HYPERTENSION NEWS

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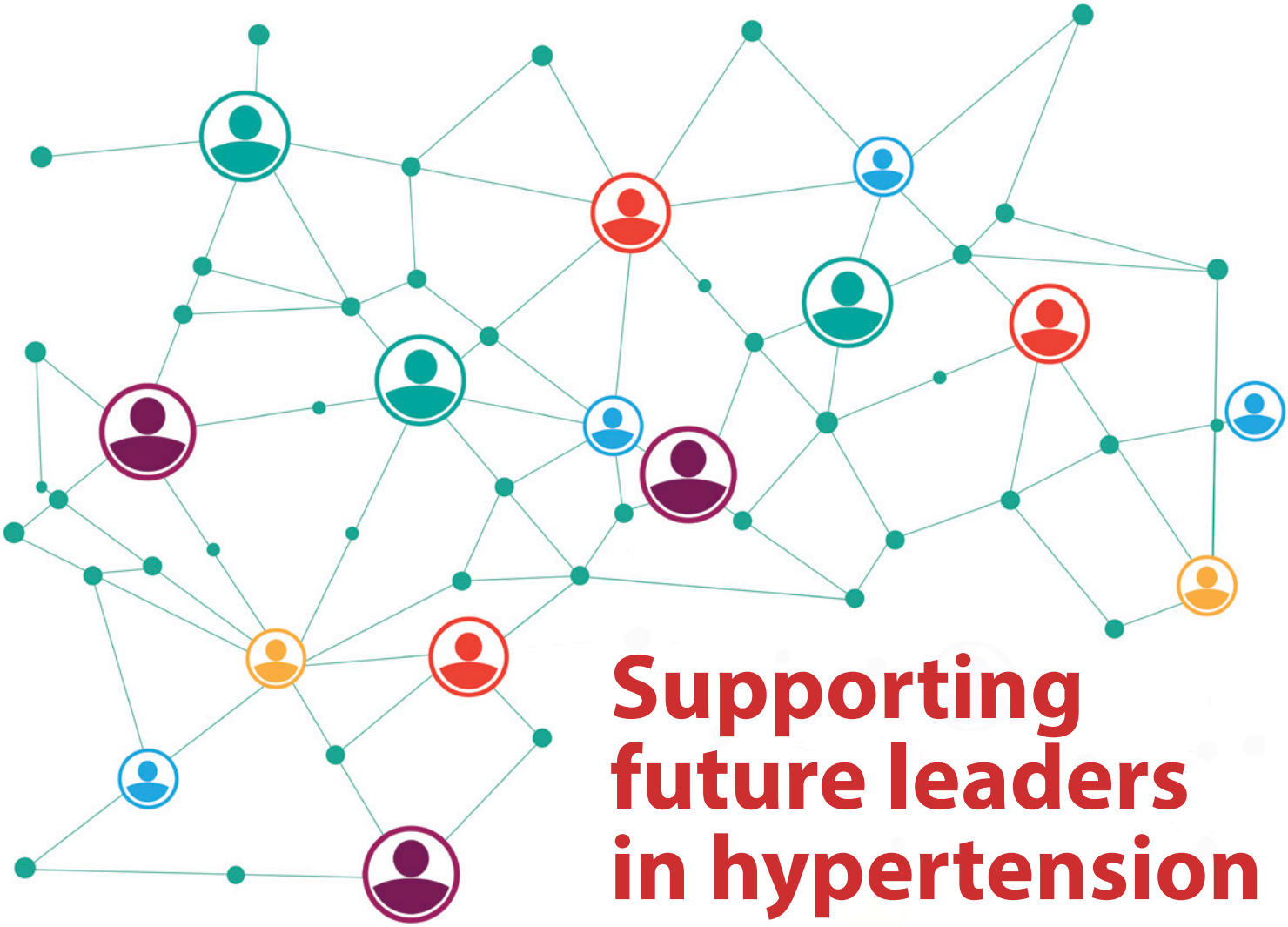

Supporting future leaders in hypertension

How a new ISH initiative will develop and connect early to mid-career researchers

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INTRODUCTION FROM THE PRESIDENT

BRYAN WILLIAMS
President, International Society of Hypertension

Welcome to another edition of Hypertension News. As this year comes to a close, one can reflect on what has been a significant year in the field of hypertension. There have been new guidelines from the European Society of Hypertension (ESH) issued in June, and by now you should have just about finished reading them! It is a weighty document and my colleagues at ESH, and Giuseppe Mancia and Reinhold Kreutz in particular, have completed a mammoth task in generating a useful reference source, in which somewhat ironically the volume of information is inversely related to the amount of change in guidance. This is perhaps a good thing, and is telling us that we are reaching a consensus on many of the key areas of clinical practice guidelines. That said, as commented on by Franz Messerli in this issue of Hypertension News, there remains controversy about the decision of the ESH to give more prominence to beta-blockers beyond guideline directed indications. I suspect this is a controversy that will run and run.

Another interesting area of debate has been the role of renal denervation in the treatment of hypertension. It seems such a long time ago, and certainly more than 10 years ago since I was first approached about participating as an investigator in one of the first renal denervation trials. It has been a roller coaster journey since then but only a few weeks ago, the US FDA first approved the Paradise Ultrasound Renal Denervation system from RECOR Medical and Otsuka Medical Devices, followed only 10 days later by the approval of MEDTRONIC's Symplicity Spyral renal denervation system. Both devices approved for the treatment of hypertension. It has been a long haul characterised by admirable persistence and it is going to be interesting to see where these technologies will land in the hierarchy of hypertension treatments.

Another area of development this year has been the explosion of cuffless devices that claim to "measure" blood pressure. There has been a major increase in all manner of devices advertised for sale online to consumers. Obviously, the availability of such technology would be a major breakthrough in terms of convenience and duration of blood pressure monitoring, but only if they work. Whether they work being a very important consideration. Firstly, it is important to note that these "devices" don't measure blood pressure, they estimate it using algorithms, usually based on analysis of a pulse wave form calibrated to the wearer's conventionally measured blood pressure. Second, there is very little, if any regulatory oversight of these devices, in some cases with the devices promoted by medical professionals, or even non-medical advocates, who often have no idea if, or how they work. There clearly needs to be an independent review and source of trusted information of where this technology is at, what it is capable of doing, and what it cannot do. Of course we welcome and must not stifle innovation but the measurement of blood pressure is such an important aspect of health care, this is no place for gimmicks, only facts will do. To this end, I have asked one of our Council members Professor Kario to lead a focus group of experts to generate a state of the art report of what we know about the various means by which these cuffless devices aim to measure blood pressure, whether the data justifies their claims and what the future might hold, in the face of major technological and data science advances, for blood pressure measurement and its regulation.

Finally, one cannot fail to be excited about re-emergence of interest in developing new therapeutic approaches for the treatment of hypertension. In the past year, we have seen the emergence of at least three major new therapeutic approaches; (i) The development of three new

highly selective aldosterone synthase inhibitors entering into phase 2 and 3 trials, initially for the treatment of resistant or difficult to control hypertension (baxdrostat – AstraZeneca and Larundrostat – Mineralys). This coincides with the recognition that undetected aldosteronism undoubtedly plays an underappreciated role in the genesis of hypertension and organ damage. A third aldosterone synthase inhibitor from Bayer (BI 690517) was recently evaluated in combination with an SGLT2-inhibitor in patients with chronic kidney disease. One could anticipate such a combination of aldosterone synthase inhibition with SGLT1-inhibitors being attractive for the treatment of hypertension, and in patients with chronic kidney disease, diabetes, and heart failure. (ii) The second attractive development is in the field of RNA therapeutics, specifically the use of RNA silencing (Zilebesiran, from Alnylam) to inhibit the transcription of angiotensinogen (AGT) in the liver, AGT being the key substrate for renin angiotensin system activation. A single subcutaneous injection of Zilebesiran suppressed circulation AGT by over 90% and lowered blood pressure in adults with mild-to-moderate hypertension for up to six months. With adherence to therapy being a major issue in controlling blood pressure, this extraordinary duration of action could be a major asset. Furthermore, this whole field of RNA silencing holds great promise for the treatment of many conditions where it would be desirable to knock down the synthesis of a single protein manufactured by the liver. Although, I suspect a reversal agent also needs to be developed. (iii) The third novel development is another approach using a biologic, specifically a humanised monoclonal antibody that specifically targets neuropeptide receptor 1 (NPR1) which is the receptor activated by atrial and brain natriuretic peptides. This approach will produce long-lasting stimulation of the NPR1 receptor, for weeks, with all the attendant potential cardiovascular benefits. Two molecules are in development (Novartis and Regeneron) and mindful of the impressive results in hypertension and in heart failure with sacubitril:valsartan, these conditions are the natural targets for early phase ongoing trials with these agents.

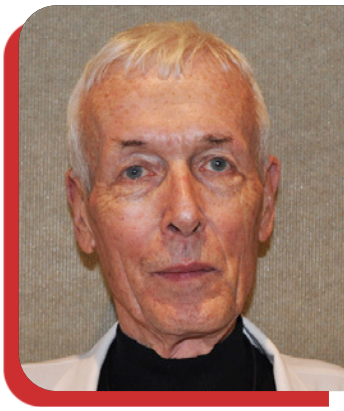
It is going to be fascinating to follow the progress of these new therapeutic developments for the treatment of hypertension and associated comorbidities.

So, it has been an exciting year of change and advances in the field of hypertension. We will continue to feature new developments in the field in future issues of Hypertension News but for the moment, enjoy this new edition, packed with news and information and wherever you are in the world, on behalf of the ISH, I wish you all a happy, healthy and hopefully peaceful 2024.

Bryan Williams - president@ish-world.com

PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

Beta-Blockers upgraded for Hypertension – the bad, the ugly, and the not so good



FRANZ H. MESSERLI AND JERZY GASOWSKI

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In June of this year the European Society of Hypertension (ESH) issued new guidelines for the management of hypertension.[1] In this document, Beta-Blockers (BBs) as a class were upgraded and put on an equal footing with thiazide diuretics, renin–angiotensin system blockers (e.g., angiotensin receptor blockers, angiotensin-converting enzyme inhibitors), and calcium channel blockers. In contrast, most other guidelines advise that BBs should be used for specific guideline-directed indications only.

This unexpected move sparks a few simple questions and considerations:

1. Was this upgrade evidence-based or convenience-based?

   The authors of the ESH guideline freely admit that there is no new evidence for this move. Hence it must have been solely based on convenience. The simple but important question here is of course, convenience for who? In this context, we should recall that some fixed combinations of BBs with other drugs have recently become available. To even remotely suspect that this in any way has been related to the upgrade seems utterly preposterous.

2. The BBs lower brachial BP largely by reducing cardiac output. However, when BP-reducing effect of BBs was concomitantly assessed both on brachial artery and centrally (in the aorta), the reduction in the latter was on average more than 4 mm Hg less pronounced.[2] Population-wise, such difference can translate into a lesser risk reduction by 5-12%.[3] Little surprise that BBs have been documented to be less efficacious than other drug classes to prevent the risk of stroke.[4]

3. The use of BBs comes at a price. Even though a recent meta-analysis purported not to demonstrate any increase in depression fatigue or sexual dysfunction when treated with BBs[5], a reanalysis of the same data showed a 2 to 5 times higher withdrawal rates in BB patients due to sexual dysfunction or fatigue, compared with placebo. For every event prevented, three patients experienced impotence due to BBs. In an another eight, fatigue resulted in withdrawal from such therapy.[6] For an asymptomatic disease such as essential hypertension, such an appalling risk-benefit ratio begs for second thoughts.

4. Today, the advice to use a particular drug class or a particular medication is driven by the outcomes in randomized clinical trials. BBs have been consistently shown to be less efficacious in preventing major outcomes, especially stroke, when compared to ACEi/ARBs or CCBs.[7,8,9] To some extent the guideline authors based their decision to upgrade BBs on a network meta-analysis.[10] However, a closer look at this meta-analysis showed that BBs had no effect on cardiovascular mortality and reduced stroke between 35% and 49% less well than did CCBs, ACEIs, ARBs, and thiazides, respectively. If anything, this meta-analysis corroborates that BBs should keep their downgraded status as most other recent national and international guidelines indicate.

5. There is no doubt that BBs may offer some benefits in many conditions coinciding with hypertension. As underlined by the ESH guidelines, more than 50 such "twofer indications" can be found, ranging from post myocardial infarction (with weak evidence at

best), to heart failure (strongest evidence). It may appear attractive, convenient and less expensive to do a BB twofer, i.e. to lower BP and to concomitantly confer cardioprotection in a post-MI patient. However, the post-MI patient has also been documented to be at an excessively increased risk of stroke (30-fold for the first month and 3-fold for the first year).[11] To us it seems irresponsible to lower BP with a drug class that has a track record of little if any efficacy in reducing the risk of stroke. If indicated, the post-MI patient certainly should receive a BB, but for hypertension an evidence-based therapeutic strategy should be selected that will not only lower mmHg but also, and more importantly confer cerebroprotection. Lowering BP with generically available drug classes such as CCBs, renin–angiotensin system blockers, and long-acting thiazides has been shown to grant outstanding stroke protection. Rather than for convenience's sake to pursue a BB twofer and put the patient at risk, evidence-based therapy should be prescribed.

6. Undoubtedly, the bad, the ugly and the not so good of BBs mostly originated from studies done with atenolol. The argument goes that newer BBs such as carvedilol, nebivolol etc. are different in that they exhibit a more favourable hemodynamic and metabolic profile. True, but then;

a) there are no outcome studies with the newer BBs in hypertension and

b) the ESH guidelines have upgraded all BBs, including atenolol.

As stated, in the ESH guidelines, there is no new evidence justifying a BB-upgrade to first-line therapy. We are concerned that this move might lead to widespread harm because of inferior stroke protection.[12]

It has been said that guidelines in medicine are merely created to offer ammunition to lawyers and to prevent doctors from thinking. Contrary to this dictum, the unexpected upgrade of BBs by the ESH guidelines should enliven physicians to think again and perhaps to more than ever remember Hippocrates's precept of first do not harm.

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NEW SYSTEMS OF CARE FOR HYPERTENSION

Digital hypertension and telemedicine for home blood pressure-centered management of hypertension

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1. What is digital Hypertension

Hypertension is increasing dramatically worldwide, yet its control rate remains poor, with significant disparities among countries and regions.[1] We are confronted with numerous challenges in detecting and controlling hypertension, spanning from healthcare to medicine. Recently, in the digital era, individuals could connect with healthcare providers and medical professionals, leading to the emergence of virtual management of hypertension. Telemedicine has gained significant position in clinical practice during COVID-19 pandemic.[2,3] In 2022, the International Society of Hypertension released a timely consensus paper on virtual management of hypertension, emphasizing the importance of mutual feedback interactions between patients and medical professionals. This approach includes educational publications, phone call education, online group sessions, and interactive digital tools, among other options, which can be selected by patient preferences.[4]

Scientifically, "digital hypertension" is a novel academic research field that leverages the latest digital technology to add value in resolving unmet needs for challenges in hypertension management (Table 1).[5] At a macro-level, it involves conducting population research to provide recommendations for healthcare policy. On a micro-level, it offers optimal individualized medical care by consolidating data on individual blood pressure (BP) variability, control status, lifestyle, medication adherence, laboratory values, and health insurance claims through the use of digital technology. This includes the development of wearable BP monitors, the creation of new indices through the analysis of big data, the use of artificial intelligence (AI) for risk prediction, and the development of BP applications aimed at lowering BP.[5] The goal of digital hypertension research in clinical practice is to establish personalized anticipation medicine.

2. Home blood pressure-centered approach

The home BP-centered approach is the most reliable and practical approach for digital hypertension management. This recommendation is based on evidence indicating that home BP serves as a significant predictor of cardiovascular, cerebrovascular and kidney disease in patients with hypertension.[6,7] Furthermore, the integration of a lifetime personalized health record (PHR)-based home BP monitoring system with telemonitoring, along with co-interventions has demonstrated more effective BP reduction than the traditional approach based on office BP measurements. Thus, home BP emerges as a key metric for lifelong personalized anticipation medicine **(Figure 1)**. Morning home BP assumes a primary role as the initial target and a metric of quality control of antihypertensive medication. This is because the efficacy of antihypertensive medication is at the weakest in the morning, just before taking the pills.

An example of the practical implementation of digital remote management of hypertension can

Figure 1

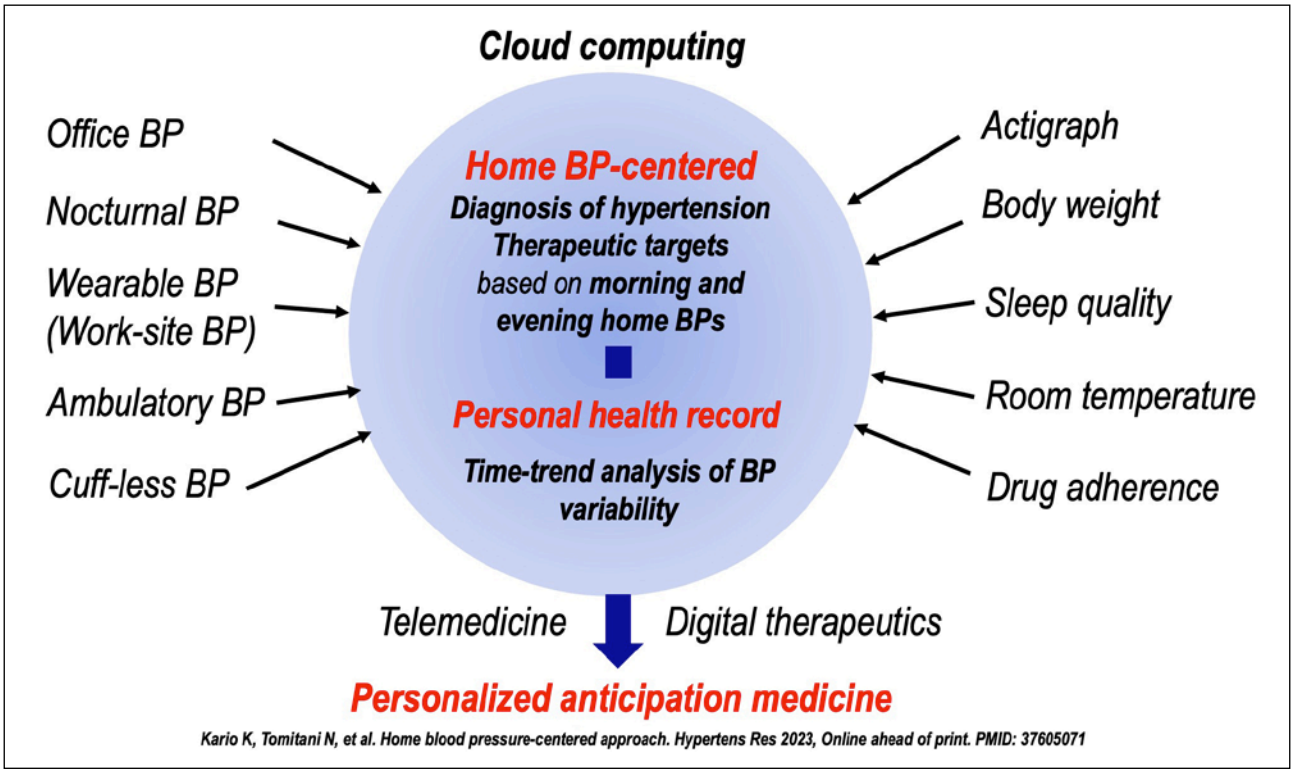
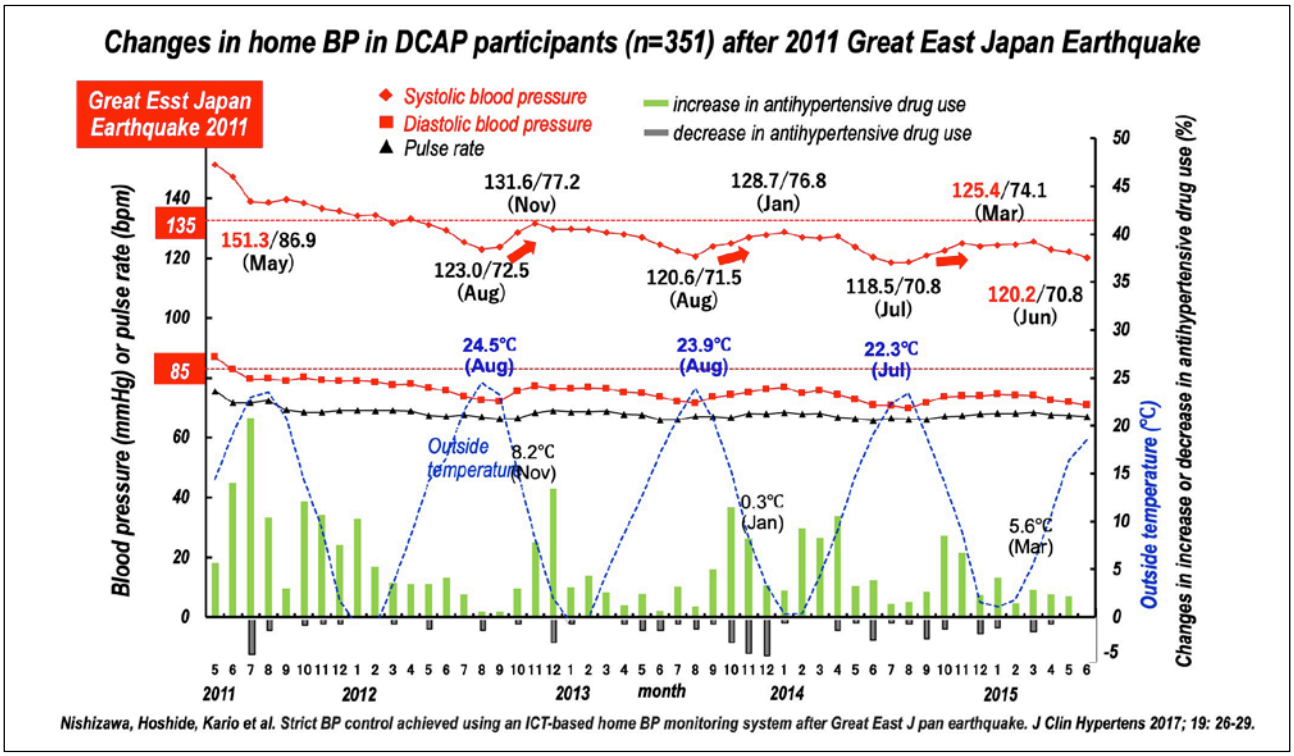


Figure 2



be observed in a study conducted after the Great East Japan Earthquake on March 11, 2011. The Disaster Cardiovascular Disease Prevention (DCAP) network system was introduced into the major shelter in Minamisanriku town devastated by the earthquake and subsequent tsunami, enabling strict BP management to be conducted at home. It is a system using remote ICT BP monitoring with cloud computing. This system has proven successful in minimizing seasonal BP fluctuations for several months to years following the disaster and during COVID-19 pandemic **(Figure 2)**.

3. Blood pressure variability is the master biomarker of digital health

The primary role of digital healthcare lies in "connecting information across time and place." It involves integrating signals emitted by various organs and applying them to current medical practice. Among these signals, BP stands out as the most vital clinical biomarker. BP varies overtime, including changes over the years, throughout the seasons, daily fluctuations, and variations with each heartbeat. They are also influenced by lifestyle conditions (diet, salt intake, exercise, sleep patterns, etc.) and environmental conditions (temperature, humidity, etc.). BP can also be seen as an indicator of one's psychological and organ conditions. Mechanical pressure loads resulting from BP surges play a significant role in triggering various cardiovascular events. In other words, when BP is at its highest, a person's cardiovascular event risk is at its peak. This surge BP is generated by the resonance of each BP surge with difference time-phases (the resonance hypothesis of blood pressure surge).[8]

4. Wearable blood pressure monitoring device and digital technology for anticipation medicine

The development of non-restrictive high-precision wearable BP monitoring devices allows the accumulation of long-term 24-hour BP data with simultaneous environmental data.[9] By analyzing the chronological BP data with environmental and other biological parameters using AI, it becomes possible to assess the risk of organ damage and predict future cardiovascular disease risk. Through the prediction of dynamic pathological surge BP, which trigger cardiovascular events, based on BP variability data and by adjusting the necessary behavioral modifications and medication dosages optimally, personalized anticipation medicine can be achieved. One prerequisite for achieving this is the development of high-precision cuffless BP measurement technology. While various cuffless BP measurement devices are under development, unfortunately, none of them have yet proven suitable for clinical use. Furthermore, data processing and detection of abnormal signals of big chronological data, and developing algorithms to predict risks from obtained data and verifying the accuracy in individual cases represent important directions in the field of digital hypertension. In addition to automated detection of abnormal BP signals, the development of algorisms utilizing machine learning techniques to predict BP changes and the onset of hypertension is needed.

Achieving personalized and predictive healthcare based on individual BP variability is the ultimate goal of digital health. However, there remain numerous challenges to be addressed in the pursuit of individualized and anticipation medicine.

5. Digital therapeutic apps

In recent years, the development of therapeutic apps has become increasingly active. Notably, in 2021, an open-label randomized controlled trial demonstrated the effectiveness of a digital therapeutic system for hypertension, marking the first such achievement worldwide.[10] This digital therapeutic app received regulatory approval in 2022 and is now available for clinical use in Japan through medical insurance. Digital interventions can help facilitate uptake of important guideline-recommended lifestyle modifications such as salt reduction, body weight reduction, exercise, sleep improvement, alcohol reduction, stress management, promoting home blood pressure monitoring, decrease therapeutic inertia, and improve medication adherence. These lifestyle improvements are personalized for each patient through the app. Responders to digital hypertension therapeutics tend to have a higher body mass index and report higher salt intake scores at the baseline, which they can subsequently reduce. Additionally, the effectiveness of digital therapeutics is partly influenced by daily self-reported behavioral efficacy records (SER), which are the number of times a patient inputs daily activity recall into the app. These records are affected by self-efficacy and the app's user-friendliness.

6. Hypertension is now on the stage of implementation medicine

We have a clear understanding of the significant risk hypertension poses to our health, and effective management can mitigate this risk. However, the real-world scenario shows that hypertension is under recognized and untreated among community-dwelling people and is poorly

controlled in medicated hypertensive patients. Digital technology holds the potential to address these unmet needs. Hypertension is now on the stage of implementation medicine, focusing on how to improve detection through screening and how to achieve BP control below target BP thresholds throughout 24-hours. Facilitating research in digital hypertension and integrating telemedicine into clinical practice are promising directions for better management of hypertension.

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NEW SYSTEMS OF CARE FOR HYPERTENSION

From the ashes of COVID to the rise of the PHOENIX: Implementation of Mobile Health Units for hypertension management

Phillip Levy

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Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in the United States[1] with hypertension (HTN) being the primary contributor.[2] This is particularly apparent in marginalized communities such metropolitan Detroit, Michigan, USA where our team has led a decades-long program focused on population health research as well as preventive care screenings and chronic disease management. However, due to the recent COVID-19 pandemic, we underwent a major revision in our approach by providing individualized healthcare resources in the communities via mobile health units (MHUs) and are now applying these strategies to investigate new systems of HTN care and CVD risk reduction.

Rising from the ashes of COVID: Outpatient testing and community health

Prior to 2020, our team conducted CVD research by recruiting subjects via urban emergency departments (EDs) but the emergence of COVID effectively halted ED research and thus, subject recruitment. As such, the ever-changing pandemic required innovative and adaptable strategies to continue serving these communities. While we initially began conducting drive-through COVID-19 testing in fixed locations, we quickly learned that social vulnerability, particularly transportation challenges and low socioeconomic status, proved to be a steep barrier, thus increasing risk in this population.[3] To help alleviate these barriers, we formed a partnership with the Ford Motor Company (Dearborn, MI, USA) wherein a fleet of vehicle-based health platforms now known as MHUs were developed to bring our testing services directly to the community, targeting areas of greatest need and social vulnerability.

As the MHU program grew and the pandemic progressed, we expanded its services to provide a wider range of preventive screenings and resources. Currently, the MHUs offer screenings to promote cardiovascular, metabolic, and kidney health including blood pressure (BP) measurement and testing for diabetes, renal function, and hyperlipidemia, as well as immunizations, HIV and hepatitis C testing, and linkages to primary care providers (PCPs).

The Rebirth of HTN research and overcoming negative social determinants of health

Detroit communities suffer from the highest rates of HTN in the state of Michigan (https://www.cdc.gov/places) and starting in 2020 our MHUs began

screening patients for high BP. In the first year, 3039 people were screened for HTN with 63% having an abnormal BP (≥120/80 mmHg), a subset of whom (32%) met criteria for stage-II HTN.[4] These communities are also challenged by numerous social determinants of health (SDoH). Negative SDoH, including low socioeconomic status and poor access to medical care, among others, are important contributing factors to disparities in HTN and CVD across communities.[5-7] In contrast to traditional healthcare models, the mobile nature of the MHU program makes it uniquely capable of directly addressing such determinants and subsequently reducing the burden of CVD in socially vulnerable populations. Mobile, preventive care enables us to fill crucial gaps in the existing healthcare system and promote cardiovascular health equity in the community by meeting people where they work, worship, live, and play.

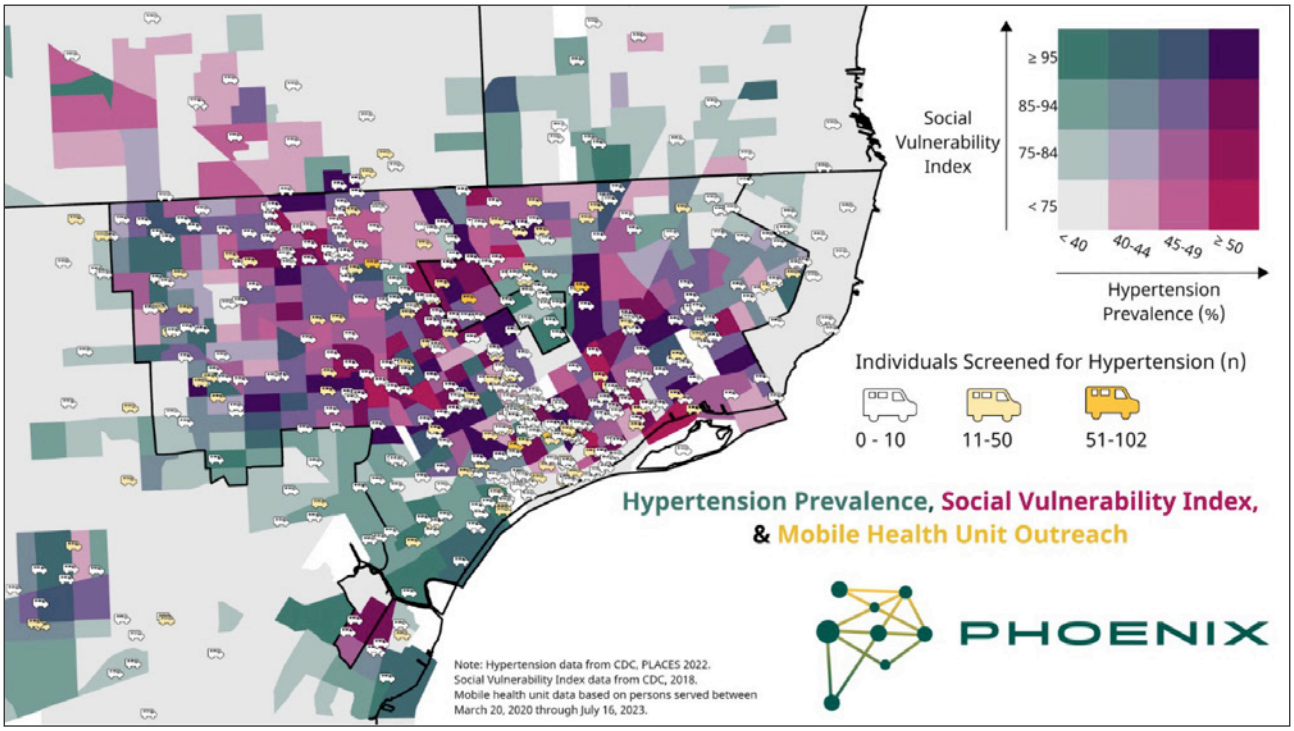
Rise of the PHOENIX: Directing MHUs to socially vulnerable communities

Given our mission to increase access to preventive care in socially vulnerable populations, geographic deployment of the MHU program is strategic and data driven. We leverage Wayne State University's (Detroit, MI, USA) Population Health OutcomEs aNd Information eXchange (PHOENIX) program, which aggregates publicly available data, to map out "hotspots" of high social vulnerability and chronic disease burden. As a result of spatial analysis and data driven vehicle deployment, 41% of MHU patients live in communities in the top quartile of social vulnerability.[3] As shown in **Figure 1**, this approach also allows us to cross matrix SDoH and CVD risk at a census tract level, and directly target outreach to communities that need it most.

A LEAP of Faith to ACHIEVE GREATER: Using MHUs for HTN research

One of our first studies that transitioned from ED to MHU-focused recruitment was "Bring it Down". This state funded project enrolled patients with systolic BPs ≥130 mmHg and connected them to PCPs and social services with follow-up health information captured for quality improvement. Of these participants, 42% had no previous diagnosis of HTN, illustrating the urgent need for continued screening and disease identification in the community.[4] Thereafter, the MHUs were deployed to enroll patients into "Linkage, Empowerment, and Access to Prevent Hypertension" (LEAP-HTN), a program that is part of the American Heart Association Funded RESTORE Health Equity Research Network, with a goal to halt

Figure 1: Social vulnerability and hypertension prevalence in Detroit with overlay of MHU deployment.



disease progression in Black Detroiters at risk of developing HTN.[8] Uniquely, LEAP-HTN engages community health workers (CHWs) to directly address negative SDoH, alleviating the impacts of social vulnerability on HTN risk.[8] We have also received funding from the National Institute of Minority Health and Health Disparities (NIMHD) Health Equity Action Network for ACHIEVE GREATER (Addressing Cardiometabolic Health Inequities by Early preVEntion in the GREAT lakEs Region) which is dedicated to reducing cardiometabolic health disparities in Detroit, MI and Cleveland, OH. Both programs recruit exclusively through our MHUs and utilize CHWs to directly address individualized, negative SDoH. The intervention groups are part of a collaborative care program called PAL2 (Personalized, Pragmatic, Adaptable Approaches to Lifestyle and Life circumstances) that uses team-based care, with CHWs and clinical pharmacists, to manage HTN and prevent disease progression. Given the widespread shortage of PCPs and the promising role of CHWs in HTN management, we believe that the PAL2 template may pave the way for a more efficacious and cost-effective alternative care model for HTN.[9,10]

From the Flames to the Rise of the PHOENIX: The future of MHUs

Just as the myth goes and the Phoenix was consumed by the flames before it was reborn again from the ashes, our historic research program that has addressed HTN and CVD was forced out of our urban EDs and has been reborn in the form of MHUs and active community engagement and early identification of social vulnerability. As we continue to grow and evolve, we continuously seek innovative ways to improve cardiovascular health in community settings. While we do not know if our program's successes are generalizable to other communities, we believe that the MHU program provides a framework for a nationwide mobile health program dedicated to filling gaps in preventive care and promoting health equity in socially vulnerable communities.

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NEW SYSTEMS OF CARE FOR HYPERTENSION

Tactics to improve Chronic Disease Care in forcibly displaced migrant populations

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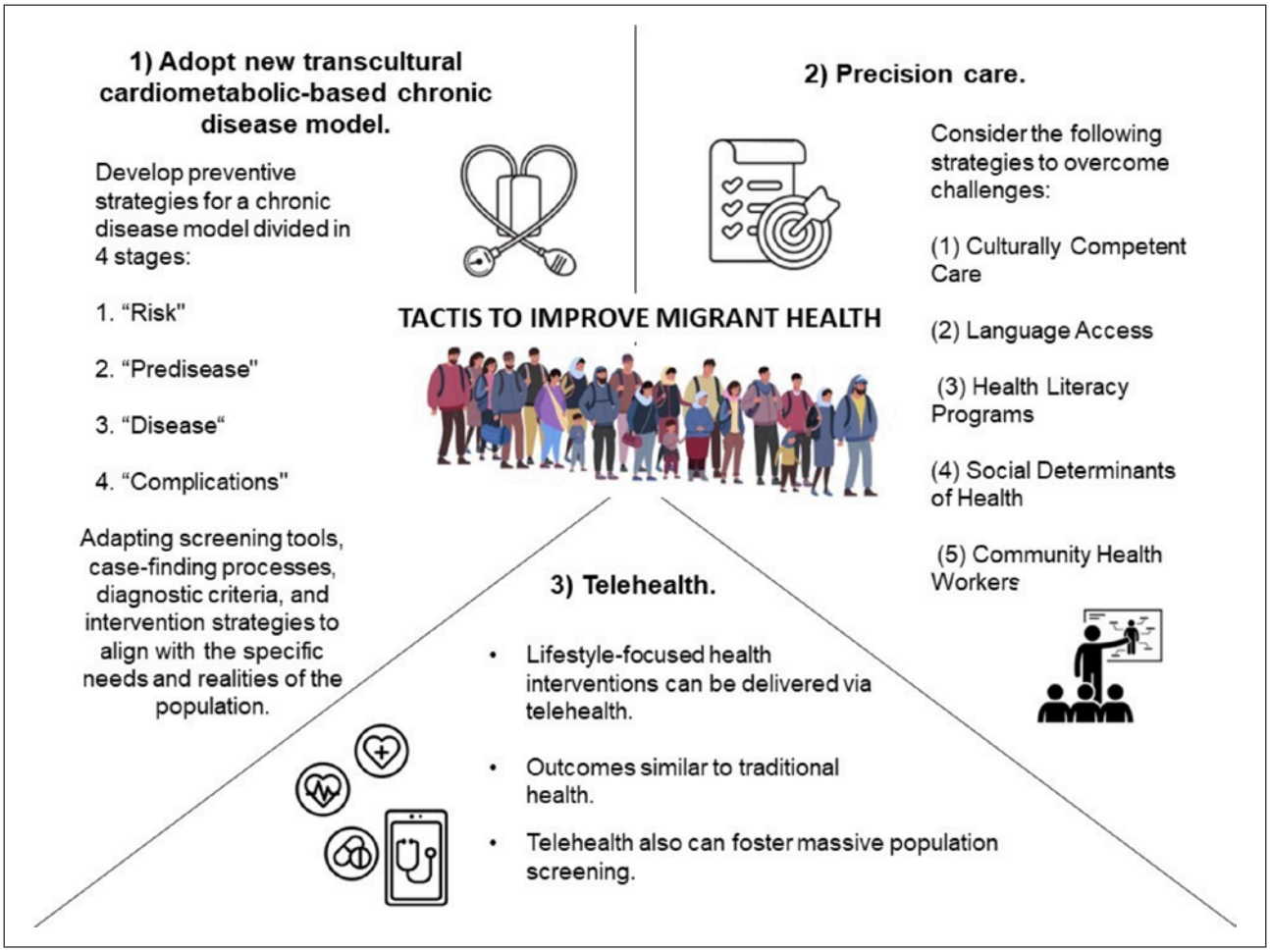
Introduction

The global migrant population is heterogeneous regarding vulnerability, medical needs, and access to quality health care. Migrants who are forcibly displaced due to conflict, persecution, or environmental disasters (e.g., refugees, asylum seekers, and undocumented persons) increased in an unprecedented fashion from 153 million in 1990, to nearly 272 million in 2019.[1] Currently, the forcibly displaced migrant (FDM) population tends to be more affected by chronic diseases, such as type 2 diabetes (T2D), hypertension, cardiovascular disease, and cancer, than infectious diseases.[2] In a recent meta-analysis, the pooled incidence of cardiovascular disease in refugees from Syria and Libya to Europe was 1.71 (95% CI: 1.03, 2.83) times higher compared with non-refugee counterparts. In the U.S., FDM's had a higher prevalence of chronic conditions than the general population, particularly T2D and hypertension.[3] Various factors can promote negative health outcomes in migrants: the interruption of medical treatment and preventive care during the migratory route and post-resettlement; stressful situations, racism, and xenophobia; hostile environment policies; living in refugee camps; and trauma-related mental health problems.[4] The management of these conditions is challenged by several barriers, including limited access to quality healthcare and linguistic/cultural barriers experienced by patients and healthcare professionals.[5]

A healthcare system infrastructure is necessary that can manage complex chronic disease scenarios including multimorbidity preventive care approaches;[6] continuity of care in humanitarian crisis settings; community-based management, engagement, and outreach; and health promotion. Migrants also face difficulties accessing quality healthcare[7] which represents an enormous challenge for governments and the healthcare systems of the country of destination.[8] In this article, we recognize the critical issues surrounding chronic disease care in migrants and propose three tactics to address this situation.

Central Figure: Tactics to improve migrant chronic disease care.



Tactics

Tactic 1. Adopt a new transcultural cardiometabolic-based chronic disease model.

The complex interplay of biological and social determinants of health in vulnerable migrant populations necessitates a suitable pathophysiological model for optimal care. The transcultural cardiometabolic-based chronic disease (tCMBCD) model offers a three-dimensional framework.[9-11] The first dimension involves the progression of chronic disease, consisting of four stages: 1. "risk," 2. "pre-disease," 3. "disease," and 4. "complications." These stages are amenable to various preventive strategies. The second dimension incorporates primary (genetics, environment, behavior) and secondary/metabolic drivers. These driver-based chronic diseases (driver-BCD) are abnormal adiposity (Adiposity-BCD or ABCD) dysglycemia (Dysglycemia-BCD or DBCD), hypertension (Hypertension-BCD or HBCD), dyslipidemia (Lipid-BCD or LBCD), and residual factors like inflammation. These drivers culminate in cardiovascular disease. The third dimension considers the application of social determinants of health and cultural factors to each cell in the "stage x driver" matrix to enhance precision in clinical interventions aimed at preventing CMBCD progression.

Interventions primarily target early stages (e.g., stages 1 and 2) and focus on lifestyle changes. The goal is to mitigate the development and progression of tCMBCD stages, with a focus on physiological, economic, and quality of life metrics. When applying the tCMBCD model to forcibly displaced migrants, cultural aspects from both the countries of origin and destination must be considered and a transculturalization process should be implemented to include the unique biological and social determinants inherent to the target population.[4,12,13] This entails adapting

screening tools, case-finding processes, diagnostic criteria, and intervention strategies to align with the specific needs and realities of the population.[9, 14]

Tactic 2. Precision care. Transcultural adaptations of clinical practice guidelines (CPG) and evidence-based interventions to migrant populations.[12]

To effectively assist FDM, cultural aspects from both their countries of origin and destination must be considered. Begin by addressing the immediate needs of the most vulnerable individuals by continuing their medical care from their place of origin. Innovative prevention strategies should be tailored to the patient's health literacy including their understanding of disease symptoms and complications, beliefs, and how illness affects healthcare outcomes. Compared to the native population, refugees often face challenges in self-care and monitoring the progression of disease. Additionally, this population tends to have poor dietary habits and physical activity, and lower socioeconomic status and education levels, which negatively impact their chronic disease outcomes.[15]

To address these challenges some factors should be considered: **(1) Culturally Competent Care:** Healthcare providers should be trained to understand and respect the cultural norms, beliefs, and values of the migrant population to enhance trust and patient-provider communication; **(2) Language Access:** Healthcare facilities should ensure access to interpreters and translated materials to facilitate effective communication; **(3) Health Literacy Programs:** Migrant populations often have limited health literacy, making it essential to provide educational programs tailored to their needs; **(4) Social Determinants of Health:** migrants are often vulnerable to social issues, such as housing, employment, and access to healthy food. It is necessary to develop policies that promote social equity to enhance the care of FDM; **(5) Community Health Workers:** Employing community health workers from the same cultural background can bridge gaps in healthcare delivery and help educate, navigate the healthcare system, and provide social support for FDM.[16]

Tactic 3. Telehealth.

In a recent review, we explored the role of telehealth in enhancing the cardiometabolic health of migrants, particularly focusing on lifestyle interventions for hypertension and dysglycemia.[4] Telehealth effectively treats chronic metabolic conditions like hypertension[17] with outcomes similar to traditional healthcare. Lifestyle-focused health interventions can be delivered via telehealth and have been shown to reduce cardiometabolic risk, T2D, hypertension, and high cholesterol.[18] Schrauben et al,[19] used a dietary app-supported telecounseling approach, resulting in decreased sodium intake (-638 mg/day, $P < 0.001$), systolic blood pressure (-5.7 mm Hg, $P = 0.02$), and diastolic blood pressure (-4.1 mm Hg, $P = 0.01$).[19] Moreover, other studies found telehealth to be as effective as in-person visits for weight loss and glycemic control.[20] Riza et al[21] applied an electronic algorithm to enhance healthcare for migrants, highlighting the need for mental health support, vaccination advice, weight control, and dental care.[21] Thus, culturally adapted telehealth services can benefit migrant populations by improving healthcare and reducing the burden of chronic diseases.

Telehealth also can foster massive population screening. Recently, we participated in a campaign that got a Guinness World Record attempt to gather the most T2D screening forms in one week. A total of 47,267 individuals from 21 Latin American and Caribbean countries were screened using the Finnish Diabetes Risk Score (FINDRISC) applied via telehealth and we found 35% of subjects at high risk of T2D. This project highlighted how screening tools can be easily implemented with eHealth technology across social networks to detect individuals at risk.[22]

Conclusion

Improving cardiometabolic care in migrant populations requires a multifaceted approach that, if framed within the cardiometabolic-based chronic disease model, can address not only medical care but also the social, cultural, and lifestyle determinants of health. Transcultural adaptations and culturally competent care, language access, health literacy, community engagement, and policy changes are all essential components of a comprehensive strategy to reduce health disparities. Telehealth demonstrates outcomes comparable to those of traditional health care and offers an excellent opportunity to improve

the healthcare of difficult-to-reach populations such as FDMs. By implementing these tactics, healthcare systems, and policymakers can work toward more equitable cardiometabolic care for all.

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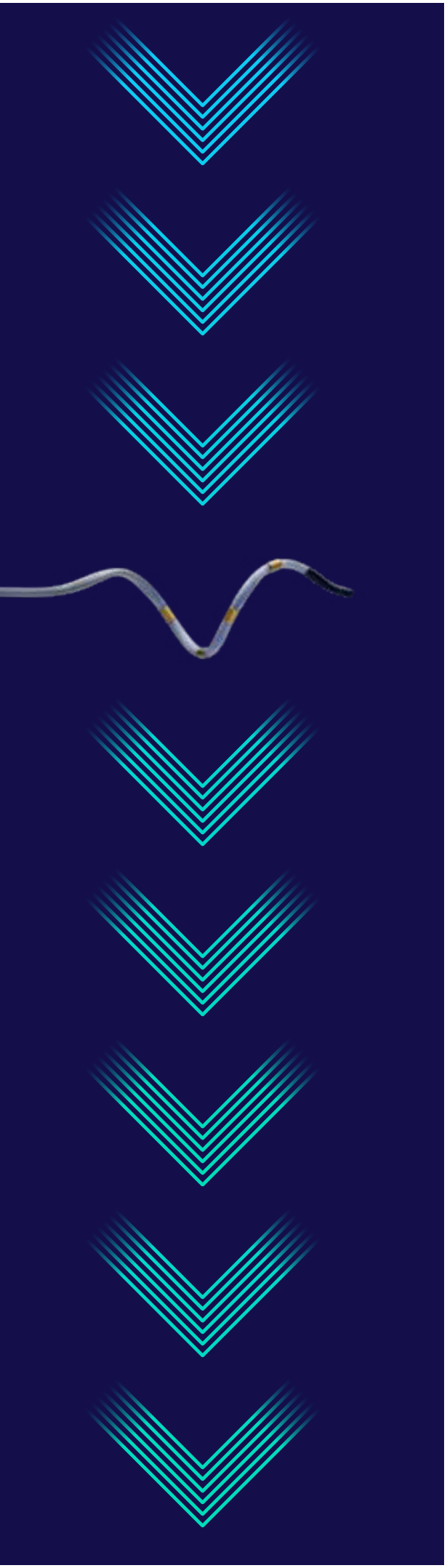

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NEW SYSTEMS OF CARE FOR HYPERTENSION

Systems of Care Programs for Hypertension Management

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High blood pressure is the primary modifiable risk factor for global cardiovascular fatalities, contributing to over 11 million deaths yearly.[1] A staggering 1.4 billion individuals worldwide grapple with uncontrolled blood pressure, with the majority of those affected in low- and middle-income countries.[2]

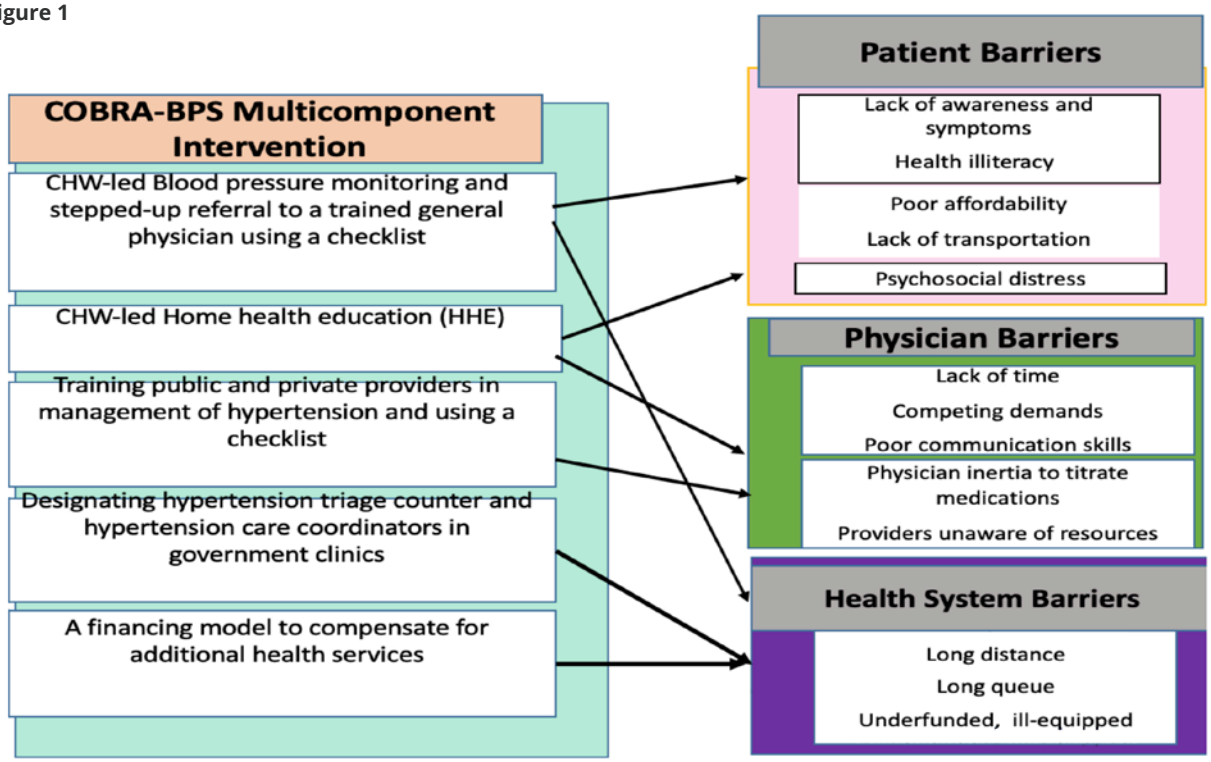
Despite numerous clinical guidelines for hypertension management and evidence showing clear benefit of blood pressure (BP) control, achieving optimal BP control remains a challenge.[3] Furthermore, disparities persist among racial and income groups, even within high-income countries, resulting in disadvantaged subgroups facing greater difficulty in controlling blood pressure, leading to higher rates of cardiovascular mortality.

Barriers obstructing effective blood pressure control manifest at various levels, encompassing the patient, provider, health systems, and communities at large. Evaluations of trials through systematic reviews reveal that singular interventions, such as solely educating physicians or patients, deploying automated reminders, or distributing home blood pressure monitors, do not yield significant population-level benefits in blood pressure control.[4,5] On the contrary, strategies implemented at the systems level, addressing barriers across multiple tiers and fostering behavioral changes at the organizational, community, and individual levels, demonstrate clinically meaningful benefits and a higher likelihood of sustainability.[4,5] Notably, making use of existing health infrastructure enhances feasibility, cost-effectiveness, scalability, and sustainability.

One promising model involves team-based care especially if led by non-physician health workers (NPHWs) guided by behavior change theories, providing increased social support and time for empathetic listening. Such models operate under physician supervision, delivering algorithm-driven care through collaborative agreements, and have exhibited considerable benefits.[6] However, these care models are primarily assessed in research settings within urban, high-income environments and need to be expanded to incorporate screening for social needs and response protocols in primary care to ensure equitable access to marginalized communities for maximum impact.

Health systems in low- and middle-income countries suffer from significant underfunding and have traditionally concentrated on addressing communicable diseases, as well as maternal and child health. Evidence from these countries, including findings from major multi-country trials, suggests that comprehensive interventions addressing contextually relevant barriers to hypertension care at various levels have the potential to enhance blood pressure control and reduce cardiovascular risk. For instance, the multi-country **COBRA-BPS** cluster randomised trial demonstrated the effectiveness, cost-effectiveness, and acceptance of a non-traditional model **(Figure 1)** involving trained community health

Figure 1



workers conducting blood pressure monitoring at home, providing healthy lifestyle counseling using behavior change communication strategies, and referring patients to trained physicians, all tailored to the local public healthcare infrastructure, in rural communities across Bangladesh, Pakistan, and Sri Lanka.[7]

The community health workers were trusted individuals within the community, collaborating closely with households and employing behavior change communication strategies. They recommended healthful diets, emphasizing seasonal produce that could be accommodated within the household budget, and encouraged physical activities that were both practical for the environment and culturally suitable. Referrals were made to the local community physician, equipped with training in the latest hypertension management techniques and utilizing a comprehensive checklist. As these health workers provided in-home health education and conducted blood pressure measurements, the entire family, including children and adolescents, reaped the benefits.

This intervention led to an enhancement in blood pressure control and was cost-effective, amounting to less than US$2 per person annually from the perspective of the healthcare system.[8]

Similarly, research conducted in various low- and middle-income countries (LMICs), such as Argentina, Nepal, Kenya, and China has highlighted the advantages of implementing task-sharing strategies.[9] These involve utilizing community health workers to provide hypertension care through blood pressure monitoring, lifestyle guidance, and facilitating connections to clinics.

Furthermore, taking advantage of existing infrastructure for infectious diseases like HIV and tuberculosis enables the possibility of opportunistic screening, raising awareness, and treating hypertension. Therefore, the expansion of non-traditional healthcare models tailored for underprivileged populations is likely to significantly narrow the gaps in blood pressure control and cardiovascular disease (CVD) management.

Simultaneously, it is imperative that primary healthcare centers make antihypertensive and

lipid-lowering medications easily accessible or available at subsidized costs for patients. Universal health coverage, which encompasses affordable access to high-quality essential medicines for all, is advocated by the United Nations' Sustainable Development Goals.

Reforms in health insurance must incorporate inclusive coverage for hypertension care, including non-traditional healthcare models integrated into primary care, while also reducing out-of-pocket expenses for antihypertensive drugs.

Another illustrative example of non-traditional model of hypertension care is the integration of community pharmacists and barbers in a US barbershop setting, resulting in significant improvement in blood pressure among Black individuals through health counseling and adjustment of antihypertensive medications.[10] Despite its efficacy, integrating such models into the existing healthcare system remains a considerable challenge.

Empirical evidence, including findings from pragmatic studies in Singapore, indicates that single-pill combination (SPC) antihypertensive medications for high-risk patients, as part of the SingHypertension multicomponent intervention, are more effective and cost-efficient compared to standard care in primary care settings. These medications should ideally be available at no cost or at subsidized rates.[11] The SingHypertension program demonstrated cost-effectiveness relative to standard care, with an incremental cost-effectiveness ratio (ICER) of SG$33,474 per disability-adjusted life year (DALY) averted, based on a willingness-to-pay threshold of SG$75,000. These findings were presented recently at the AHA Scientific Sessions in Philadelphia 2023.

The World Health Organization recently launched the first Global Hypertension Report, and has also embarked on the Global Hearts Initiative with Resolve to Save Lives which resulted in the development of the HEARTS Technical Package, comprising of crucial modules for training healthcare providers. Integrating outreach programs with trained community health workers leading blood pressure monitoring and referrals is expected to enhance the program's effectiveness and scope.

Accumulating evidence underscores the potential benefits of digital health interventions in hypertension care. For instance, the use of smartphones by healthcare workers and patients for virtual follow-ups improves adherence to antihypertensive medications and promotes connections to clinics. These initiatives should be integrated into multicomponent interventions to enhance outreach and efficiency whenever possible.

Most importantly, advocacy campaigns and community engagement initiatives are essential for the widespread implementation of evidence-based healthcare systems. The International Society of Hypertension urges each country to establish a Hypertension Task Force, aiming to improve blood pressure control rates by at least 50% by 2030, relative to the rates in 2015, in order to accomplish Sustainable Development Goals 3.4.[2] Such concerted efforts are expected to save millions of lives and prevent disabilities related to hypertension worldwide.

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NEW SYSTEMS OF CARE FOR HYPERTENSION

Urban Hypertension Management

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Arterial hypertension continues to be the chronic non-communicable disease with the greatest impact on mortality worldwide.[1] Furthermore, hypertension is responsible for the largest number of associated complications, with repercussions on the quality of life of individuals and on health costs. Recently, the World Health Organization (WHO) published its first report on the devastating global impact of hypertension, including recommendations on how to diagnose and treat this silent killer.[1]

According to the report, the number of individuals living with hypertension (considering blood pressure values of 140/90 mmHg or more or taking medications) increase from 650 million to 1.3 billion between 1990 and 2019.[1] This figure is equivalent to a third of the adult population worldwide, and without proper treatment, high blood pressure can cause stroke, acute myocardial infarction, heart failure, kidney failure as well as cognitive dysfunction and other health problems. Approximately half of those with hypertension are unaware of their condition, and approximately eight out of ten people with the diagnosis do not receive adequate treatment.[1] Thus, it is very important to implement global action programs to combat arterial hypertension.

It is noteworthy that more than 75% of adults with hypertension live in low and middle-income countries. Prevention, early detection, and adequate treatment and control of hypertension are among the most cost-effective health interventions and should be emphasized by all countries as part of their national health packages offered in primary care.

The economic benefits of better hypertension treatment programs strongly outweigh the related costs. The WHO report estimates that if there is an increase in the number of hypertensive patients effectively treated for hypertension in these countries, reaching the same levels seen in high-performing countries, it will be possible to prevent 76 million deaths, 120 million strokes, 79 million incidents of acute myocardial infarction and 17 million cases of heart failure by 2050.[1]

To achieve these numbers, it is important to develop programs that involve primary care, health professionals, the community and the government, working together.[2] One of the initiatives that has shown important success is the HEARTS program of WHO for the management of cardiovascular diseases in primary health care.[3] This package, already applied in more than 40 low and middle-income countries, has reached more than 17 million people in Bangladesh, Cuba, India and Sri Lanka among others, and has helped ensure the strengthening of hypertension treatment.[3] Other successful experiences have been applied in urban regions of low and middle-income countries, with the involvement of various sectors of society, and with very significant results.[4] I want to highlight the initiative CARDIO4CITIES, a global multisector urban health initiative launched in 2018 in three low and middle-income settings, aiming to reduce the burden of hypertension and improve population cardiovascular health.[5,6] The initiative included measures for a better quality of Care, early Access, policy Reform, Data and digital recordings, Intersectoral collaboration, and local Ownership (CARDIO4CITIES).[5] The cities selected

for the program application were Ulaanbaatar (Mongolia), Dakar (Senegal), and São Paulo (Brazil).

In São Paulo, a district in the west region (Itaquera) was chosen to initially introduce the project. The program offered an extensive portfolio of health intervention options based on the local needs for hypertension care. Together, the city health authorities and local partners for the initiative (including medical societies such as the Brazilian Society of Hypertension) developed personalized intervention packages to address all the difficulties related to cardiovascular care in the population.[5]

The interventions included the following actions: 1) uniform hypertension approach for primary care health workers with easy algorithms and clinical decision support tools; 2) organized early screening for hypertension by BP measurements in health services and in places with a high number of people in the cities (such as subway stations, football stadiums or samba school rehearsals); 3) data registers for monitoring indicators of blood pressure control and outcomes; 4) supporting data-driven decision-making.[5,6]

After less than two years of the implementation of the CARDIO4Cities program, BP control rates among patients in primary health centers increased from 12% to 31% in São Paulo, from 7% to 19% in Dakar, and from 3% to 19% in Ulaanbaatar **(Figure 1)**.[5] Besides that, in another study we model the long-term population health impact and cost-effectiveness of this multisectoral urban population health initiative, provide evidence that the multisector interventions adopted in the program could have a great impact to long-term CV health outcomes in the urban population, and are possible cost-effective.[6]

Thus, initiatives as the CARDIO4Cities approach and HEARTS program can be effective solutions to alleviate the growing cardiovascular disease burden in cities across the world.

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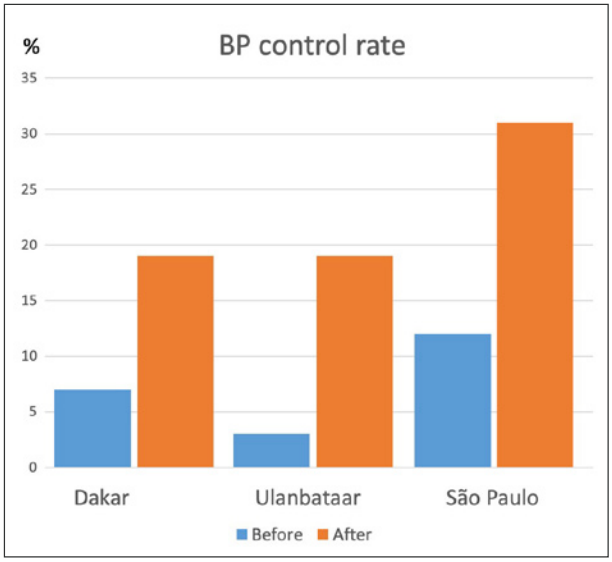
Figure 1: Control rate of blood pressure before and two-years after implementation of CARDIO4CITIES program



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PERSPECTIVES ON SINGLE PILL COMBINATION TREATMENT AROUND THE WORLD

Introduction

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Hypertension is viewed as a major global risk factor for cardiovascular and kidney disease.[1] Prevention and effective and up-to-date management of hypertension are very important to address this major risk factor. In this vein, lifestyle modifications are important along with use of multi-drug regimens. Realizing that more than one medication is oftentimes needed to lower high blood pressure, various hypertension guidelines worldwide recommend single pill combination therapy as an option to simplify medical regimens and promote use of combinations of drugs that are complementary for treatment of hypertension. Recently published data also demonstrates an association between lower rates of adverse outcomes and use of single pill combination therapy.[2]

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In this article, members of the Americas Regional Advisory Group (RAG) invited other ISH members from countries around the world to comment on the use of single pill combination therapy in their own respective countries. The goal is to better understand current practices around use of single pill combination therapy and challenges on a global level to managing hypertension and use of guideline recommended therapeutic options. Ultimately, the hope is to increase knowledge of global practices and barriers to providing up-to-date hypertension management. In doing so, we may find that we are more similar than different.

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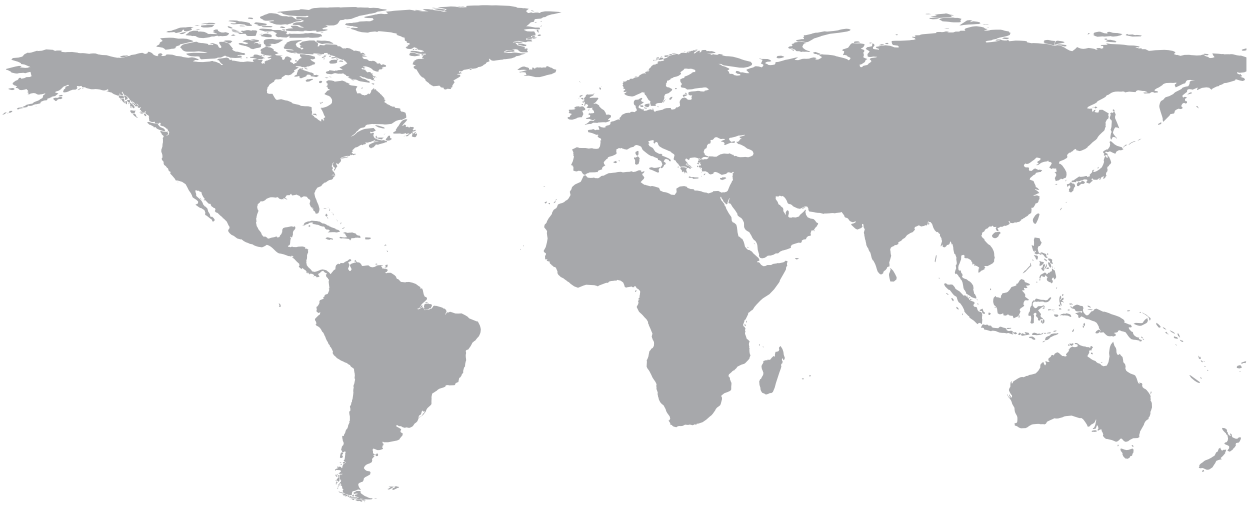

Africa

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Despite considerable evidence demonstrating the superiority of single pill combination (SPC) antihypertensives, use in sub-Saharan Africa is limited. There is limited literature on the prevalence of SPC use, but in a small study from Nigeria it was reported to be 56.8%.[1] However, this is not representative of African proportions due to the differences in healthcare models. There are numerous reasons for the low uptake of SPC, many of them are related to financial constraints, either at an individual level or a policy maker level.

The costs of managing hypertension and the consequences thereof are nearly insurmountable in low- and middle-income countries. The direct costs for treating hypertension in South Africa (an upper-middle income country but with a low resource environment where patients access government healthcare services) were estimated to be ZAR 10.1bn.[2] These expenses cover the cost of medication as well as the costs for care of hypertension mediated organ damage. In Africa, a large proportion of people self-fund all medical expenses and do not have access to government funded healthcare, including medications. Some pay insurance, but the majority are just unable to afford basic healthcare, never mind ideal healthcare.

Direct costs do not include societal costs, which are close to three times the direct costs.[2] These hidden costs are seldom accounted for. Until we account for all expenses and losses from hypertension, we will continue to overplay the cost of medication at the expense of the individual and the populations we serve. While we do need to account for these expenses, we also need to ensure equitable access to quality affordable antihypertensive SPC medications to limit the rising cardiovascular scourge.

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Americas

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The International Society of Hypertension initiated activity May Measurement Month showed that only 20% to 30% of Latin American hypertensives are within recommended blood pressure targets. Affordability and accessibility for approved hypertension drugs, patient's lack of treatment adherence and persistence and practitioner's inertia are between the most well-known challenges to improve hypertension control.

The database of the Lombardy Region showed that a two-drug single pill fixed dose combination (SPFDC) strategy as first step in hypertension treatment reduced cardiovascular end points.[1] The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension study (Accomplish) increased the achievement of blood pressure targets from 37% to almost 80% with SPFDC treatment. The Systolic Blood Pressure Intervention Trial (SPRINT) required 2 or more drugs in 60% of patients in the standard arm and almost 85% in the intensive arm to achieve the goals.

The 2,017 Argentina National Registry of Hypertension (Renata-2) showed that 73.4% of hypertensive patients were treated with monotherapy and only 8.3% were treated with SPFDC, despite Argentina Hypertension Guideline recommends in grade 1 and 2 hypertension SPFDC treatment (class of evidence I level of evidence C; class of evidence I level of evidence A, respectively).[2] The CHARTER (**C**ontrol de la **H**ipertensión **ART**erial por **E**specialistas en A**R**gentina [hypertension control by specialists in Argentina]) study included 1,146 patients in 10 hypertension specialist centers in Argentina. The consumption of SPFDC was 42.5%. The fragmentation of the health system in Argentina is the main barrier for the use of SPFDC. Private health funders agree to finance SPFDC, whereas state and unions social services and the retirement institute do not cover the prescription of SPFDC.

The START study by Schmieder R et al in a retrospective claims data supports the notion that SPFDC reduces mortality and cardiovascular events compared to identical drugs as multipills.

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Asia Pacific (APAC)

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Data from the Korean Fact Sheet 2023 indicates that two out of three patients with hypertension have one or two comorbidities such as diabetes and dyslipidemia. And three out of five patients with hypertension need two or more drugs to control their blood pressure. One or two out of five adults have some problems in swallowing their medication according to reports from the general population.[1] The prevalence of swallowing difficulties will become much higher in the context of aging populations around the world. In particular, elderly patients who have had a stroke, or who take a variety of drugs from various specialised clinics, are more likely to have swallowing diffiicultes.

Asia-Pacific is the region with the highest prevalence of hypertension and cardiovascular morbidities and mortalities and this is ever increasing. And in most Asian hypertension clinics including mine, the initial prescription of single-pill combinations (SPCs) is not the first choice, even though this is the recommendation from national societies of hypertension, but we try to reduce the number of pills using SPCs as early as possible after stabilization of medication.

The big barriers of dose flexibility and pill size are not problematic any more due to various SPC combinations and bio-technical advances.

From reports from Korea and China, the penetration rate of SPCs is increasing this decade with improving adherence and control rates.

The START-Study of Schmieder RE, et al is important and a strong point of reference to increase SPCs by those who still hesitate to prescribe them in their clinics.

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Europe

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Persistence to treatment is a crucial issue in relation to patients requiring regular treatment for clinical conditions such as hypertension, dyslipidemia, etc. Poor persistence turns into a shortage in the preventive impact of therapy with a lesser than expected beneficial effect in terms of control of CV risk factors and clinical outcome.

The situation of blood pressure control in European hypertensive patients is far from being satisfactory with a significant difference in the percentage of well controlled patients ranging from 20 to 50% according to a recent report of the NCD working group.[1]

The main reasons for poor controlled hypertension in Europe are the negative attitudes of some patients ("I do not like the drugs"), the insufficient patient-doctor relationships particularly with younger patients with higher potential CV risk,and the poor adherence to treatment, largely based on poor propensity or reluctance to take prescribed drugs, particularly in patients treated with a high number of pills.

Many possible solutions have been provided ranging from professional incentives to some individualized approach to poor persistent patients, but the only one that has provided measurable results is the use of single-pill fixed dose combinations (FDCs).

This strategy has been demonstrated to be very effective in controlling blood pressure and reducing the costs required for the management of hypertension. Unfortunately, some recent Italian data have largely limited our expectations by showing that a large number of patients are still treated with monotherapy with no increase in the prescription of FDC's over time.[2] Now we have new evidence that demonstrate that the administration of a FDC may improve both persistence and outcome in a large population of patients and according to a reliable study design and this would be another brick in the wall against hypertension.

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Middle East and North Africa (MENA)

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The benefits of Single-Pill Combinations (SPCs) for hypertension have been proven in recent studies to have enhanced treatment adherence and reduce cardiovascular risks and mortality with a better control of blood pressure yet, we are yet to achieve target for a single pill globally.

The MENA region has a vast population living in low and middle-income countries, creating flagrant economic diversity. SPCs could be

considered expensive and thus create an obstacle for physicians to prescribe and patients to adhere to. Collaborative efforts with policymakers and pharmaceutical companies should be implemented to improve pricing schemes and achieve a more balanced cost-effectiveness.

Other barriers include the lack of awareness of benefits of SPCs and availability of standardized management protocols. To help promote the use of SPCs in the region, more widespread education should be made available to train healthcare professionals on the use and benefits of SPCs. Additional data representative of the region in the realms of patient satisfaction, scientific validity, acceptability, access, cultural aspects, and cost-effectiveness, is warranted.

South and Central Asia (SACA)

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We have learnt a lot regarding hypertension in the last three or four decades. However, hypertension continues to be a disease of three paradoxes. It is:

- Easy to detect but diagnosis rates are dismal.
- Easy to treat but treatment rates are disappointing.
- Several potent drugs are available, but control rates are abysmal. More importantly, hypertension control rates are low at 11% and 20% among rural and urban patients, respectively. We need urgent measures to address this important public health issue.

The second major lesson that we have learnt is that the initiation of treatment should comprise of at least half dose of two drugs in a single pill combination (SPC). This has been emphasized by several guidelines that have been published recently. However, there are several challenges in implementing this on scale in a country like India and in South Asia. First there are no trials from South Asia addressing this issue. To obtain an answer, we are conducting the "Treatment Optimisation for Blood Pressure with Single-Pill Combinations in India (TOPSPIN)" which is a trial to compare the efficacy of three single pill combinations (SPCs) of two anti- hypertensive agents on 24-hour ambulatory systolic blood pressure (ASBP) among individuals with hypertension in India. This is a multi-centre, individual randomized single-blind, parallel-group, three-armed superiority trial.

The results of this study will provide evidence-based information to treat hypertension patients in the South Asian region effectively.

Other issues include addressing supply chain challenges of SPC, patient engagement in a team based care approach, understanding the journey of a patient with hypertension and overall a need for health system redesign to address the burgeoning burden of hypertension in India.

NEW DIMENSION SERIES

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

CATEGORY A: HYPERTENSION AND LIFE ENVIRONMENT

Hypertension as the life-environment disease

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1. Hypertension as an Environmental Disease

Until now, hypertension and subsequent cardiovascular (CV) events have been considered lifestyle-related diseases, as an individual's living behavior deeply influences their occurrence. However, in recent years, it has become evident that environmental factors such as cold weather and air pollution also have a significant impact on an individual's blood pressure (BP). Furthermore, it has been observed that in the case of environmental disruption due to disasters, hypertension and CV events can be triggered. Therefore, hypertension and CV diseases can be regarded as environmental diseases.[1]

2. Disasters Disrupting the Living Environment and Triggering 'Disaster Hypertension' Leading to a High Incidence of Cardiovascular Diseases

Japan is a country prone to frequent earthquakes. I myself have experienced two of these, the Hanshin-Awaji earthquake and the Great East Japan earthquake, and have been involved in disaster medicine. The stress from disasters and the disruption of the living environment significantly impacts the body's homeostasis, resulting in the onset of CV events.[2-5] One crucial factor contributing to this is the elevation of BP.[2] The hypertension that arises during disasters is known as 'disaster hypertension',[3] and its causes are believed to include increased salt sensitivity due to factors such as sympathetic nervous system overactivity, disruptions in circadian rhythms, and increased salt intake during meals.[3, 4] The increase in CV events stemming from disaster-induced hypertension can be controlled. After a disaster occurs, monitoring BP in shelters and homes allows for the identification of poorly managed disaster hypertension and subsequent therapeutic intervention.[2]

To be prepared for immediate use during disasters, we have developed a disaster cardiovascular prevention (DCAP) risk score based on the extent of damage and medical history, as well as a Prevention Score that assesses lifestyle factors, including salt reduction, and environmental factors like noise, light, and temperature.[2, 3]

3. What Is Thermo-Sensitive Hypertension?

CV events aren't solely caused by abrupt environmental changes like disasters. Routine environmental factors also significantly affect BP, altering the risk of CV diseases. In countries with distinct climate season changes, such as Japan, there is an increased occurrence of CV diseases like stroke, coronary artery diseases, heart failure, and aortic dissection during the winter. BP also exhibits similar seasonal fluctuations, with early morning BP rising more during the winter and an increase in BP variability. Early morning represents the time when BP changes from nighttime to daytime are most pronounced. In patients undergoing antihypertensive therapy, early morning BP

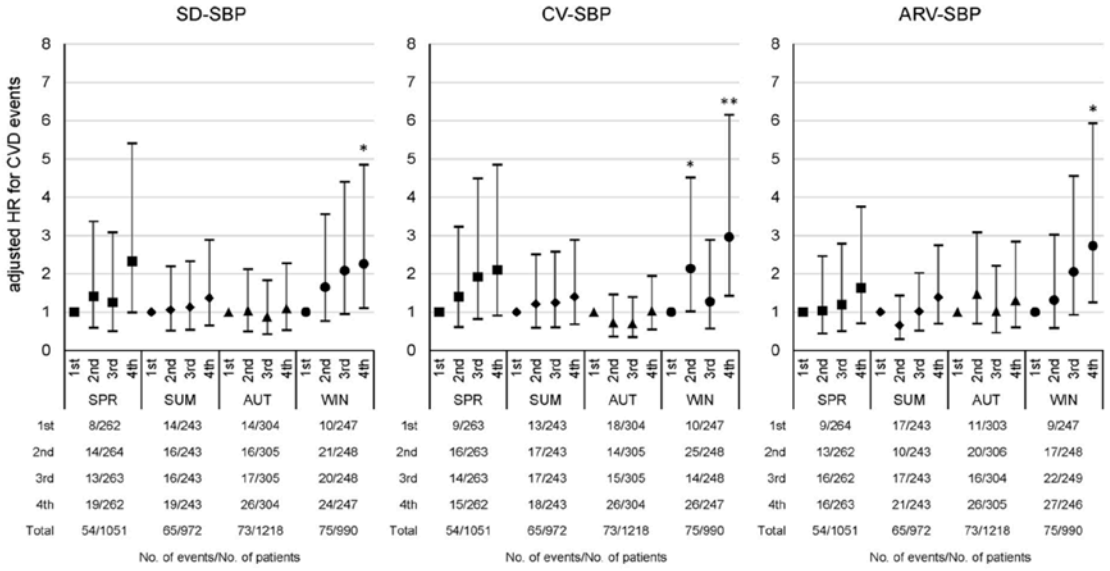
before taking medication is a critical blind spot where the antihypertensive effect is at its lowest.[6]

It's widely known that morning surges in BP and early morning home BP levels are associated with risks like stroke and myocardial infarction.[6, 7]

Moreover, an increase in the variability of home BP and peak values (an average of up to three points within a two-week period) are clear risk factors for onset of stroke.[8] Especially, the increased BP variability during the winter is linked to a higher risk of stroke **(Figure 1)**.

Figure 1. Seasonal variation of impact of BP variability on cardiovascular event risk

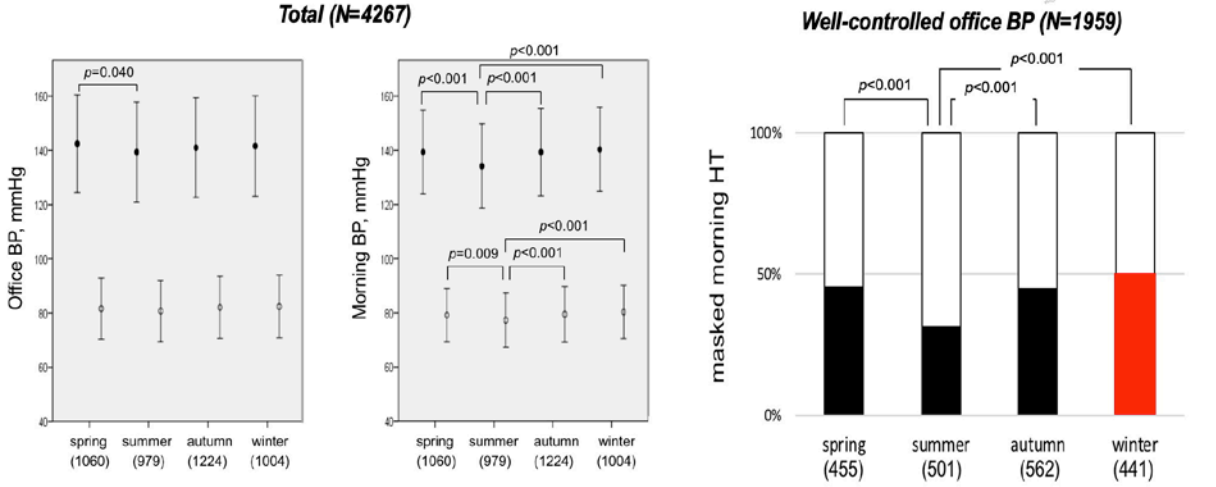
4231 patients of the nation-wide J-HOP study (Japan Morning Surge-Home Blood Pressure)



Narita K, Hoshide S, Kario K. Hypertension; 2022; 79: 2062-2070

Figure 2. Seasonal variation of blood pressure and masked morning hypertension

Data from nation-wide J-HOP study (Japan Morning Surge-Home Blood Pressure)

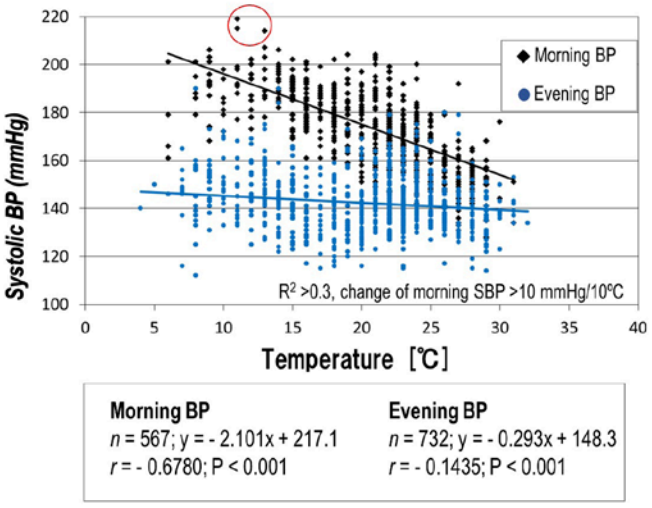


Narita K, Hoshide S, Fujiwara T, Nanegae H, Kario K. Am J Hypertens 2020; 33: 620-628.

Figure 3. Thermosensitivity and seasonal variation of actisensitivity

A. Thermosensitivity (the slope of BP against temperature)

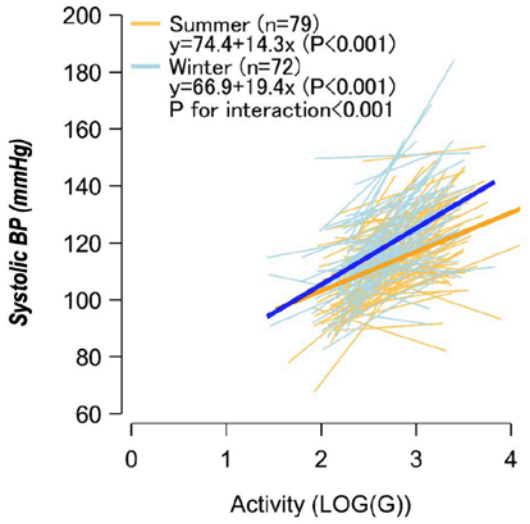
Thermosensitive hypertension *is defined by the* ***thermosensitivity*** *≥10 mmHg-increase in systolic BP/10°C-decrease in temperature*



Morning BP	Evening BP
n = 567; y = - 2.101x + 217.1	*n* = 732; y = - 0.293x + 148.3
r = - 0.6780; P < 0.001	*r* = - 0.1435; P < 0.001

Kario K. Am J Hypertens. 2021; 34: 783-794.

B. Actisensitivity (slope of BP against physical activity)



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Previous studies using Ambulatory Blood Pressure Monitoring (ABPM) have reported that nighttime BP increases during the summer, and early morning BP rises during the winter. The morning BP surge in winter has been identified as a CV risk factor for the elderly. Recent research in home BP measurements has shown that a rise in morning BP (135/85 mmHg or more) during the winter has been observed in approximately half of hypertensive patients whose office BP is controlled below 140/90 mmHg **(Figure 2)**. Furthermore, studies on nighttime home BP monitoring have found that even when morning, evening, and daytime home BPs are controlled to below 135/85 mmHg, masked uncontrolled nighttime hypertension is more frequent during the summer at 45.6% compared to 24.9% during the winter.[9] This may partly be attributed to a higher salt intake against dehydration, a decreased dose of antihypertension drugs, poor sleep quality, etc. during hot summers.[6] It has become evident that 24-hour blood pressure fluctuations are modulated by seasonal changes and temperature.

In particular, the nationwide research study known as 'Smart Wellness Housing Survey' conducted simultaneous measurements of indoor temperature and morning home BP, revealing that morning BP fluctuates under the influence of temperature, notably increasing at lower temperatures. We define the strength of this relationship as 'thermo-sensitivity,' which quantifies the extent of BP change (in mmHg/°C) in response to a 1°C temperature change **(refer to Figure 3A)**.[6] An inclination with a value equal to or greater than 1 is categorized as 'thermo-sensitive hypertension.' Thermo-sensitivity among individuals with an average age of 80 is approximately 1.02, whereas for younger individuals around 30 years of age, it is around 0.38. This thermos-sensitivity is even more pronounced in older, slender individuals. The World Health Organization (WHO) recommends maintaining indoor temperatures at or above 18°C; however, the correlation between indoor temperature and morning BP tends to diminish at around 25°C for elderly men and around 20°C for those in their early thirties.[1] For elderly individuals, it is desirable to maintain indoor temperatures of 22°C or higher even during the winter. Furthermore, this study highlights that the patients residing in non-insulation retrofitting housing are significantly affected by outdoor temperatures, and there is a considerable discrepancy in morning and bedtime home BP, along with substantial daily fluctuations.[1]

Furthermore, physical activity leads to an increase in BP, but during the winter, BP tends to rise more with the same level of exercise. We define the strength of the BP rise in response to physical activity as 'actisensitivity' **(see Figure 3B)**. When we monitored the BP of the same individuals in both summer and winter using ABPM equipped with high-sensitivity actigraphy, we observed that actisensitivity was enhanced during the winter months.[6] The timing of different types of BP surge waves during seasonal variations and physical activity may lead to resonance, generating more dynamic BP surges and suggesting the potential to act as triggers for CV events (the resonance hypothesis of BP surge).[6]

In Japan, where clear seasonal variations in CV mortality are observed, regions that have made improvements to their living environments to counter the cold during the winter have managed to suppress the increase in CV mortality during the winter.[6] Additionally, in a survey conducted before and after insulation retrofitting, a reduction in morning BP was observed alongside improvements in indoor temperature.[1] Therefore, enhancing living conditions by taking measures to address cold temperature during the winter season can result in improvements in hypertension and BP variabilities.

4. The Greatest Unmet Need: Uncontrolled Hypertension

BP control is still insufficient worldwide, and the control status varies greatly among different countries due to differences in environment, culture, and economic conditions. In Japan, the HIJAMP study, which assessed the control status of hypertensive patients receiving antihypertensive treatment using ABPM, a device also capable of measuring home BP, indicated that over 50% of the patients had not attained control of their morning BP to below 135/85 mmHg.[10] Despite the fact that uncontrolled office BP was observed in only 33% of hypertensive patients taking three or more antihypertensive medications, 54% of them had uncontrolled morning BP. These circumstances highlight the limitations of current antihypertensive medication and underscore the need for new perspectives on hypertension management, including the improvement of clinical inertia, adherence, the comprehensive use of polypills, the development of novel medications, digital therapies, renal denervation, and further enhancements in living conditions.[6]

5. What Are the SDGs of Hypertension Management?

The world is experiencing growing instability. Year after year, the effects of global warming lead to abnormal weather patterns and a surge in natural disasters such as earthquakes and floods worldwide. Furthermore, human-made disasters like wars disrupt conventional living environments, creating many situations where people's daily lives are severely affected. The destabilization of our surroundings impairs the homeostasis of individuals' CV systems, leading to fluctuations in BP. BP is not only an indicator of an individual's stress but also a direct acute risk factor for CV events. Maintaining homeostasis on a global scale, both in terms of the environment and between nations, and preserving local environmental stability, all contribute to an extended healthy lifespan for individuals. Therefore, BP serves as a key biomarker for healthcare in this context. It's crucial to measure BP under various circumstances, comprehend an individual's cardiovascular risk, and actively work towards risk reduction. By improving lifestyle and living environments, stricter control of BP levels can be achieved, maintaining the circadian rhythm of BP, and suppressing excessive BP variabilities. This is the ultimate goal of hypertension management SDGs, referred to as the "Perfect 24-hour BP Control."

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Interrelation between SDGs and Hypertension Zero

 # Category A: Hypertension and Life Environment

Hypertension & Global Warming,
- Disaster (Earthquake, Flood)

Air Pollution, Decarbonization, War

- Housing (light, noise, vibration...)
- Sleep Condition etc.

 # Category B: Hypertension and Diversity

Hypertension & Genetic Ancestry

- Poverty/Economic Disparity
- Food Availability
- Loneliness, Social Isolation etc.

 # Category C: Hypertension and Next Generation

Hypertension & DOHaD (Developmental Origins of Health and Disease)

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

NEW DIMENSION SERIES

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

CATEGORY B: HYPERTENSION AND DIVERSITY (HYPERTENSION & GENETIC ANCESTRY)

Diversity of Aldehyde Related Diseases: Learning from Aldehyde Dehydrogenase 2 (ALDH2) Polymorphism —Alcohol Intake, Flushing/Intolerance and Hypertension

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Alcohol (ethanol) flushing syndrome (AFS) including facial flushing, headache, nausea, and palpitation in response to a small amount of alcohol intake is common among East Asians but is almost absent in other populations.[1] AFS, therefore, is also called Asian flushing syndrome. Ethanol is metabolized to acetaldehyde by alcohol dehydrogenase subunit beta (ADH1B) and then to acetic acid by aldehyde dehydrogenase 2 (ALDH2).[1] There are polymorphisms in human ALDH2 genes, and the carriers of variant ALDH2 or ALDH2*2 (Glu504Lys) genotype have a severely reduced enzymatic activity, compared to wild ALDH2, ALDH2*1.[2] The carriers of these variant genes manifest AFS on alcohol intake due to an accumulation of acetaldehyde.[3] Approximately 40% of Japanese have ALDH2*2 genotype. Attenuation of ALDH2 activity increases the levels of acetaldehyde and other reactive aldehydes and induces oxidative stress because mitochondrial ALDH2 reduces the reactive oxygen species (ROS) formation related to toxic aldehydes[1] **(Figure 1)**.

Coronary spasm is an important and common disease in cardiology. Coronary spasm is prevalent among East Asians, including those in Japan, but not in the Western populations.[4] The survey on the prevalence of CSA at multi-institutions in Japan showed that CSA was documented in 921 (40.9%) of the 2251 consecutive patients with angina pectoris who underwent coronary angiography.[5] Thus, there seems to be a racial difference in the prevalence of coronary spasm between East Asians (Japanese) and Caucasians.[4] We reported that the rate of coronary spastic angina (CSA) was significantly increased in patients with ALDH2*2 genotype.[6] We further presented that ALDH2*2 genotype is a causative risk factor for ST elevated myocardial infarction (STEMI) in Japanese patients according to Mendelian randomization.[7]

ALDH2 removes not only acetaldehyde but also other toxic aldehydes, including 4- hydroxy-2-nonenal (4-HNE) and malondialdehyde from lipid peroxidation or acrolein in tobacco smoke, and thereby protects tissues and cells from oxidative damage.[1] Conversely, ALDH2 activity is suppressed by ROS and/or aldehydes.[2] It is thus likely that

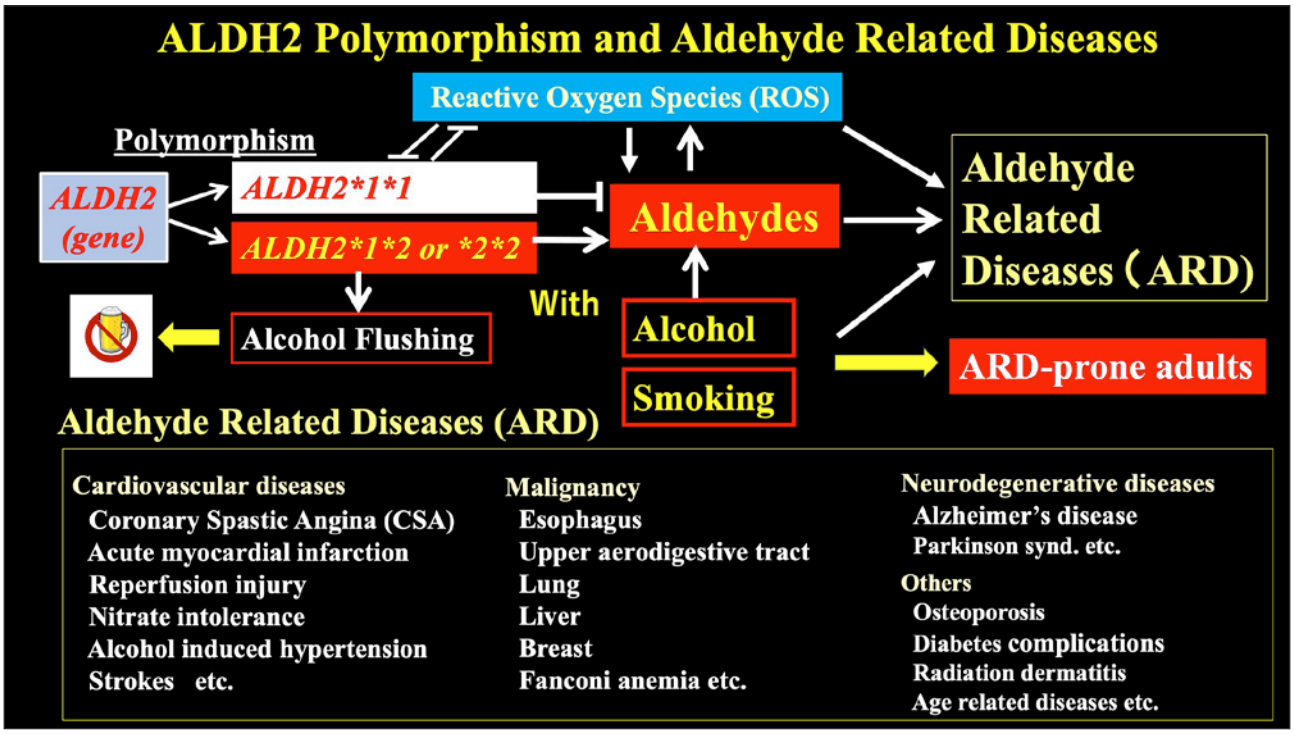

Figure 1

carriers of ALDH2*2 have increased reactive aldehydes as risk factors for coronary spasm and AMI.[6,7] We also reported that reperfusion injury in AMI is more severe in the carriers of ALDH2*2, that is, ALDH2*1*2 or ALDH2*2*2, compared to ALDH2*1*1.[7] ALDH2 may thus possess important therapeutic potential against alcoholic and other forms of myocardial damage as well.[1]

Toxic aldehydes, which increase in carriers of ALDH2*2, are also important carcinogens. Many cancers are induced and the incidence rates of various cancers, especially upper aerodigestive tract cancers, are amplified by smoking and alcohol drinking significantly in carriers with ALDH2*2.[1] Considering that cigarette smoke is also a source of toxic aldehyde, it is not surprising that smoking and heavy drinking combined with ALDH2*2 genotype carry the greatest cancer risk; indeed, ALDH2*2 carriers are frequent in the youngest patients with esophageal cancer.[1] Many diseases such as various cancers, Fanconi anemia, CSA, AMI, nitroglycerin tolerance, diabetic complications (via formation of advanced glycation end products, AGEs), osteoporosis, Parkinson syndrome, neurodegenerative diseases including Alzheimer's disease[1] could be called Aldehyde Related Diseases (ARD)". We should take great care for ARD when treating in patients for the carriers with ALDH2*2 allele. The carriers with ALDH2*2 allele are considered to have high risk for having complications with multiple ARD, especially with alcohol drinking and/or smoking. They can be considered to be "ARD-prone adults" **(Figure 1)**.

In contrast, there is an important and interesting report that ALDH2*2 genotype is a significant genetic factor for male longevity of more than 90 years in Koreans.[8] This observation suggests a possible intriguing significance of ALDH2 gene as a double-edged sword. It is inferred that ALDH2*2 genotype is thought to have favorable influence for survival in history of evolution for people living in rice-growing regions, since aldehydes may protect against infectious diseases, including parasite-born diseases, that are common in rice-growing regions. Further research is required in the diversity of genetic ancestry of this gene. In addition, there raised the possibility that the lack of ALDH activity could develop other protective pathways against ROS. It is reported that transgenic mice overexpressing ALDH2*2 induced mitochondrial aldehyde stress and subsequent stimulation of tolerance to oxidative stress with the increase of intracellular glutathione levels and pentose phosphate pathway (metabolic remodeling) in the heart.[9] This compensatory mechanism was also demonstrated in Tetralogy of Fallot patients with ALDH2*2 who exhibited more depressed ALDH2 activity in cyanosis with the

increase of glutathione level and shown to exert cardio-protection[10] Attenuated ALDH2 activity and increase of toxic aldehydes could strengthen other defense mechanisms against stresses ("Hormesis") on some occasions and may be related partially to longevity of Japanese.

As for the relationships between ALDH2 genotypes and hypertension, a meta-analysis including 19,608 subjects found that ALDH2*2 was the most crucial SNP related to the blood pressure variation in East Asians.[11] ALDH2*2 genotype presented low levels of both systolic and diastolic blood pressure compared with those of wild type[11] Considering that ALDH2 encodes the crucial enzyme involved in ethanol metabolism, its effect on blood pressure could be tightly associated with alcohol intake. Ethanol and/or acetaldehyde are known to activate sympathetic activity, stimulate the expression of angiotensin II type 1 receptor or impair endothelial nitric oxide activity for elevation of vascular tone and promotion of vascular remodeling, which could contribute to high blood pressure and its complications.

It is well recognized that individuals with ALDH2*2 mutation tend to limit or even abstain from alcohol intake due to the adverse effects such as facial flushing and palpitation[12] **(Figure 1)**. Ota et al. reported that by analyzing 1,225 male Japanese workers, the genotype frequencies of ALDH2 genetic polymorphism were 62.3, 32.4 and 4.7% for *1*1, *1*2 and *2*2, respectively. ALDH2 *1*1 group consumed a significantly higher amount of alcohol with more elevated alanine aminotransferase (ALT) and aspartate transaminase (AST), and exhibited significantly higher blood pressure, compared to ALDH2 *1*2 or 2*2 group (125.5±13.7 mmHg vs 122.2±13 mmHg in systolic and 78.6±81 mmHg vs 76.0±11.0 mmHg in diastolic blood pressure; mean ± SD). There was a positive relation between systolic blood pressure and the amount of daily alcohol intake in ALDH2 *1*2 or 2*2 group.[13]

Although the enzymatic activity of ALDH2*1*2 is less than 20% of *1*1, because of the dominant effect of ALDH2*2, the average alcohol intake of ALDH2*1*2 is around 70% of ALDH2*1*1, and 10-20% of alcoholics are ALDH2*2 carriers,[14,15] indicating that alcohol drinking behavior is determined by other additional factors, including the polymorphism of ADH1B, since blood acetaldehyde concentration is mainly determined by the activities of ADH1B and ALDH2.[16]

Alcohol drinkers with ADLH2*2 genotype are demonstrated to have high risk for ARD, such as alcoholic liver diseases or macrocytic anemia.[17] ALDH2*2 genotype, therefore, generates ARD at high probability and in great severity, in combination with the enormous aldehyde suppliers, including smoking as well as alcohol **(Figure 1)**. In precision medicine, ARD-prone adults should be strongly counselled to quit smoking and alcohol and take special attention for medical care.

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ISH NEWS AND PARTNER ACTIVITIES

Launch of the ISH Capacity Building Network (CBN) - a joint initiative from the NIC, MTC and WiHR committees

New ISH initiative to support early to mid-career researchers

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As chairs of the Women in Hypertension Research Committee (WiHRC), the New Investigator Committee (NIC), and the Mentorship and Training Committee (MTC), we and our committees are very excited to have launched a new ISH initiative to offer career development and networking opportunities for early and mid-career researchers and those from under-represented backgrounds.

The ISH Capacity Building Network (CBN) will organise webinars and workshops, produce podcasts, and create online videos and resources to help equip investigators with the skills they need to progress in research.

The first resources developed by the CBN – a series of videos on putting together a winning conference abstract – are available now on the CBN web pages of the ISH website: ish-world.com/cbn.

The videos – recorded by experienced ISH investigators – are published ahead of the abstract call for the 2024 ISH scientific conference.

Whilst our focus with the CBN is on researchers in the earlier stages of their careers, all members of the ISH are welcome to attend events and to sign up to the CBN mailing list.

Specific awards granted by the CBN are open to early and mid-career researchers and those from under-represented backgrounds who are members of the ISH.

To register to the mailing list and keep up to date on CBN activity, please contact: secretariat@ish-world.com.

The videos we have just published on the ISH website will be part of an Emerging Leaders programme from the CBN, which will initially focus on providing comprehensive guidance on developing conference abstracts.

The programme will include an abstract competition, and six winners of this competition will

receive a travel grant to support their attendance of the ISH2024 conference in Cartagena.

Other CBN activities we are organising will include a full day symposium held on Wednesday 18th September 2024, the day before the main ISH2024 meeting, with seminars, an awards ceremony, and opportunities to network with colleagues and leaders in hypertension research. The MTC, WiHRC and NIC will also be arranging usual activities and awards in line with the priorities of each of their committees.

The CBN will also highlight, compare and contrast career development stories from ISH investigators around the world to help ISH early and mid-career researchers understand the different roadmaps to a successful career in hypertension research and science and how diversity plays an important role.

We hope all members of the ISH, and in particular early and mid-career researchers and those from under-represented backgrounds, will find great value in the resources and events we will be delivering over the coming weeks, months and years.

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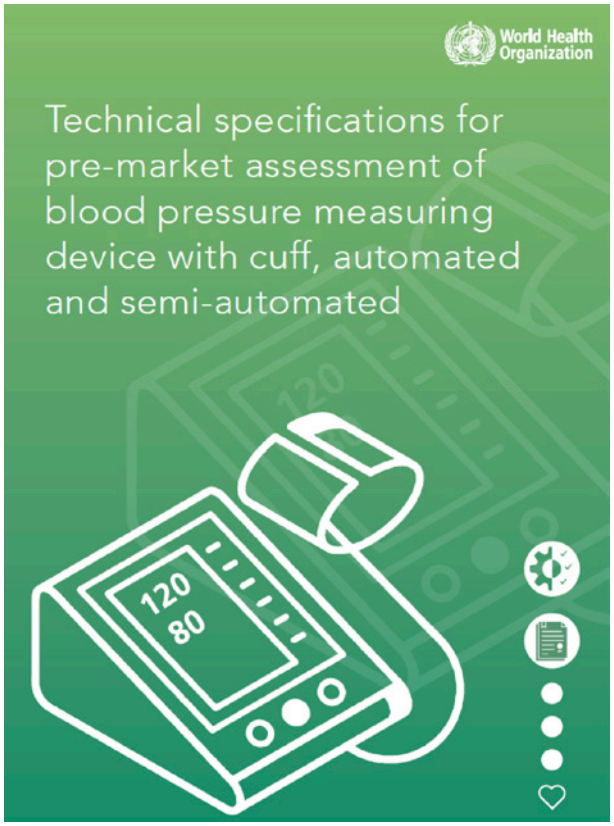
ISH NEWS AND PARTNER ACTIVITIES

News in technical and practical guidance for blood pressure measurement

World Health Organization (WHO) technical specifications for pre-market assessment of automated cuff blood pressure measuring devices

GEORGE STERGIOU

ISH Secretary, University of Athens, Greece



In 2022 the global market size of blood pressure (BP) measuring devices was estimated at US $2.5 billion, and by 2028 it is expected to reach US $5 billion, exhibiting in this period an annual growth rate of 13%.[1] Automated electronic upper arm cuff BP devices are currently recommended for clinical practice to evaluate BP by all methods, in the office/clinic, at home, and with 24-hour ambulatory monitoring.[2,3]

Normally, all the electronic BP monitors which are available on the market would be expected to be properly tested for their measurement accuracy before being approved for clinical use. However, STRIDE BP (www.stridebp.org), which is endorsed by the International Society of Hypertension, the European Society of Hypertension, and the World Hypertension League and performs independent reviews of all the published evidence on the accuracy of electronic cuff BP monitors, recommends less than 10% of those available on the market to be used in clinical practice, as only these have been properly validated using an established protocol.[4]

An important step to dealing with this issue is a recent statement published by the World Health Organization (WHO) with the purpose of ensuring that only accurate devices are available on the market for clinical use.[5] This WHO statement is intended for manufacturers and as a reference for regulators for pre-market assessment, and presents the "minimum" technical specifications for BP measuring devices. A Technical Advisory Group of international experts was appointed and coordinated by the WHO to develop this statement, with considerable contribution by International

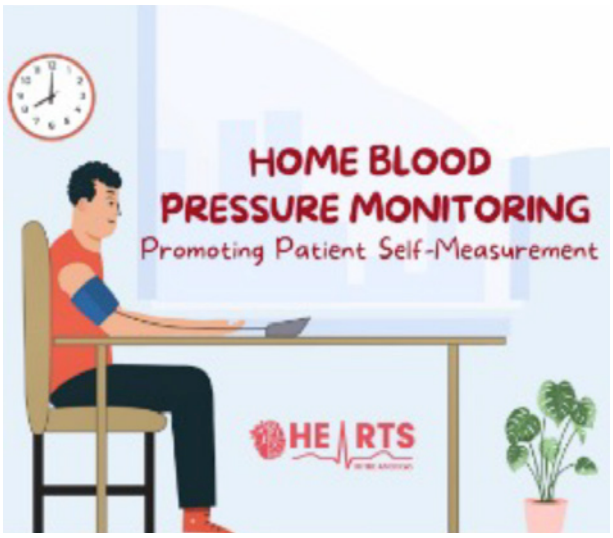
Society of Hypertension officers and members, including George Stergiou, Alta Schutte, Kazuomi Kario, and Anastasia Mihailidou.

The WHO requirements are divided into six categories: (i) regional administrative requirements, (ii) submission context, (iii) non-clinical evidence, (iv) clinical evidence, (v) labelling and promotional material, and (vi) quality management system procedures and (vii) quality management system device-specific information. Importantly, in the clinical evidence section, the 2018 Universal Standard developed by an international collaboration of the American Association for the Advancement of Medical Instrumentation (AAMI), the European Society of Hypertension (ESH), and the International Organization for Standardization (ISO) [AAMI/ESH/ISO – ISO 81060-2:2018][6] is recommended to be implemented independently by certified institutions to ensure the accuracy of devices.

Initiatives such as the development of a Universal Validation Standard for global use, the STRIDE BP lists of accurate devices, and the recent WHO statement for BP device specifications are major steps for improving the accuracy of BP evaluation. However, the next important step is to make these requirements mandatory before a device is approved to be put on the market. It is an important task of scientific organizations to persuade regulators around the world to demand that only properly validated devices are used in clinical practice.

Home Blood Pressure Monitoring Virtual Course by the Pan American Health Organization (PAHO)

All current guidelines for hypertension acknowledge that the measurement of BP in the office is important but can often be misleading, and confirmation with out-of-office BP evaluation is necessary in most cases.[2,3] Although 24-hour ambulatory BP monitoring is regarded by many as the best method currently available for diagnosing hypertension, it is not available in many settings, it is not well accepted by some patients particularly during sleep and at work, and is not suitable for repeated use. Thus, home BP monitoring appears to be the most realistic solution for out-of-office BP evaluation in clinical practice.[7] However, to be



useful for decision making home BP monitoring requires patient training to ensure that (i) an accurate device with appropriate cuff size is used, (ii) measurements are taken following proper methodology (conditions and body position), and (iii) the recommended monitoring schedule is followed. Thus, it is important to have educational tools developed specifically for patients, to guide them in obtaining home BP information which is valid and useful to the health care professionals.

The Pan American Health Organization (PAHO) has recently developed a virtual educational course aiming at promoting the wide and proper implementation of self-home BP monitoring.[8] The course is intended for the general public, and mainly for individuals with suspected, diagnosed, or treated hypertension, and is available online at https://www.campusvirtualsp.org/en/course/home-blood-pressure-monitoring-promoting-patient-self-measurement-2023. Primary healthcare providers, including general practitioners, nurses, and pharmacists, will also find this course helpful as a guidance to educate their patients. The course was developed with support by the ISH, STRIDE-BP, World Hypertension League, Hypertension Canada, Resolve to Save Lives, Lancet Commission on Hypertension Group, and Québec Society of Vascular Sciences [8]

The PAHO home BP measurement course uses a step-by-step approach providing information regarding the optimal self-measurement methodology to train people on why and how to self-measure BP at home and how to interpret the results. It includes (i) an illustrated video, (ii)

links to online resources for selecting validated automated BP measuring devices, (iii) an illustrated guide on the optimal measurement methodology, (iv) a printable 7-day self-measurement log, and (v) a final quiz to self-evaluate knowledge and a certificate is provided upon successful completion.[8]

As home BP monitoring is well accepted by most patients and is already widely used in many countries, it will probably become the primary diagnostic and monitoring method for hypertension in the future combined with telemonitoring. A problem, however, is that in routine office visits healthcare professionals do not have enough time to train their patients in proper self BP measurement. This is an important barrier in obtaining reliable out-of-office BP evaluation, which can be overcome by advancements in technology, with automated BP devices and software guiding users in proper BP measurement, and by educational modules developed specifically for patients.

STRIDE BP also has accredited educational modules for home BP monitoring, and also for office and ambulatory BP measurement, developed using modern interactive e-learning techniques (https://www.stridebp.org/training). However, these are intended for healthcare professionals and are not suitable for patients and the public. The World Hypertension League also has on its website a 12-minute infographic video to guide people in performing proper home BP monitoring (https://www.whleague.org/hypertension-resources/certification-course-blood-pressure-measurement). Educational tools developed specifically for patients, such as the one described above by PAHO, need to become available in all languages and be widely disseminated to healthcare professionals and patients to ensure that self-home monitoring is properly performed to provide trustful BP information which can influence decision making.

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SPECIAL REPORTS

Screening for high blood pressure in children/adolescents – why it matters

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High blood pressure continues to be the main risk factor for cardiovascular disease despite our collective efforts in research and screening. In addition to new treatments and lifestyle modifications to control it, early detection and preventive efforts starting in childhood are needed to reduce the global burden of hypertension We have an effective screening program with May Measurement Month to raise awareness among adults, and although we consider it challenging to implement a similar program for children, we have a unique opportunity to adopt initiatives to initiate change and engage our community for self-management of hypertension. Global efforts being implemented by members of the ISH Communications Committee, as well as other international colleagues from Africa, Australia, Japan and the USA, are outlined below.

Japan

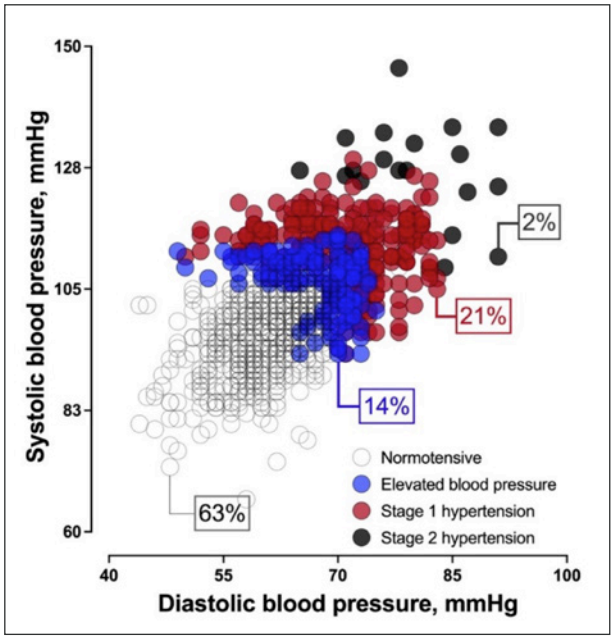
The first initiative is from Japan with Hidehiro Kaneko and Akira Nishiyama identifying that opportunities for young individuals to undergo blood pressure measurements during routine physical examinations are exceedingly limited. Consequently, their comprehension and awareness of blood pressure remain restricted, and the precise blood pressure levels within this demographic have yet to be ascertained. As a result, there exists no comprehensive national data offering an accurate depiction of the prevalence of hypertension among young individuals. Earlier investigations suggested that not only stage 2, but also stage 1 hypertension was associated with an increased risk of developing heart failure and atrial fibrillation among the relatively younger population in Japan.[1] The association of

hypertension with incident cardiovascular disease was more pronounced in younger people than in older people.[2] Cardiovascular health metrics clearly stratified a risk of developing both stage 1 and stage 2 hypertension among young adults, suggesting the clinical importance of modifiable risk factors in the development of hypertension in young adults.[3] This underscores the pressing need for educational initiatives geared towards raising awareness about blood pressure among young people and implementing preventive measures to curb hypertension within this age group. To address this issue, the Japanese Society of Hypertension (JSH) is actively advocating for the inclusion of blood pressure measurements as a standard component of health checkups for high school students. They are proposing to use the Saga Prefecture, the home prefecture of the current JSH chairman, as a model case to pilot this approach. Furthermore, JSH is actively engaged in efforts to promote blood pressure measurement awareness and practices among young people more broadly.

Africa

In Africa the combined prevalence of elevated blood pressure and hypertension in children is just under 22%.[4] This prevalence remains highly debated due to childhood blood pressure nomograms are lacking across Africa and the rates of hypertension are based on guidelines developed in countries with the lowest to no number of children from African ancestry.[5] The applicability of international blood pressure nomograms in Africa remains uncertain as described by a study done in South Africa that compared several international reference values with a cohort profile from the Eastern Cape region. Normal blood pressure was largely underestimated by all international references (by ±20%), while elevated blood pressure (7.2-11.4%), stage 1 (17.7-20.2%) and stage 2 (7.9-10.8%) hypertension was overestimated by all international references compared to the South African cohort defined reference.[6] In South Africa, a recent analysis using the 2017 AAP CPG blood pressure classification reported a combined prevalence of almost 37% of children with elevated blood pressure (14%), stage 1 (21%) and stage 2 (2%) hypertension[7], see **Figure 1**. The mean blood pressures were calculated using the 3 lowest measurements of the 5 total measurements, highlighting the frighteningly high prevalence of elevated blood pressure in these children.

Figure 1. Blood pressure distribution and prevalence of hypertension by automated blood pressure measurements in 5–9-year-old children (n=1062) from South Africa.



In the same study, boys and girls of similar age (mean age 7.43 years) showed no differences in body composition (except for boys being on average 1cm taller than the girls), brachial systolic blood pressure or central systolic and diastolic blood pressure. Office diastolic blood pressure, total vascular resistance and central pulse pressure were higher in girls compared to boys.[7] The higher brachial diastolic blood pressure may be a result of a lower vasodilator capacity as reflected by higher total vascular resistance and a potential forward pulse wave propagation that contributes to the higher central pulse pressure. Further work is currently underway to understand

the sex differences at various levels including basal metabolism, genetics and endocrine regulation.

From the paediatric hypertension research done by Ruan Kruger and his team, it became clear that health education and awareness of the dangers of high blood pressure from as early as childhood had to be addressed. A series of educational tools were developed by the Hypertension in Africa Research Team of the North-West University in South Africa to promote community screening programs and awareness initiatives, especially in the school setting. A superhero character was developed, namely Captain Heart, and was used in a comic book developed and translated into 3 of the 11 official languages of the country for distribution in primary schools. A video was further developed that plays in community healthcare facilities and is distributed to libraries in schools, while information cards for parents were developed to inform them of the dangers of unhealthy lifestyle behaviours and how to address these from a young age. These resources are publicly available here: https://health-sciences.nwu.ac.za/examin-youth-sa/home

Despite several efforts to understand childhood onset of hypertension in Africa, remaining challenges include limited access to healthcare, inadequate resources for screening and diagnosis, and poor awareness among caregivers and healthcare professionals regarding the importance of early detection and management. Overall, the studies addressing childhood hypertension have emphasised that research, resources, and policies need to be upscaled to address this burgeoning public health concern. Therefore, to further expand on the research and improve healthcare in children with early hypertension risk, the Childhood Hypertension Consortium of South Africa (CHCSA) was established, a non-profit organisation under the presidency of Ruan Kruger. The CHCSA consists of experts in the field of paediatric hypertension, representing all provinces in the country with a primary focus on cardiovascular health in children and adolescents in South Africa. The CHCSA aims to drive policy change in healthcare for children and adolescents in South Africa and contribute to ongoing community engagement and outreach to promote health education among parents, teachers and children. The CHCSA is driving a national research

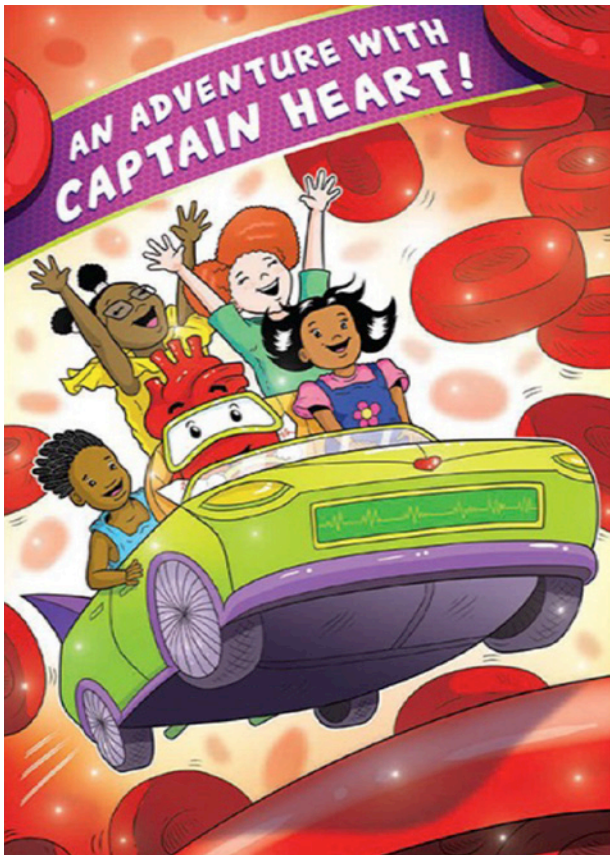


Figure 2. The cover page of the English version of "An adventure with Captain Heart" comic book developed for primary school children

study (ClinicalTrials.gov: NCT05982847) in South Africa aimed at improving hypertension care and management among the childhood and adolescent populations of the country and to develop the first South African blood pressure nomograms in paediatrics and will in future expand expertise to other African countries. To learn more about the consortium, please visit the website here: https://www.chc-sa.org

USA

In the United States there has been publication of updated normative blood pressure (BP) data and adoption of the lower adult BP cut-points for adolescents ≥13 years of age in the 2017 American Academy of Pediatrics Clinical Practice Guideline (AAP CPG).[8] This has led to identification of greater numbers of American children as having high BP. Using the prior normative data from the 2004 "Fourth Report" in an analysis of data from the US National Health and Nutrition Examination Survey (NHANES) collected between 2008 and

2012, the incidence of hypertensive-range BP (≥95th percentile) in participants between 8-17 years of age was 1.6%, with another 9.4% having BP readings in the high-normal/elevated range (≥90th and <95th percentiles), for a combined prevalence of 11%.[9] When similar NHANES data were re-analyzed after publication of the AAP CPG, the prevalence of high BP (combining elevated and hypertensive categories) increased from 11.8% to 14.2%, with many of the children who were reclassified to a higher BP category having other cardiovascular risk factors such as high body mass index and dyslipidemia.[10]

Two recent analyses of NHANES data confirm an overall prevalence of hypertension of about 4% in American children. In a detailed analysis of BP trends among US children and adolescents over several NHANES cycles over 1999-2018, the prevalence of hypertension was 4.6% in children 8-12 years of age and 3.7% in adolescents 13-17 years of age, with another 6-8% having elevated BP.[11] Other findings of interest were that BP was higher in youth with overweight and obesity than those of normal weight, that boys had higher BP than girls, and that non-Hispanic Black children had higher BP than non-Hispanic White children. Finally, a combined analysis of BP data in children 8-18 years of age collected in NHANES surveys conducted between 2011-2018 and BP data from the China Child and Adolescent Cardiovascular Health study collected between 2013-15 showed that the age-standardized prevalence rate of hypertension was 4% in US children and 18.5% in Chinese children.[12] Interestingly, obesity was associated with hypertension in US children but not in Chinese children.

Australia

In Australia the prevalence of paediatric hypertension is similar to that reported globally, with 3-7% classified as hypertensive and a further 4-8% with elevated blood pressure, with no difference between males and females.[13,14] Australian hypertension guidelines currently address adults only, which creates the conception amongst many clinicians that paediatric hypertension is not an issue that needs to be addressed. We have therefore created a professional network called BPOzKids, which together with Hypertension Australia, is developing Australia's first clinical guidelines for paediatric hypertension. Another key gap in Australia is a feasible avenue for hypertension screening in children. We are therefore currently conducting a pilot "Healthy Hearts @ School" program where we are investigating acceptability of and optimal methodology for screening in this context. The program incorporates two rounds of screening during school hours several weeks apart, along with targeted 24-hour ambulatory monitoring in a subset of consenting students. A rewarding aspect of this program has been delivery of a heart health education program to all Grade 3-6 students at the participating schools, and seeing the student's enthusiasm for learning about how the cardiovascular system works, how we can look after it, and what blood pressure is all about (teaching the kids to say "sphygmomanometer" has been a particular highlight!).

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Correction from the September issue of Hypertension News

In the last edition of Hypertension News, the following sentence appeared on page 33: "We are aware that afferent renal sympathetic nerves stimulate juxtaglomerular cells, which, in turn, increase renin release, decrease renal perfusion, and increase sodium reabsorption."
In this sentence, the word 'afferent' should have been 'efferent'.

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