is identified, treatment begins. There was a lot of discussion about avoiding treatment inertia. Indeed, there was a pharmacy within the primary care centres so that anti-hypertensives can be taken home

immediately – this is quite different to Australia. Patients identified with high blood pressure have monthly checks and where necessary up titration, until control is achieved. There are challenges though. Access to certain medications that other regions may take for granted, and access to and cost of validated automated devices. Overcoming these challenges will require ongoing advocacy.

High blood pressure control rates remain poor in most corners of the world.[3] We can all learn from each other to implement best practice, evidence-based health care that delivers for patients. I was privileged to learn from the HEARTS in Mexico and HEARTS in the Americas teams firsthand, but there are also many resources available should readers wish to gain insights.[4-6]

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References

1. HEARTS: Technical package for cardiovascular disease management in primary health care: Risk-based CVD management (who.int)

2. Rosende A, DiPette DJ, Martinez R, Brettler JW, Rodriguez G, Zuniga E, Ordunez P. HEARTS in the Americas clinical pathway. Strengthening the decision support system to improve hypertension and cardiovascular disease risk management in primary care settings. Front Cardiovasc Med. 2023;10:1102482. doi: 10.3389/fcvm.2023.1102482

3. PAHO accompanies Yucatan in the implementation of the CUIDA TU CORAZÓN strategy, strengthened by the HEARTS initiative - PAHO/WHO | Pan American Health Organization

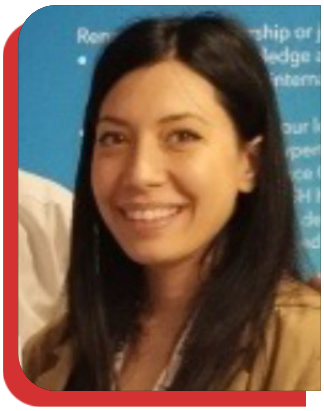
4. Global report on hypertension: the race against a silent killer (who.int)

5. HEARTS in the Americas. Compendium of essential clinical tools 2023 (paho.org)

6. HEARTS en las Américas - OPS/OMS | Organización Panamericana de la Salud (paho.org)

7. HEARTS in the Americas - PAHO/WHO | Pan American Health Organization

ESH 2024 – 33rd EUROPEAN MEETING ON HYPERTENSION AND CARDIOVASCULAR PROTECTION



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INTRODUCTION

We attended with enthusiasm the 33rd European Meeting on Hypertension and Cardiovascular Protection (ESH 2024), held this year in Berlin, Germany at the Estrel Congress Centre May 31-June 3, 2024. ESH 2024 with its 85 scientific sessions and more than 2,000 participants from more than 100 different countries (several countries outside Europe) was a prestigious conference promoting education and innovation and offering a comprehensive platform to explore the latest advancements, research findings and clinical perspectives in hypertension and cardiovascular medicine. Importantly, the meeting was supported by a broad international faculty including many new and young members.

The scientific program included two main session pathways, the first focusing on the 2024 ESH Clinical Practice Guidelines for Hypertension Management and the second on Hypertension and Cardiorenal Diseases. Many investigators (including our research team) had the opportunity to present their research work in oral and poster sessions, and all conference abstracts are available in a supplement issue of the *Journal of Hypertension* (https://journals.lww.com/jhypertension/toc/2024/05001).

This issue highlights the main key points of the meeting that caught our attention and are presented below in three sections: (A) Scientific sessions and research highlights, (B) Innovations, and (C) Personal highlights.

A. SCIENTIFIC SESSIONS AND RESEARCH HIGHLIGHTS

ESH 2024 Clinical Practice Guidelines

The ESH 2023 Guidelines for the management of arterial hypertension was published last year and is an extensive document and a valuable source of updated knowledge and detailed information in nearly 200 pages and with more than 1,700 references. The ESH 2024 Clinical Practice Guidelines were presented during the 2024 ESH meeting in Berlin and aimed to summarize and provide a novel concise hands-on version of the 2023 Guidelines highlighting the "ESH MASTERplan" for the management of hypertension. The official document is available online at https://www.eshonline.org/spotlights/2024-esh-clinical-practice-guidelines/.

The ESH 2024 Clinical Practice Guidelines session was a pivotal part of the scientific program where experts presented the rationale and essential points emphasizing the critical information that healthcare professionals need to know for clinical practice. The components of the ESH MASTERplan for the management of hypertension are: Measure BP-Diagnose, Assess Patient, Select Therapy, and

Evaluate Response. An open discussion session followed, allowing for an engaging and meaningful conversation. This interactive format ensured the dissemination of the key messages of the practice guidelines rendering the session very informative and practical.

Clinical Cases

The ESH 2024 meeting included an interesting session on challenging clinical cases that provided valuable insights into the practical application of current research and clinical guidelines. Highlights included two cases of secondary hypertension, one attributed to polyarteritis nodosa and the other to middle aortic syndrome. Each presentation offered in-depth analysis and discussion, highlighting the importance of personalized patient care.

Future of BP measurement – Cuffless devices

The current status and future potential of BP measurement using novel cuffless technologies and devices has been one of the most challenging topics discussed in the context of the ESH Working Group on Blood Pressure Monitoring and Cardiovascular Variability round tables. Indeed, in the era of artificial intelligence implementation and big data analysis the field of cuffless BP monitoring is the most popular and exciting research topic regarding the future development of BP monitoring.

ESH Awards

A special session was dedicated to the ESH awards, celebrating outstanding contributions in the field of hypertension and cardiovascular medicine. The Honorary Professor of Nephrology and Hypertension Michel Burnier received the Paul Milliez Award, the Alberto Zanchetti Life Achievement Award was given to Professor Renata Cífková, the ESH Honorary Membership was granted to Professor Margus Viigimaa and the Björn Folkow Award to Jan Danser, Professor of Pharmacology. Professor Danser gave an exciting lecture including insights into the novel upcoming antihypertensive treatment regimens which constitute a fascinating and promising field for future basic and clinical research and application.

B. INNOVATIONS

ESH Young Investigators (YI)

The YI group had a very active role in the organization of the ESH 2024 meeting. Under the supervision of Professor Jan Danser and Professor Jana Brguljan the YI group contributed considerably to various activities during the ESH meeting. They organized a scientific session with interesting topics, including artificial intelligence in hypertension, novel drugs for hypertension treatment, and cuffless blood pressure measurement technologies. They also hosted a social evening event offering the opportunity to young attendees to socialize and communicate with each other and with senior ESH members. To promote a healthy lifestyle, they also organized a run in Berlin during the last day of the ESH congress. This year, YI members had the opportunity to act as co-chairpersons in poster sessions, enhancing their experience and abilities to coordinate such events. Furthermore, they participated in the judging of the poster awards, gaining valuable experience by evaluating new ideas, identifying pros and cons of research work, and sharing opinions with experts.

Opening session

The opening session of the ESH 2024 congress was a memorable event, featuring a performance by the Music Barenboim-Said Akademie. This wonderful musical presentation set a positive and engaging tone on the opening of the congress giving the opportunity to multicultural musicians to perform.

Poster of the ESH Congress run.

C. PERSONAL HIGHLIGHTS

The 2024 ESH meeting was uniquely memorable for us – the authors of this article. The first author, Dr Ariadni Menti was for the first time actively involved in the ESH YI group contributing to the organization of the ESH 2024 congress. She had the opportunity to participate in the judging process for posters and co-chaired a poster session and was honoured to be selected as a new ESH member. Moreover, the second author, Dr Konstantinos Kyriakoulis was deeply honoured to be selected as the winner of the SOMNOmedics Young Investigators Award 2024 for the research project proposal entitled "Nighttime blood pressure variability assessed using ambulatory and home monitors in patients with hypertension and prediabetes/diabetes type 2: Association, agreement, and relationship with preclinical target-organ damage".

After our tremendous experience in the ESH 2024, we are sincerely looking forward to the next ESH 2025 in Milan, Italy!!!

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Our personal ESH highlights: Above: ESH vice President Professor Andrzej Januszewicz and new ESH member Dr Ariadni Menti.
Below: ESH 2024 Meeting Chair Professor Reinhold Kreutz, Dr Konstantinos Kyriakoulis (awardee), and Mrs Tinta Visser (SOMNOmedics).

CORRECTION: in the December 2023 issue of Hypertension News, on page 2, 'neuropeptide receptor 1' should have read: 'natriuretic peptide receptor 1'.

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