HYPERTENSION NEWS

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Adherence in hypertension

Why non-adherence to medication persists, and what to do about it

IN THIS ISSUE:

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INTRODUCTION FROM THE PRESIDENT

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Dear ISH members and friends,

I would like to begin the introduction to this new edition of *Hypertension News* by sharing some important updates from the ISH.

ISH will be moving to holding a scientific meeting every year, rather than every two years as is currently the case. The rationale for this change is clear: this is what our members, partners, affiliated societies, and industry want. Holding a meeting every two years is no longer sufficient. To keep up with the pace of change, we need to meet annually.

This shift will help accelerate advances in the field of hypertension and give everyone in the hypertension community more opportunities to connect and form new collaborations. It will also expand the chances for participation: wherever you are in the world, you will now have greater possibilities of attending an ISH meeting. We will come to your region sooner.

Annual ISH meetings begin in 2026, when we meet in Dubai in October. In mid-December 2025, we will be inviting bids to host our 2027 meeting. Bids are welcome from all regions, except on this occasion from Middle East and Europe, as we will meet in these regions in 2026 and 2028 respectively.

This year we did considerable work in restructuring ISH. We put emphasis on orchestrating the activities of our 6 Regional Advisory Groups across the world, and we strengthened our business team. In this way, we will become more efficient in communicating our messages, and in increasing our impact in hypertension care across the world. 2026 will be a super-busy year for ISH. Make your plans now to join us in Dubai from 22nd to 25th October for our 2026 ISH/ECS meeting, to see our progress and work with us to reshape hypertension care.

I am proud to present to you another excellent issue of *Hypertension News* – the last one for 2025. Once again, ISH members and friends from around the world have provided a rich and timely selection of articles that reflect the rapid pace of scientific and clinical progress in hypertension and related conditions.

This edition opens with summaries of several important new pieces of research. We highlight exciting developments in aldosterone synthase inhibition, new evidence on mineralocorticoid receptor blockers, and important trial data on de-prescribing antihypertensive therapy in frail older adults. We also include commentaries on recent recommendations from the British and Irish Hypertension Society and the American Heart Association/American College of Cardiology.

In our perspectives section, we feature contributions on topics including fibromuscular dysplasia, hypertensive disorders in pregnancy, emerging approaches to cardiovascular risk assessment – and much more.

A special section in this issue is dedicated to patient adherence to antihypertensive treatment, which remains a huge challenge in hypertension care. ISH is part of a coalition coordinated by the World Heart Federation to advance understanding of its importance and to support practical solutions. The focal point of this initiative is World Adherence Day (27 March each year) but - as this section makes clear - adherence needs sustained attention throughout the year.

Continued on next page.

As always, I would like to thank all our ISH members and friends who contributed to this edition of *Hypertension News*. Special thanks go to ISH Treasurer Cesar Romero, who coordinated the section on adherence.

I hope you enjoy reading this edition. And finally, season's greetings from all of us at the ISH! Wherever you are, I wish you a peaceful and restorative time with family and friends, and warmest good wishes for the year ahead.

George Stergiou – president@ish-world.com

International Society of Hypertension

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NEW PAPERS

2025 position statement by the British and Irish Hypertension Society on BP treatment thresholds and targets: lower, better, or just moving?

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This year, the British and Irish Hypertension Society (BIHS) is the latest Hypertension Society to call for more aggressive BP treatment and target thresholds. They call for a treatment threshold of ≥135/85 mmHg and a BP target of <130/80 mmHg for all people with hypertension, irrespective of patient risk level and the method used to measure BP.[1] This represents a significant shift from earlier guidelines and highlights an overall global trend towards earlier, more aggressive, and streamlined management of hypertension.

The Society's position statement raises three important points for us to consider. The first is the lower BP target of <130/80 mmHg or lower if tolerated. Recent major randomized clinical trials, beginning with the SPRINT study, demonstrated that a more intensive BP target <120 mmHg was associated with a significant reduction in composite cardiovascular events across age groups 50 years and older compared with less intense, historical targets of 140/90 mmHg.[2] These findings were recently corroborated with the publication of three key trials from China, which confirmed benefits of lower BP targets across diverse clinical populations. The STEP trial in 2021 randomized 8,511 patients aged 60–80 years to a systolic BP target of 110–130 mmHg vs. 130–150 mmHg.[3] The more intensive targets were associated with a significant reduction (Hazard Ratio [HR] 0.74; 95% Confidence Interval [CI] 0.60–0.92) in major composite cardiovascular events. The ESPRIT trial in 2024 randomized 11,255 people aged 50 years and older with hypertension and increased CV risk (e.g., prior stroke, diabetes) to a systolic target of <120 mmHg or <140 mmHg.[4] After 3.4 years, intensive SBP control was associated with reduced MACE outcomes (HR 0.88; 95% CI 0.78–0.99). The BPROAD trial in 2024 enrolled 12,821 adults aged ≥50 years with type 2 diabetes to an intensive systolic target of <120 mmHg vs. <140 mmHg.[5] Over approximately 5 years, tight BP targets was associated with a significantly lower risk of MACE compared to a higher target (HR 0.79; 95% CI 0.69–0.90). On the basis of these accumulated data from RCTs and long-standing observational data demonstrating increased CV risk beginning even as low as in the 120s mmHg, Hypertension Societies advocated for tighter BP control (**Table 1**).

The second important aspect was setting the treatment threshold for hypertension to ≥135/85 mmHg irrespective of office, attended or unattended, 7-day home reading, or daytime ambulatory BP measurements. This lowering of the definition of hypertension, much like the 2017 ACC/AHA hypertension guidelines, increases the number of people who will be diagnosed with hypertension.[6] In the US, where the diagnosis of hypertension was set at ≥130/80 mmHg, almost 13% of patients (~30 million) were labelled as hypertensive overnight. These reclassified hypertensive patients are typically younger, aged <45 years. This could translate to increased health resource utilization with follow-up visits, medication use or intensification, resulting in greater medication-related adverse effects for low-risk individuals. The position statement also assumes an equivalency between office, 7-day

home average, and average daytime ambulatory BP readings. While studies report only modest reproducibility between different modalities, Yeh et al. found measurement discrepancies between these modalities were greatest at higher BP but reduced to minor differences at SBPs in the 120s mmHg range.[7] Cost-analysis models demonstrate even accounting for BP measurement errors, reaching intensive targets of <120 mmHg or <130 mmHg remains cost-effective.[8]

The third important aspect of these guidelines is that the recommended thresholds to treat and targets apply regardless of patient risk level. In an era of increasing patient complexity, this greatly simplifies treatment thresholds and targets and better approximates recent evidence. These trials converge on the premise that lower BP is better across a variety of important subgroups that we had applied varying targets for, such as prior CVD, type 2 diabetes, stroke, chronic kidney disease, and the elderly. The guideline authors further contend it is unethical to withhold antihypertensive therapy until irreversible subclinical or clinical sequelae of hypertension emerge. However, it is important to note that the clinical trials only included moderate to high-risk patients and patients older than 50 years. According to these guidelines and others, if a 26-year-old man has a BP of 138/85 mmHg, they would be diagnosed with hypertension and started on long-term antihypertensive therapy. Their overall 10-year CV risk, although cannot be precisely estimated using Framingham risk calculators, would be approximately <2%. Extrapolating a CV relative risk reduction of 25% with antihypertensive therapy, we would recommend that this low-risk person take medication daily for 10 years to reduce their absolute CV risk from 2% to 1.4%. For an individual low risk patient, this cost benefit ratio may not be worthwhile.

The British and Irish Hypertension Society's position statement reflects a broader global shift toward earlier and more aggressive BP management through simplified and streamlined approaches. This strategy is promising to reduce therapeutic inertia, save lives and reduce health care costs at a population level. However, simplification also risks overtreatment for some, especially younger and low risk populations. In an era of augmented intelligence tools, simplification may not come at a cost of personalizing hypertension management while still providing earlier and more aggressive care as called on by BIHS for those who need it.

Table 1. Blood Pressure Targets Among Various Hypertension Societies

Society	Year	Recommended BP Target*
BIHS	2025	<130/80 mmHg
ACC/AHA	2017/2025	<130/80 mmHg
Hypertension Canada	2025	<130 mmHg, No diastolic target
ESC/EAC	2024	120–129/70–79 mmHg (but note <120/70 mmHg in research conditions optimal)
ESH	2023	<140/80 mmHg initially for most; if well tolerated, aim <130/80 mmHg in adults up to ~79 years; SBP of 120–129 mmHg may be considered but not below 120 mmHg
ISH	2020	<130/80 mmHg, if tolerated and for patients <65 years Persons ≥65 years or those with frailty, the target is less stringent e.g., <140/90 mmHg (or <140/80 mmHg for some elderly)

*Guideline bodies recommend raising the target if not tolerated or for frail elderly to as low as reasonably achievable

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NEW PAPERS

2025 AHA/ACC multi-society guidelines for hypertension: Recommendations for the US – Messages to the world

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INTRODUCTION

We believe most colleagues were curious to read the new American guidelines for hypertension. Not only because the history of American guidelines is older than half a century, with the first Joint National Committee (JNC) report published in 1977, but also because the Americans often introduce new concepts and definitions and tend to provide clear and practical recommendations. Thus, although their guidelines are intended for medical practice within the US healthcare system which has much more resources than most places in the world, it is always interesting and useful to see how our US colleagues see the translation of the current research evidence into hypertension care in clinical practice and what changes they propose for hypertension management.

It is not the scope of this short article to present all the AHA/ACC multi-society guidelines, or to compare them to other recent guidelines, but to highlight some important recommendations which deserve to be considered in defining optimal practices that meet patients' needs in different regions and healthcare systems around the world.

MESSAGE 1: The American plan

An important element of the 2025 AHA/ACC multi-society guideline is that it was developed in collaboration with and endorsed by 11 other USA-based organizations whose representatives included physicians, cardiologists, geriatricians, general practitioners, nurses, and pharmacists. The writing committee included cardiologists, nephrologists, internists, epidemiologists, practice nurses, a neurologist, a gerontologist, a clinical pharmacist, a physician associate, and a patient advocate. This is important considering the size of the problem among US adults, with prevalence of hypertension (with the US definition of BP ≥130/80

mmHg) estimated at 50% of men (59 million) and 44% of women (56 million). If you add to this those with "elevated BP", then probably less than one third of the adult population in the US have "normal" BP according to US definitions. Thus, many different healthcare professionals need to be engaged to tackle hypertension, not only cardiologists, nephrologists, and those with special interest in hypertension.

The development of these recommendations certainly required considerable time and effort and collective work by many expert scientists devoted to hypertension and cardiovascular medicine research. Like the recent ESH and the ESC guideline papers, this manuscript is long (80 full journal text pages, plus references and other information). The authors probably realised that only a few of the huge number of healthcare professionals who deal with hypertension will read the full paper. Thus, they start the guideline by presenting "What Is new" and 10 top take-home messages.

MESSAGE 2: Blood pressure measurement and diagnosis

Blood pressure devices: In line with European and other societies, the new American guideline recommends a standardized methodology for office BP measurement, preferably using validated automated cuff BP devices, and advises healthcare professionals to avoid cuffless devices.

Out-of-office blood pressure: In 2017, ACC/AHA made it crystal-clear that treatment initiation and titration should not be based exclusively on office BP measurements, and that in most cases 24h ambulatory (ABPM) or home BP monitoring (HBPM) is required. According to their 2025 guidelines ABPM/HBPM is needed in (i) untreated and treated individuals with office BP 130-159/80-99 mmHg (to exclude white-coat hypertension), or <130/80 mmHg (to exclude masked hypertension), (ii) untreated with white-coat or masked hypertension (to exclude transition to sustained hypertension), and (iii) in resistant hypertension (to exclude the white-coat effect). Thus, most of the 47% of US adults with hypertension and of those with elevated BP need ABPM/HBPM, which is almost two-thirds of the adults (except those with too low or too high BP).

ABPM vs HBPM: The 2025 guidelines gave an "evidence advantage" to ABPM due to "more data linking it to cardiovascular events", and an "application priority" to HBPM, recommending it for both the initial diagnosis and for treatment titration, whereas ABPM is primarily recommended for confirming the initial diagnosis. They also acknowledge that HBPM is more practical than ABPM and may be more reproducible and accessible.

HBPM is widely available in several countries, is preferred by most patients compared to ABPM, seems to have similar prognostic ability as ABPM, and has been shown to improve medication adherence and hypertension control. On the other hand, ABPM is rarely available and infrequently used when available. Thus, HBPM is far more feasible for wide clinical use, and therefore it is the most realistic 'central' method for decision making in hypertension in clinical practice.

MESSAGE 3: When to screen for primary aldosteronism

The American guidelines extended the list of indications for screening as presented in **Table 1**. However, they do not endorse other recent recommendations to screen 'everybody' with high BP, which is unrealistic in most settings around the world. Screening is now recommended while continuing antihypertensive drugs (except MRAs and beta-blockers which reduce renin and can give false positive results), which is particularly useful as many of these patients have high BP levels. Reviewing the list, it is clear that many more

Table 1. Indications to screen for primary aldosteronism[1]

1.	Resistant hypertension, even without hypokalemia
2.	Hypokalemia, spontaneous or diuretic induced
3.	Sleep apnea
4.	Incidentally discovered adrenal mass
5.	Family history of early-onset hypertension,
6.	Stroke at age <40 years
7.	To be considered also in stage 2 hypertension

patients with aldosterone dysfunction are likely to be identified with future screening.

MESSAGE 4: How to identify patients at high risk

The American guideline recommends using the AHA Predicting Risk of CVD Events (PREVENT) model to estimate 10-year cardiovascular risk for adults with hypertension without clinical cardiovascular disease.[2] It also assesses atherosclerotic cardiovascular disease risk and heart failure risk. The PREVENT model incorporates novel optional kidney and metabolic predictors (urinary albumin/creatinine ratio, HbA1c, BMI) and a social deprivation index to enhance equity in risk assessment.[2] It can be used to estimate 10 and 30-year total cardiovascular disease risk in people aged 30-79 years, with high-risk threshold at 10-year risk >7.5%.

MESSAGE 5: Blood pressure level to start treatment

The American guideline recommends that treatment should be promptly started in all adults with BP >140/90 mmHg and in those at high-risk with BP >130/80 mmHg. And they recommend the same BP threshold for starting treatment in lower risk patients, but after a few months of lifestyle modification (**Table 2**).

This recommendation requires an accurate estimation of BP, which is often overestimated in the initial assessment and can lead to overdiagnosis and overtreatment. The authors of the guideline acknowledge that too often BP is not properly taken, and recommend using standardized methodology, automated devices, and out-of-office BP evaluation (see above).

Table 2. Blood pressure level to start treatment[1]

Blood pressure	Population
>140/90 mmHg	• All adults
≥130/80 mmHg	• Those with diabetes, or CKD, or 10y CVD risk ≥7.5% (PREVENT)
	• Those with 10y CVD risk <7.5% (PREVENT) after 3-6-month lifestyle intervention

MESSAGE 6: Blood pressure goal of treatment

The American guidelines recommend that a BP of 130/80 mmHg is not acceptable for most adults. This is their single BP number for starting treatment and for controlling hypertension. They go a step further to 'encourage' reaching systolic BP <120 mmHg in most patients (**Table 3**).

This recommendation opposes the 2024 ESH guideline which recommends BP not to be reduced <120 mmHg. It is based on a recent metanalysis of 6 outcomes studies (80,220 patients followed for 3,2 years),[3] which compared the cardiovascular benefits and the adverse events of a systolic BP goal <120 vs. <130 mmHg. The results showed considerable benefits in reducing cardiovascular events with systolic BP <120 mmHg, together with increased risk of adverse events, and eventually an overall net benefit.[3]

The question now is how to select among our patients those who will most likely benefit from a more aggressive BP reduction, but without the risk of adverse events. With these lower BP targets, meticulous evaluation of BP for preventing treatment-induced excessive BP decline resulting in adverse effects, is now much more important than in the past.

Table 3. Blood pressure goal of treatment[1]

Overarching goal	BP <130/80 mmHg for all adults, except if (i) require institutional care, (ii) have limited predicted lifespan, (ii) are pregnant.	
Increased CVD risk	Encouragement to achieve BP <130/80 mmHg to reduce CVD events and total mortality.	Class of recommendation 1 (Strong)
Not increased CVD risk	Encouragement to achieve BP <120/80 mmHg may be reasonable to reduce risk of further BP elevation.	Class of recommendation 2b (Weak)

MESSAGE 7: When to start with mono- or combo- therapy

Most recent guidelines recommend starting with a 2-drug combination, preferrable in a single pill, in most patients, and present a list of cases in which starting with monotherapy is preferred. The 2025 American recommendation is as follows:

- **Stage 1 hypertension** (BP 130-139/80-89 mmHg): Reasonable to start with 1 drug
- **Stage 2 hypertension** (BP ≥140/90 mmHg): Start with 2-drug combination, ideally single-pill

The American guidelines give a simple recommendation, which is exclusively based on the BP level. Its implementation requires accurate BP evaluation, as BP is often overestimated at diagnosis, and individualisation by considering the overall health condition of each patient.

MESSAGE 8: When to consider renal denervation

The American guideline recommends considering renal denervation in patients with resistant hypertension (giving a strict definition) and in special cases with uncontrolled hypertension.

1. **Resistant hypertension:** ≥140/90 mmHg on ≥4 antihypertensive medications at optimal dosages (ACEi/ARB + CCB + thiazide-type diuretic + MRA).
2. **Uncontrolled hypertension:** BP ≥140/90 mmHg and unable to take antihypertensive medications at optimal dosages or additional medications.

With renal denervation now recommended by most scientific organisations and available in most countries, it is important for primary care doctors to have clear guidance on how to identify which of their patients cannot reach good BP control with drug treatment and should consider renal denervation, and refer them to an expert centre for reducing the excess risk due to uncontrolled BP.

MESSAGE 9: Framework to improve hypertension control

This is a very important section of the American guideline. The recommendations on 'when to do what' are important, but it is their efficient implementation in the general population that will reduce the burden of hypertension and its complications. Eight elements of success are discussed (**Table 4**) and all are very important as each of them represents an important cause of failure, or a useful tool for success. No country has enough doctors to deal with the large proportion of the general population with sustained or borderline hypertension, and a team-based approach involving non-doctor healthcare professionals is a necessity everywhere. The American guideline provides guidance on the responsibilities and roles for the members of the hypertension team.

Table 4. Framework to improve hypertension control[1]

1.	Team-based approach
2.	Accurate BP measurement
3.	Prompt treatment
4.	Patient engagement
5.	Ongoing review of home BP measurement
6.	Evaluate drug adherence + response
7.	Monthly visits until control
8.	Electronic health record - Telehealth

CONCLUSIONS AND PERSPECTIVES

The American guidelines for hypertension represent a half-century old story with eight Joint National Committee (JNC) reports followed by AHA/ACC reports. Several other organisations followed by publishing their own guidelines, and all of them together transformed the practice of hypertension care by establishing the use of evidence-based recommendations. Indeed, hypertension is a great case for evidence-based medicine, as results of many outcome studies are available to inform on the key decisions that the practising doctors routinely make in patients with hypertension. Along with the AHA/ACC, several organisations recently updated their recommendations, including the ESH, ESC, and other regional and national societies of hypertension.

ISH has a global mission, and we are sceptical about the disappointing rates of hypertension control in most countries, despite the solid evidence on the benefits of its optimal management and the availability of many effective drugs at low cost and of guideline statements with exceptional

quality in all regions. In 2020, ISH published its "Global Hypertension Practice" guidelines and introduced the concept of "Essential" and "Optimal" recommendations. Several practising physicians around the world found these recommendations very practical for their routine clinical work. We are currently working on a new model for disseminating our recommendations, aiming at improving their implementation in practice.

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ISH Regional Advisory Groups (RAGs)

Our six ISH Regional Advisory Groups (RAGs) provide a platform for members to connect and collaborate in their region and for ISH to pick up messages and send messages to the world. The ISH RAGs lead initiatives which serve the specific needs of their regions.

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NEW PAPERS

When and how to reduce antihypertensive treatment in nursing home residents: results of the RETREAT-FRAIL trial

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Very old patients consume a large number of medications, especially those intended for the prevention or treatment of cardiovascular (CV) diseases. Since hypertension is the most common risk factor in people over 80 years of age, with a prevalence reaching more than 70%, most people in this age group receive chronic antihypertensive drugs, which have demonstrated, in randomized clinical trials (RCT), substantial benefits in the prevention of cardiovascular complications.[1,2] However, RCTs generally exclude the very old and the frailest patients, who are more likely to experience adverse effects of antihypertensive drugs.[3] Thus, the population habitually consuming several of these drugs has always been excluded from randomized clinical trials that have evaluated the benefits and risks of these treatments. On the other hand, numerous observational studies indicate that in old frail patients, low blood pressure (BP) is associated with higher CV morbidity and mortality, particularly in the presence of antihypertensive treatment.[4,5] These observations raise major questions regarding the management of hypertension in frail old patients.[6] Recent European guidelines on the management of hypertension[7,8] emphasize the need to establish BP targets and therapeutic strategies according to the level of frailty, and to consider gradual reduction of antihypertensive treatment in frail older patients with low BP. However, evidence on the benefit/risk ratio of drug deprescription in these patients is currently very limited.

We designed and conducted the RETREAT-FRAIL RCT to answer these questions: Is the increased mortality in frail older patients with low BP on multiple antihypertensive therapy reversible by reducing antihypertensive treatment? What are the benefits and risks of reducing antihypertensive treatments in these people with high CV risk?

RETREAT-FRAIL was a multicenter RCT in nursing home (NH) residents in France, aged 80 years and older, treated with more than one antihypertensive drug and with a sitting systolic BP (SBP) below 130 mmHg. 1048 patients from 108 nursing NHs were randomized to either a gradual step-down of antihypertensive treatment strategy (intervention group, n=528) or usual care (control group, n=520). Before randomization, we thoroughly reviewed the clinical status of the patients to determine the indications for each antihypertensive drug administered. Only drugs without compelling indications could be discontinued in patients randomized to the step-down strategy. To include even the most frail patients, the only exclusion criteria applied were patients without any antihypertensive drug that could be discontinued due to compelling indications and patients with a life expectancy of less than 3 months. Also, the ethics committee allowed family members or other close relatives to give informed consent when a patient was unable to consent themselves. Clinical follow-up of both groups took place in the NHs where they resided, at a regular pace (every month for the first six months, then every two months) and was identical for both groups, except for the reduction in antihypertensive treatment applied only to the intervention group. The first subject was randomized on April 15, 2019, and the last on July 1, 2022. The recruitment period was extended by one year compared to the initial

schedule, mainly due to the COVID-19 pandemic. Follow-up ended in July 2024, two years after the inclusion of the last patient.

Analysis of the initial characteristics of the 1,048 randomized patients confirmed the specificities of this population: an average age of 90 years, composed mainly of women (80%), taking on average more than 9 different medications per day, of which 2.5 were cardiovascular (more than 3 if antidiabetic and lipid-lowering drugs are included). According to the Clinical Frailty Scale score[9], nearly 40% of these subjects presented severe to very severe frailty and less than 10% were fit or doing well. The population treated for hypertension also had a heavy cardiovascular history: nearly 40% with atrial fibrillation, 24% with heart failure, 19% with a history of stroke and 19% with coronary artery disease. More than 23% were treated for diabetes. This population is very representative of the 700,000 subjects over 80 years old living in NHs in France, but also of many other older people living at home with a loss of autonomy, cognitive impairment, mobility problems, and related difficulties, needing continuous assistance for most daily activities.

The primary endpoint was all-cause mortality. Secondary endpoints included major adverse cardiovascular events, systolic BP (SBP) levels, number of antihypertensive medications, functional status, falls, fractures, quality of life, non-cardiovascular deaths, and COVID-19-related deaths. During a median follow-up of 38.4 months, the number of antihypertensive medications was reduced from a mean of 2.6 to 1.5 in the step-down strategy group and from 2.5 to 2.0 medications in the usual care group. The between-group difference in SBP throughout the follow-up period was 4.1 (1.9-5.7) mmHg. All-cause mortality was observed in 61.7% of patients randomized in the step-down strategy and in 60.2% of patients in usual care [HR: 1.02 (0.86-1.21), p = 0.78]. The step-down strategy tended to be more beneficial on all-cause mortality in the frailest patients (interaction between step-down strategy and frailty level, p = 0.08). Changes in autonomy, cognitive function, muscle strength, gait, and quality of life were not different in the two treatment groups, as well as, non-cardiovascular mortality, falls, fractures, and other serious adverse events. A lower number of COVID-19-related deaths was observed with the step-down strategy (1.1% vs. 3.1%).

In summary, in NH residents aged over 80 years, with a SBP less than 130mmHg, the deprescribing strategy resulted in a long-term reduction in the number of antihypertensive medications compared to usual care, resulting in a slight but significant increase in BP without changes in morbidity, mortality, functional status, or adverse effects. These results show that deprescribing antihypertensive treatments is possible subject to a thorough assessment of the clinical condition of patients and regular monitoring, in the same way as when prescribing a medication.

In conclusion, RETREAT-FRAIL is the first clinical trial demonstrating that deprescribing antihypertensive drugs does not increase mortality, morbidity or other adverse effects. This strategy could therefore be considered in very old subjects with low blood pressure levels, particularly the most frail, in whom polymedication constitutes a major problem.

*The main results of this study have been published here: A. Benetos, S. Gautier, A. Freminet et al. Reduction of Antihypertensive Treatment in Nursing Home Residents. N Engl J Med. 2025 Aug 29. doi: 10.1056/NEJMoa2508157. Online ahead of print. PMID: 40879421

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NEW PAPERS

Baxdrostat, an aldosterone synthase inhibitor, a novel mechanism for uncontrolled hypertension

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Primary aldosteronism has been recognised as a cause of hypertension since 1955, when Conn's syndrome was first described. However, it is now recognised that adenomas are not the only presentation for aldosterone dysregulation which is a spectrum of disease due to somatic mutations, that lead to inappropriately elevated aldosterone levels, relative to the sodium status of the patient – effectively generating a salt sensitive state which is the hallmark of most hypertension. In many cases, there is no visible adenoma, just microadenomas, or even aldosterone producing cell clusters, all of which are undetectable by conventional imaging. It is likely that aldosterone dysregulation is a major cause of difficult to control hypertension.

Aldosterone acts in the principal cell of the cortical collecting duct of the kidney to increase sodium reabsorption, thereby increasing blood pressure. Hypertension due to inappropriate aldosterone is associated with excessive cardiovascular and kidney disease due to increased oxidative stress, inflammation and fibrosis. There is also an increased risk for insulin resistance, further driving fibrosis and inflammation.[1]

The mainstay of treatment for aldosterone-driven hypertension has been to block the mineralocorticoid receptor (MR). MR antagonists have been around for the treatment of hypertension since 1957, when spironolactone was found to improve blood pressures. However, MR antagonists can have intolerable side effects that hinder their use. The three final steps in aldosterone synthesis are catalysed by aldosterone synthase (CYPIIB2), an enzyme in the adrenal gland. Thus, blocking this enzyme has become an attractive target to decrease circulating aldosterone and control blood pressure.

Aldosterone synthase inhibitors (ASI's) represent a novel class of antihypertensives. In a phase two trial in patients with resistsnt hypertension, the ASI baxdrostat reduced blood pressure over a three month period[2]: the placebo adjusted blood pressure changes for baxdrostat 1mg and 2mg were 8.1/2.6 mmHg and 10.9/5.1 mmHg, respectively. Another ASI, lorundrostat, has also demonstrated effective blood pressure lowering with 41% achieving a target systolic blood pressure of <125 mmHg compared to 18% of those on placebo.[3]

The phase three trial results for baxdrostat were released at the European Society of Cardiology meeting with simultaneous publication in the New England Journal of Medicine.[4] This global trial enrolled people over 18 years with uncontrolled (systolic blood pressure between 140-170 mmHg on two agents) or resistant (uncontrolled on 3 or more agents) hypertension, including a diuretic. After a two week run-in period on placebo added to their background antihypertensives, adherent participants were randomised to placebo, 1mg baxdrostat or 2mg baxdrostat for 12 weeks.

The primary efficacy endpoint was the placebo controlled change in seated systolic blood pressure

from baseline to 12 weeks. Of the 2591 patients that were screened, 796 were randomised and 794 received at least 1 dose of treatment. Participants were similar across the three arms of the first part of the trial and representative of typical patient populations with uncontrolled or rersistant hypertension. The mean seated baseline blood pressure was 149/87 mmHg.

The placebo adjusted improvement in systolic blood pressure was -8.7 mmHg and -9.8 mmHg for 1mg and 2mg baxdrostat, respectively at 12 weeks. Respective placebo adjusted improvement in diastolic blood pressure was -3.3 mmHg and -3.9 mmHg. Consistent with the hypothesis that aldosterone dysregulation is playing a key role in patients with difficult to control hypertension, the effect of baxdrostat on blood pressure was remarkably consistent across all patient subgroups.

There was a strong focus on safety in this trial, as this is a new therapy, and the trial is designed to go beyond the primary outcome period of 12 weeks with 3 additional sequential parts, for a total of 52 weeks follow up, to provide longer term safety and efficacy data with baxdrostat. During the initial 12 week study period, baxdrostat was well tolerated with no unanticipated adverse events. A key focus was on potassium and reassuringly, confirmed elevations of potassium > 6mmol/l were detected in around 1% of patients on baxdrostat 1 or 2mg daily. The study also showed that potassium changes usually occurred within the first two weeks of initiating baxdrostat, remaining stable thereafter. Another safety focus was eGFR and this was reduced by about 7 ml/min/1.73m2, and just like potassium, this mainly occurred within the first 2 weeks. Of course, these early studies recruit patients with normal renal function and as with all inhibitors of the renin angiotensin aldosterone system, the risk of hyperkalemia increases in those with more substantially impaired kidney funcrion, i.e. eHGR <45 ml/min/1.73m2. Importantly the BaxHTN trial also included an 8 week placebo controlled randomized withdrawal of treatment between weeks 24 and 32. This showed that the changes in eGFR reversed following treatment withdrawal, suggesting it was functional related to changes in blood pressure.

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The BaxHTN study focussed on seated office BP as its primary end-point but also included a small exploratory ambulatory blood pressure sub study in 56 patients which revealed remarkable reductions in placebo-adjusted 24hr systolic BP of almost 17mmHg and nocturnal BP reductions of almost 12mmHg. It will be fascinating to see if this remarkable effect on 24hr BP is confirmed in the much larger, parallel, global phase III study (Bax24) which is specifically studying the effect of baxdrostat 2mg versus placebo on 24hr ambulatory BP as the primary outcome. This study will present its topline results at the American Heart Association late breaking science sessions in November.

In conclusion, it feels like we are on the cusp of a therapeutic breakthrough for the treatment of difficult to control hypertension with new treatments targeting aldosterone synthase and many new studies are ongoing, either with ASI alone, or in combination with SGLT2-inhibitors. The ASI/SGLT2i combinations are specifically being studied in patients with CKD and at risk of heart failure, or with established heart failure. It is good to see a renewed focus on aldosterone, more than 70 years on from the description of that adrenal nodule by Conn.[5]

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NEW PAPERS

Efficacy and safety of esaxerenone with and without sodium–glucose cotransporter-2 inhibitor use in hypertensive patients with type 2 diabetes mellitus: a pooled analysis of five clinical studies

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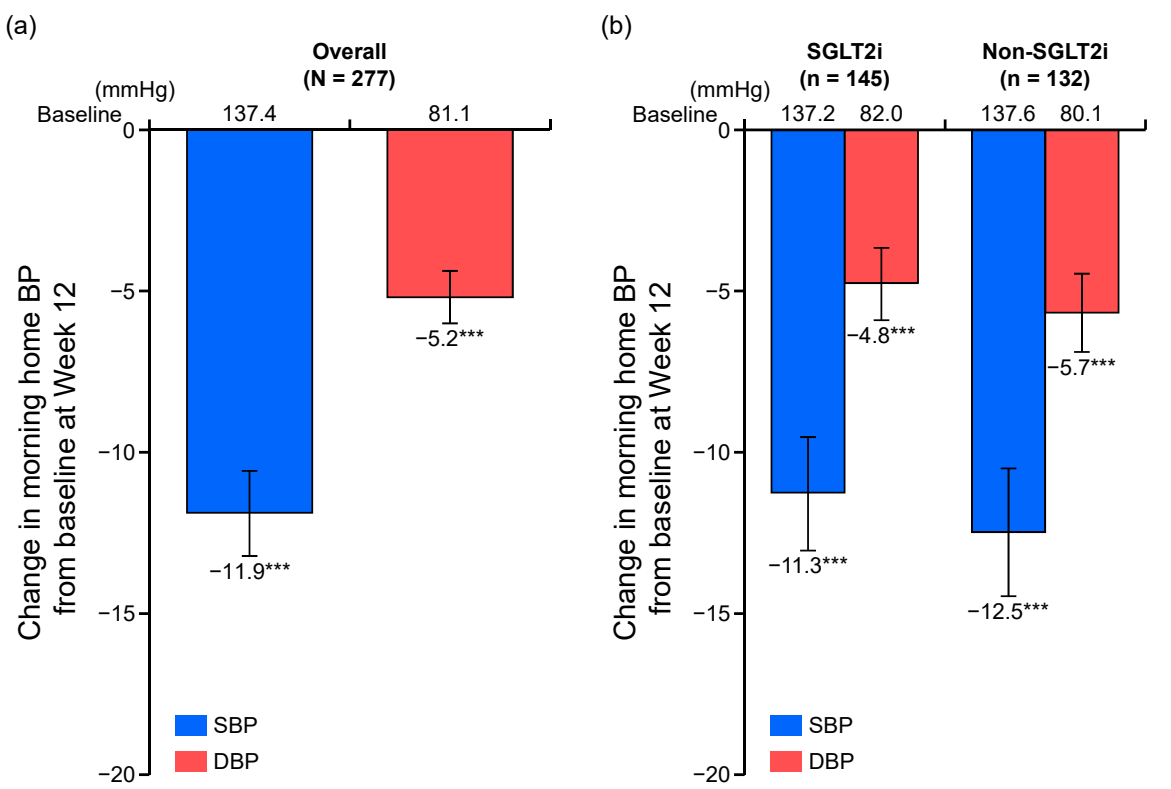
We conducted a pooled subanalysis of five multicenter, prospective, open-label, single-arm studies on esaxerenone: a nonsteroidal mineralocorticoid receptor blocker (MRB).[1-5] These studies aimed to evaluate the efficacy, organ-protective effects, and safety of esaxerenone in hypertensive patients with type 2 diabetes mellitus (T2DM), with and without concomitant sodium–glucose cotransporter-2 inhibitor (SGLT2i) therapy. In total, we enrolled 283 and 279 patients in the safety (with SGLT2i, 148; without, 135) and full analysis sets (with SGLT2i; 145; without, 134), respectively. Significant changes in morning home systolic/diastolic blood pressure (SBP/DBP) from baseline to week 12 were shown in the overall population (mean change: −11.9/−5.2mmHg, both $P < 0.001$) and both SGLT2i and non-SGLT2i subgroups (−11.3/−4.8 and −12.5/−5.7mmHg, respectively, all $P < 0.001$) (**Figure 1**). Similar findings were observed in bedtime home and office SBP/DBP.

The proportions of patients who achieved target home SBP/DBP of under 135/85mmHg were 71.2% (overall population) and 70.5% and 71.9% in the SGLT2i and non-SGLT2i subgroups, respectively. The urine albumin-to-creatinine ratio significantly improved from baseline to week 12 in the overall population and SGLT2i subgroups (percentage change in geometric mean from baseline: −42.8%, −43.0%, and −42.6%, respectively, all $P < 0.001$) (**Figure 2**). N-terminal pro-B-type natriuretic peptide levels improved in all groups.

In terms of adverse events, serum potassium levels increased up to week 2 after starting esaxerenone treatment but stabilized thereafter through week 12 in both subgroups (**Figure 3**). The incidence of serum potassium ≥5.5mEq/L was 2.0% vs 5.2% in the SGLT2i vs non-SGLT2i subgroups. We concluded that esaxerenone demonstrated significant BP-lowering effects, and improved renal and cardiovascular parameters, regardless of SGLT2i use.

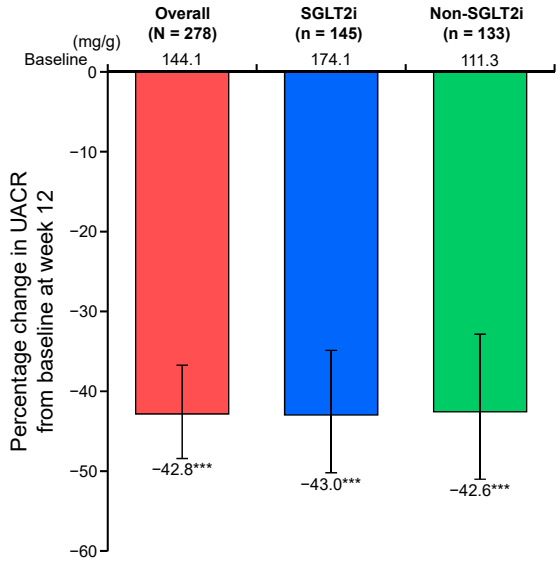
Regarding the safety of esaxerenone administration, the safety profile of esaxerenone was consistent, regardless of SGLT2i use, with the numerically lower incidence of serum potassium ≥5.5mEq/L in the SGLT2i subgroup suggesting a potential mitigating effect of SGLT2is on the risk of hyperkalemia. Thus, concomitant use of an SGLT2i may help further enhance its safety profile regarding the mitigation of hyperkalemia risk in hypertensive patients with T2DM. Of note, the consistent beneficial effects observed with esaxerenone across both subgroups in our study might suggest that the use of MRBs from an earlier stage in the clinical course could provide additional advantages. Moreover, in patients whose BP remains uncontrolled despite the addition of

Figure 1



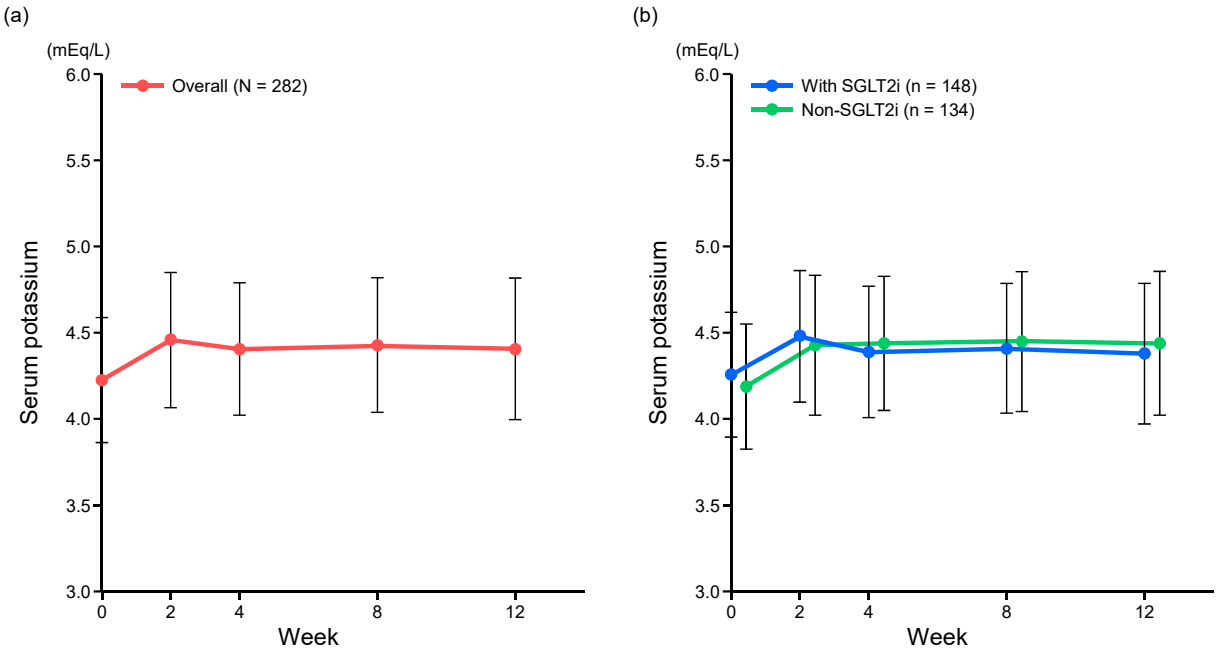
renin-angiotensin system (RAS) inhibitor, calcium channel blocker (CCB), and SGLT2i, enhanced volume management through MR blockade may help achieve more robust BP lowering. Conversely, in patients who are not receiving an SGLT2i, a relatively small degree of MR blockade may more readily reduce fluid volume and thus facilitate BP control, potentially reflecting heightened sensitivity to MR blockade in this population. SGLT2is exert their effects via the enhancement of glucose excretion through the urine while inducing natriuresis (sodium loss) and diuresis (fluid loss). In contrast, the mechanism underlying the antihypertensive effects of esaxerenone is the inhibition of sodium retention and consequent fluid overload, both of which are vital contributors to its antihypertensive effects. Therefore, the two drug classes exert their effects simultaneously without antagonizing each other, as they work via distinct biochemical pathways.

Figure 2



Importantly, esaxerenone is indicated for the treatment of hypertension; however, finerenone is not indicated for its antihypertensive effect (i.e. the treatment of hypertension). Therefore,

Figure 3



when selecting MRBs to treat hypertension, esaxerenone is suitable instead of finerenone. The JSH 2025 guideline[6] recommend MRBs as second-line therapy and permit the administration of esaxerenone as an additional antihypertensive agent when there is an inadequate antihypertensive effect with ARB or CCB monotherapy. The 2024 Japanese Clinical Practice Guidelines for the diagnosis and treatment of CKD[7] recommend SGLT2is as first-line agents for CKD complicated by T2DM, and RAS-based inhibitors for hypertension with proteinuria. Additionally, nonsteroidal MRBs are recommended for persistent albuminuria. Finerenone is recommended if serum potassium levels are normal and only the improvement of albuminuria is needed, while esaxerenone is recommended if both improvement of albuminuria and hypertension are needed.

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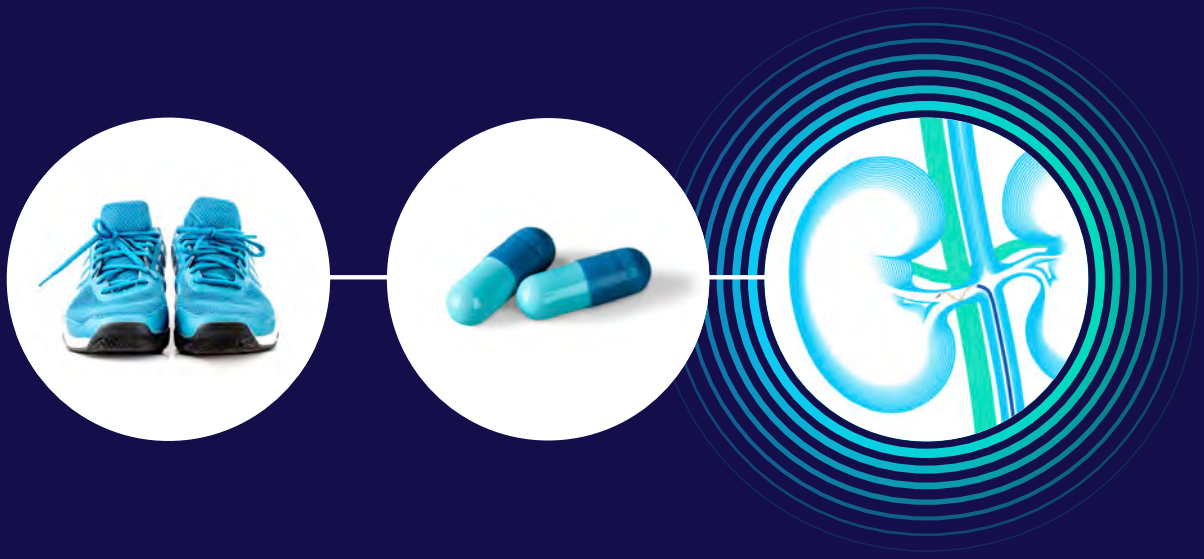
Medtronic

ACC/AHA hypertension guidelines are here!



Renal denervation now recommended.[1]

The American College of Cardiology (ACC) and American Heart Association (AHA) hypertension guidelines now include renal denervation (RDN) as a class IIb recommendation, serving as an adjunctive treatment option alongside lifestyle and medication management to control blood pressure.[†,1]

Review highlights from the published guidelines, including RDN recommendations related to patient selection, shared decision-making, and care pathway.

U.S. healthcare professionals

International healthcare professionals

† See ACC/AHA hypertension guidelines for specific patient selection recommendations.

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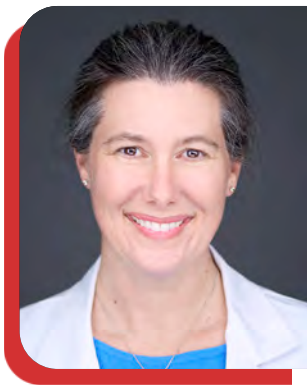
PERSPECTIVES IN HYPERTENSION



Are hypertensive disorders of pregnancy an overlooked predictor in cardiovascular risk assessment in women?

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Hypertensive disorders of pregnancy (HDP) – including gestational hypertension, preeclampsia and eclampsia – are associated with an average two-fold increased risk of long-term cardiovascular disease in women. The endothelial dysfunction and vascular injury related to these disorders has been linked to subclinical cardiac and vascular changes, which become clinically apparent in the first year postpartum and persist throughout a woman's life.[1-3] Numerous recent studies have shown that women with HDP have an increased risk of developing cardiovascular risk factors (e.g. chronic hypertension, hyperlipidemia, diabetes, renal dysfunction) as well as cardiovascular disease (e.g. coronary artery disease, stroke, heart failure, atrial fibrillation, peripheral vascular disease).[3-6] This association appears to correlate with the severity of HDP, earlier age of onset, earlier gestation of onset, and recurrence in subsequent pregnancies.[1, 3-4]

Although patients with HDP are sometimes regarded as high risk and monitored closely by our obstetrical colleagues during pregnancy, longitudinal care after the postpartum period is not standardized.[8] Internists and other subspecialists who care for these patients throughout their lifetime need to have a heightened awareness of a history of HDP. In response, international societies including the American Heart Association (AHA), American College of Cardiology (ACC), European Society of Cardiology (ESC), and International Society of Hypertension (ISH), have recommended incorporating a history of HDP into the risk assessment for primary prevention of cardiovascular disease.[1,8-10] However, there is no consensus in the recommended monitoring metrics and intervals across guidelines.

As practicing clinicians, we routinely assess individual cardiovascular risk for our patients in the context of office visits. Commonly used methods to estimate cardiovascular risk, including the Pooled Cohort Equation (PCE),[11] the Systematic Coronary Risk Equation 2 (SCORE2)[12] and the more contemporary Predicting Risk of cardiovascular disease EVENTs (PREVENT™) calculator,[13] account for a range of known risk factors such as age, sex, tobacco use as well as the presence of underlying hypertension, diabetes, hyperlipidemia, renal disease, and obesity. However, a history of HDP or other adverse pregnancy outcomes, a well-established marker of future cardiovascular risk, remains conspicuously absent (**Figure 1**).

Researchers have attempted to fill this gap by modeling how the inclusion of HDP may improve cardiovascular risk prediction with mixed findings. Stuart et al. found that the inclusion of HDP to the PCE did not improve 10-year risk prediction, which is likely due to the collinearity with existing risk factors in the PCE model.[14] A subsequent

study by Stuart et al. found that existing risk factors accounted for 84% of the risk conferred by gestational hypertension but only 57% of the risk conferred by preeclampsia.[15] This is consistent with findings that a history of preeclampsia is associated with a higher risk for cardiovascular disease than a history of gestational hypertension, highlighting the phenotypic heterogeneity within the umbrella of HDP.[3-4] In a Norwegian study, Markovitz et al. found that inclusion of HDP made only small improvements to cardiovascular disease risk prediction.[16] In a Canadian study, Gladstone et al found that inclusion of HDP reclassified many women into the high-risk category who otherwise would've been considered low risk.[17]

A major reason for why the addition of HDP into risk calculators has not shifted test characteristics significantly could be due to the lack of robust pregnancy data in the cohorts from which these equations are derived. As clinician-researchers, we should be asking about pregnancy history and adverse pregnancy outcomes when designing cohorts and clinical trials. Future studies should seek to find ways to capture that unaccounted risk, especially with the use of models that are built from updated and more diverse population data.

As nature's stress test, pregnancy provides clinicians a window into the subclinical cardiovascular dysfunction that may already be present in a woman's early to mid-life. Like

Figure 1. Comparison of cardiovascular risk factors included in PCE, SCORE2, and PREVENT calculators

Risk Factor	PCE (2013)[11]	SCORE2 (2021)[12]	PREVENT™ (2023)[13]
Age	x (40-75)	x (40-69)	x (30-79)
Sex	x	x	x
Race	x (optional)	-	-
Current Smoking	x	x	x
Total Cholesterol	x	x	x
HDL-C	x	x	x
Statin Use	-	-	x
Systolic BP	x	x	x
Antihypertensive Use	x	-	x
Diabetes	x	- (excluded)	x
HbA1c	-	-	x
BMI	-	-	x
eGFR	-	-	x
UACR	-	-	x
Geography	-	x (risk region)	x (zip code)

angina, HDP should be treated as a harbinger for elevated risk for subsequent cardiovascular disease. A step in the right direction, the AHA/ACC 2019 guidelines on the primary prevention of cardiovascular disease and 2025 guidelines on hypertension management included considering HDP as a sex-specific risk enhancer.[8, 18] The 2025 ESC guidelines also highlight the importance of primary care follow up after delivery for patients with adverse pregnancy outcomes to continue blood pressure monitoring at regular intervals.[19] However, in practice, the lack of its inclusion in standardized calculators make the adoption of this risk stratification difficult. We hope that future international society guidelines will evaluate emerging findings about the sequela of HDP to make stronger recommendations on long-term risk stratification and management, including the potential benefit of pharmacotherapy for primary prevention in this high-risk population.

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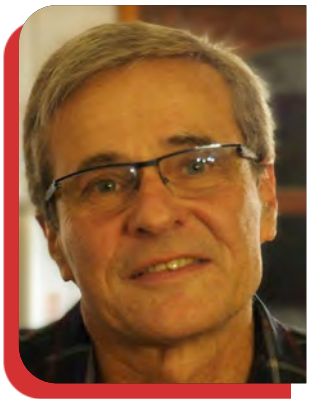
PERSPECTIVES IN HYPERTENSION

Nocturnal hypertension in pregnant women, cause or consequence of placental ischemia?



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The first observation linking elevated nocturnal blood pressure (BP) with preeclampsia (PE) was reported by Redman et al. in Oxford in 1976.[1] In a small cohort of hypertensive pregnant women, they described a reversal of the normal diurnal BP pattern in those with PE, with peak arterial pressure occurring at night. In contrast, women with uncomplicated essential hypertension retained a normal circadian BP rhythm.

Two decades later, Brown et al.[2] conducted a landmark study of 158 women with hypertensive disorders of pregnancy. They demonstrated that nocturnal hypertension was common in these women and – remarkably – was more prevalent in those who developed PE (79% vs. 45%, $p < 0.001$). Moreover, nocturnal hypertension (NH) was strongly associated with adverse maternal and fetal outcomes, including renal insufficiency, liver dysfunction, thrombocytopenia, and low birth weight.

In 2016, we published our first report on the association between nocturnal hypertension and PE.[3] In nearly normotensive and hypertensive pregnant 90 women (mean age ~29 years, mean gestational age ~30 weeks), nocturnal hypertension – defined as BP >120/70 mmHg during the night – was present in 42.5% of participants. Importantly, 27% of these women had normal 24-hour BP values on ambulatory monitoring, revealing a distinct phenotype of isolated nocturnal hypertension. In this study, nocturnal hypertension, whether isolated or combined with daytime hypertension, markedly increased the risk of PE. The risk for isolated nocturnal hypertension was almost fivefold higher (adjusted OR 4.72, 95% CI 1.25–19.43). Moreover, when analyzed as continuous variables, nighttime systolic and diastolic BP levels emerged as the strongest predictors of PE.

The risk of PE rises further when nocturnal hypertension coexists with elevated serum uric acid (SUA). In a recently published study including ~500 women without pre-existing renal disease,[4] participants were stratified into four groups according to nocturnal BP and SUA levels (high SUA was defined by the top quartile: >4 mg/dL): (1) normal SUA + nocturnal normotension, (2) high SUA + nocturnal normotension, (3) normal SUA + nocturnal hypertension, and (4) high SUA + nocturnal hypertension. The absolute risk of PE increased progressively across these groups: 6.5%, 13.1%, 31.2%, and 47.9%, respectively. These findings suggest a synergistic effect between nocturnal BP elevation and hyperuricemia; women with both abnormalities (nocturnal BP >120/70 mmHg and SUA >4 mg/dL) had an extremely high risk of PE (adjusted OR 13.11, 95% CI 6.69–25.70).

PE is a heterogeneous disorder. Early-onset PE (before 34 weeks) is the most severe phenotype and is primarily driven by impaired placental perfusion, whereas late-onset PE is more

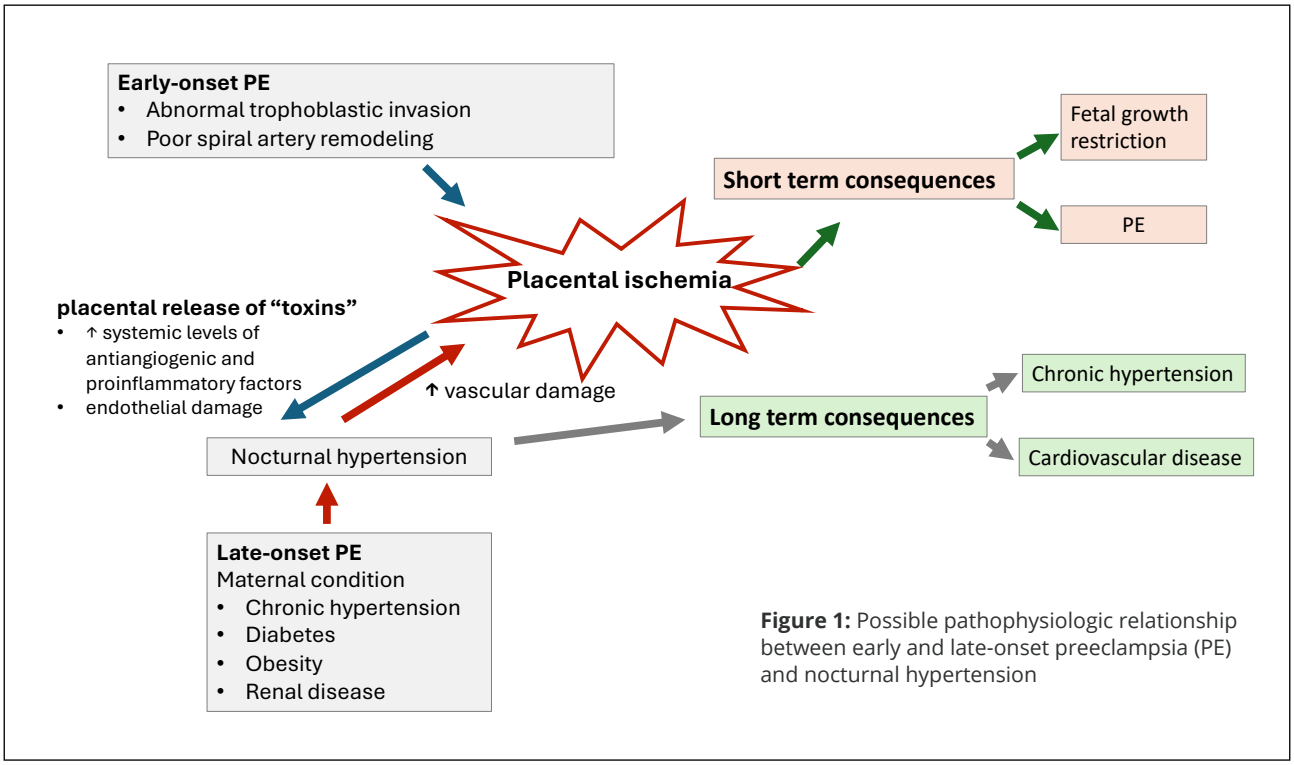

Figure 1: Possible pathophysiologic relationship between early and late-onset preeclampsia (PE) and nocturnal hypertension

closely related to maternal comorbidities such as hypertension, diabetes, and obesity.[5] In a cohort of 477 high-risk pregnancies, we found that nearly 90% of women who developed early-onset PE had nocturnal hypertension.[6] Conversely, early-onset PE was rare in women with normal nocturnal BP (<2%). Nocturnal hypertension was a stronger predictor of early- than of late-onset PE (adjusted OR 5.26, 95% CI 1.67–16.60 vs. 2.06, 95% CI 1.26–4.55). Strikingly, elevated nighttime BP often preceded the clinical onset of PE by several weeks, and in adjusted models, nocturnal – but not daytime – hypertension independently predicted early-onset PE.

Because gestation involves dynamic hemodynamic changes, the relationship between nocturnal hypertension and PE may vary by gestational age. To explore this, we performed ambulatory BP monitoring in 1,363 high-risk pregnant women (mean age ~30 years) at 12–19, 20–27, and 28–36 weeks.[7] The prevalence of isolated nocturnal hypertension increased during the second half of pregnancy, when it became a strong predictor of PE and preterm PE (adjusted OR 3.25, 95% CI 1.95–5.41, and 5.11, 95% CI 3.38–7.97, for 20–27 and 28–36 weeks of gestation, respectively). Before 20 weeks, however, nocturnal hypertension predicted PE only when combined with daytime hypertension (sustained hypertension). These findings suggest that in early gestation nocturnal hypertension may reflect underlying maternal vascular conditions, while later it often emerges as an isolated phenotype, likely reflecting placental dysfunction.

Hypertensive disorders of pregnancy are now recognized as independent risk factors for long-term cardiovascular disease, particularly early-onset PE. In a 30-year follow-up study, cumulative cardiovascular survival was 85.9% in women with early-onset PE, compared with 98.3% in those with late-onset PE and 99.3% in unaffected women.[8] The risk of cardiovascular death was especially elevated among women with PE onset ≤34 weeks. Nocturnal hypertension may help explain this association. In a study of 200 women with prior severe PE assessed by ABPM one year postpartum, Benschop et al. found that 41.5% had hypertension, with nocturnal hypertension being the most prevalent abnormality.[9]

Traditionally, hypertension has been regarded as a cause of vascular injury. Maternal conditions linked to PE – chronic hypertension, diabetes, obesity, renal disease – are often associated with nocturnal

hypertension and may contribute to placental senescence and ischemia, mechanisms most relevant to late-onset PE. By contrast, early-onset PE stems from abnormal trophoblastic invasion and defective spiral artery remodeling, leading to placental ischemia. The ischemic placenta releases antiangiogenic and proinflammatory factors into the maternal circulation, which drive endothelial dysfunction, elevated nighttime BP, and increased SUA levels. Supporting this mechanism, Bouchlariotou et al.[10] showed that nocturnal hypertension in PE was associated with elevated von Willebrand factor (vWF) and soluble adhesion molecules, both markers of endothelial injury.

In conclusion, the relationship between nocturnal hypertension and placental ischemia is likely bidirectional. In early pregnancy, nocturnal hypertension may reflect pre-existing maternal conditions and typically coexists with daytime BP elevation. After 20 weeks, however, isolated nocturnal hypertension often emerges as an early high-risk marker, potentially reflecting systemic endothelial dysfunction driven by placental ischemia. This dysfunction can persist postpartum and carries not only short-term risks (PE, fetal growth restriction) but also long-term implications for maternal cardiovascular health (**Figure 1**).

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PERSPECTIVES IN HYPERTENSION

Fibromuscular Dysplasia – personal trajectory and joint achievements

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I have been interested by Fibromuscular Dysplasia (FMD) since my mentor Prof. Jean-François De Plaen (Nephrology Department, Cliniques Universitaires Saint-Luc, Université catholique de Louvain) involved me in the diagnosis and follow-up of several complex cases in the 1990s. By that time, FMD was still considered by many solely as a rare cause of renovascular hypertension in young women.

Since then, mostly thanks to the contribution of the French and US FMD registries, the outlook on FMD has evolved to a systematic, not so rare arterial disease affecting virtually all middle-sized arteries of the body, with a wide range of presentations going from an asymptomatic, silent condition to a severe disease leading to resistant hypertension, renal infarction, carotid dissection or subarachnoid haemorrhage. Besides stenotic lesions, the most frequent being the so-called string of beads, characterized by an alternation of arterial narrowing and dilations (Figure), the clinical picture of FMD has been progressively extended to include aneurysms, dissections and arterial tortuosity.[1] However, despite recent genetic breakthroughs,[2-3] the aetiology and pathophysiology of FMD remain elusive, and management of FMD has not substantially changed since the early 2000.

My view on FMD has been shaped by fruitful contacts with experts from both France and the United States: the French highly cartesian school (Pierre-François Plouin, Michel Azizi, Xavier Jeunemaitre) and the US more empiric but equally successful approach (Heather Gornik, Jeffrey Olin). I was privileged to coordinate the First International Consensus on FMD[1] with Heather Gornik (Cleveland, Ohio), which as of today remains the main source for clinical management of the disease. In the wake of this publication, with a number of motivated experts, we developed the European International FMD registry and initiative (FEIRI) which over the years evolved from a Belgian to a European and now international initiative, including Argentina (PI: Lucas Aparicio), China (PI: Jiguang Wang), Japan (PI: Kan Zen) and Québec (PI: Sébastien Savard).

As of today, the achievements of the FEIRI initiative include, between others:

1. large-scale confirmation of the differences between multifocal and focal FMD, and of the association of arterial dissection with male gender in FMD patients;[4]
2. demonstration of an increased risk of hypertensive disorders of pregnancy in women subsequently diagnosed with FMD;[5]
3. identification of a tentative urinary proteomic signature of FMD, mainly constituted of collagen peptides.[6]

Furthermore, with David Adlam, lead of the EORP-SCAD registry, we analysed in depth extra-coronary FMD lesions in patients with Spontaneous Coronary Artery Dissection (SCAD) and healthy controls from the United Kingdom.

We documented a lower proportion of widespread and complicated FMD, aneurysms and extra-coronary dissections in patients with SCAD compared with patients with primary FMD.[7] Along with genetic and pathologic findings, these results suggest that SCAD and FMD are distinct though overlapping entities rather than different presentations of the same disease. Analysis of proteomic profile of SCAD patients with or without extra-coronary FMD compared with primary FMD may shed more light on the extent of the overlap (submitted manuscript).

Still, a number of major issues relevant to clinical practice remain to be clarified.

First, over 90% of available data on FMD are derived from subjects of Caucasian descent.[1] We recently performed a meta-analysis suggesting a distinct clinical presentation of FMD in patients of Asian descent[8] and are planning to compare characteristics of Asian versus Caucasian patients within the FEIRI registry. Further analysis of FMD presentation in patients of different ethnicities will be needed to understand regional variations in presentation of FMD and to propose truly global recommendations for the diagnosis and management of the disease.

Secondly, there is currently no non-invasive way to assess the haemodynamic significance of renal FMD-related stenosis, and therefore to decide which patients may benefit from angioplasty. Renal Duplex is highly operator-dependent and cut-offs for haemodynamic significance are extrapolated from atherosclerotic renal artery stenosis. The use of pressure gradient measurements during catheter-based angiography has been recommended[1] but due to limited availability, time and money constraints is in reality seldom used. Based on anatomical quantification of lesions and application of fluid dynamics laws in collaboration with engineers, we are currently attempting to predict pressure gradients and therefore response to angioplasty based on non-invasive imaging, with promising preliminary results.[9,10]

Third, compared to analysis of coronary arteries in the context of ischemic heart disease, analysis of images in extra-coronary arteries affected by FMD is clearly lagging behind. For decades, the dichotomic classification of FMD has allowed a welcome standardisation but it does not account for the high variety of clinical presentations of FMD. Based on the imaging resource associated with the FEIRI registry, we are currently developing a novel, more granular and inclusive classification. In association with quantitative assessment of lesions,[9,10] enhanced or not by artificial intelligence, it may prove instrumental to develop a common language across different registries, establish correlations between morphology and clinical presentation, genetic and proteomic profile and to assess progression of lesions over time.

Finally, many patients currently referred to expert centres are in a grey zone: young patients with multiple aneurysms or dissections but without typical string of beads or focal stenosis, in the absence of argument for early atherosclerosis, inflammatory disease or inherited arteriopathy. We are currently unable to answer their questions: do I have FMD, which follow-up should be proposed, and what is my prognosis? Again, baseline characterization of these patients by advanced imaging methods and proteomic profiling combined with extended follow-up may help to address these questions in the next decade.

Past and ongoing work performed within FEIRI rests on collaboration with expert teams from all over the world. The support and contribution provided by centres such as Brussels (PIs: Tom Robberechts and Patricia Van der Niepen), Warsaw (PI: Andrzej Januszewicz), Maastricht (PI: Peter de Leeuw), Reggio Emilia (PI: Marialuisa Zedde) or Manchester (PI: Constantina Chrysochou) and the corresponding national initiatives is invaluable.

Also invaluable is the support of patient-led initiatives, such as BEL-FMD and FMD-EU, developed with an incredible efficiency and dedication by Mrs Cathlin Jamison.

Finally, I would like to express my gratitude to the numerous investigators who are not explicitly mentioned in this short outline. Their names are or will be acknowledged in current or future publications.

While this article is in the first person and attempts to explain my own trajectory, it is obvious for me that our achievements are the result of a collaborative endeavour involving trust, hard work, exchange of ideas and experience. Which may be the nicest part of the story.

10 facts about FMD

1. The diagnosis is based on the presence of the so-called string of beads (multifocal FMD) (Figure) or less frequently of a focal or tubular stenosis (focal FMD). This dichotomous classification does not account for the whole spectrum of clinical presentations of the disease.
2. Besides stenotic lesions, FMD is often associated with arterial dissections, aneurysms and marked arterial tortuosity.
3. Up to 5% of apparently healthy subjects may harbour FMD lesions.
4. The mean age at diagnosis of FMD in current registries is ~50 years.
5. Despite the overall female predominance of FMD, coexistence of arterial dissection with FMD is strongly associated with male gender. The proportion of males is also higher among children/adolescents with FMD, patients with focal FMD and patients of Asian descent.
6. In more than half of patients, FMD is present in two or more arterial beds. Renal and cerebrovascular arteries are the most frequently affected.
7. Women with undiagnosed FMD at the time of pregnancy are at increased risk of gestational hypertension, preterm birth and, to a lesser extent, preeclampsia.
8. While a substantial proportion of patients with Spontaneous Coronary Artery Dissection (SCAD) have FMD-like lesions of extra-coronary arteries, the relation between both entities remains controversial.
9. Patients with FMD appear to display a unique urinary proteomic profile, which may be indicative of an increased collagen turnover.
10. Quantitative assessment of renal FMD lesions may allow predicting their haemodynamic significance, and therefore orient the decision to perform renal angioplasty.

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PERSPECTIVES IN HYPERTENSION

Diagnosis and treatment of renal artery stenosis

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Whenever we are confronted with a newly referred patient with hypertension, the question comes up whether we should look for the presence of renal artery stenosis, and if we find one what we should do about it. Although our clinic has treated hypertensive patients with renal artery stenosis for decades, questions about the most appropriate diagnosis and treatment persist.

In our experience, most cases of renal artery stenosis are atherosclerotic in origin but in recent years we have seen an increasing number of patients with fibromuscular dysplasia (FMD), probably because of greater awareness among clinicians of this condition (**figure 1**). Studies have shown that these two forms of renal artery stenosis do not share common pathophysiological mechanisms. Whereas in atherosclerotic renal artery stenosis (ARAS), flow disturbances and intrarenal inflammatory processes play a paramount role, the kidney of patients with FMD is relatively spared and resembles more the kidney of patients with primary hypertension.[1] In this short overview, we will focus primarily on ARAS.

Diagnosis of renal artery stenosis

When do we have to suspect the presence of renal artery stenosis and how should we shape the diagnostic process? Roughly speaking, the main clinical features a patient with renal artery stenosis may present with are resistant hypertension, ischemic nephropathy or so-called cardiac destabilization syndromes as 'flash' pulmonary edema, recurrent episodes of heart failure and acute coronary syndrome. Sometimes an abdominal bruit or unexplained hypokalemia may alert the physician that renal artery stenosis may be present. Overall, laboratory examination is unremarkable in patients with FMD but in the case of ARAS, one may find a reduced estimated glomerular filtration rate (eGFR) and/or urinary albumin loss. Recently, we evaluated in our clinic whether certain clinical

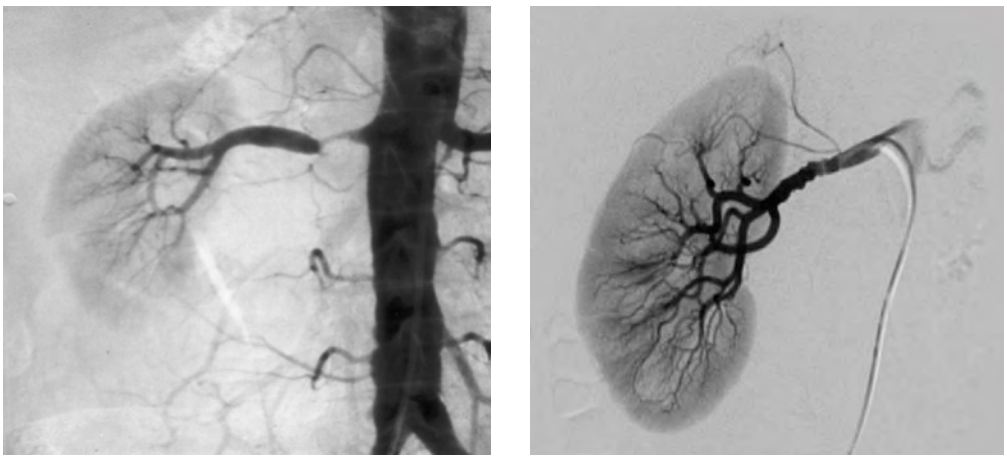

Figure 1: Examples of atherosclerotic renal artery stenosis (left) and fibromuscular dysplasia (right). Authors' series.

clues and patient characteristics could predict the results of renal angiography. Most clues had only limited predictive value because of low prevalence, lack of discriminative ability or lack of additional information over and above other patient characteristics. Only three clues (a length difference between kidneys of 10% or more, the presence and extent of extra-renal atherosclerosis, in particular peripheral artery disease, and recent onset of hypertension), proved to be independent predictors (unpublished data). However, patients can also be completely symptomless. Thus, when clinical suspicion is high, we still have to ascertain whether a stenosis is present and whether the stenosis is hemodynamically, or even more importantly, clinically significant.

In essence, we have four diagnostic modalities to screen for stenotic lesions in the renal artery: duplex ultrasound (DUS), magnetic resonance angiography (MRA), computed tomography angiography (CTA) and digital subtraction angiography (DSA). **Table 1** summarizes some of the advantages and limitations of each of these modalities.[2] Clearly, these techniques provide only information on anatomical lesions of the renal arteries and do not tell us anything about the clinical significance of the abnormality. Even DUS lacks enough sensitivity and specificity to fulfill such a role.

Unfortunately, there are as yet no reliable tests or biomarkers to differentiate between true renovascular hypertension from ARAS secondary to hypertension or from hypertension and ARAS being totally unrelated.

Treatment of renal artery stenosis

While the diagnosis of renal artery stenosis is already problematic for the clinician, decisions regarding treatment are even more so. In essence, there are three options: surgery, percutaneous transluminal renal angioplasty (PTRA) with or without stenting and medical treatment. With the advent of PTRA, the surgical approach has faded into the background. There is only one randomized study which compared PTRA to a surgical approach and by and large, this trial did not find significant differences in outcome after the two treatments.[3] However, after PTRA had become the treatment of choice, trials which compared the effect of PTRA with or without stenting on top of medical treatment to that of medical treatment alone failed to show any appreciable benefit of angioplasty. Several meta-analyses of those trials came to the same conclusion. The most recent, updated meta-analysis comes from a group of Japanese and American researchers.[4] They scrutinized the trials with respect to cardiovascular disease (CVD)-related mortality, the incidence of CVD events, suppression of renal function decline, changes in blood pressure, changes in the number of antihypertensive drugs and serious adverse events. Based on the data of 2275 patients from nine randomized controlled trials they concluded that there were no significant differences between medical therapy alone and the combination of medical therapy and PTRA with respect to any of the outcome measures except for the number of antihypertensive drugs. Combination therapy reduced this number by 0.42 (95% confidence interval: 0.12-0.71) which, although significant, is not very impressive. Additionally, they noted

Table 1. Diagnostic modalities to detect renal artery stenosis.

Test	Advantages	Limitations
Duplex ultrasound	Noninvasive, radiation-free, cheap, also applicable in patients with reduced renal function or contrast allergy.	Time consuming, highly operator-dependent, difficult in obese patient or distended bowel gas.
Computed tomography angiography (CTA)	Excellent special and temporal resolution of renal arteries and surrounding structures.	Use of iodinated contrast and ionized radiation. Severe renal artery calcification may obscure luminal narrowing.
Magnetic resonance angiography (MRA)	High-quality noninvasive anatomic images of the renal arteries and surrounding structures.	High cost, contraindicated in patients with ferro-magnetic implants and those with eGFR < 30 ml/min.1.73m^2, when using group 1 gadolinium-based contrast.
Digital subtraction angiography (DSA)	Direct hemodynamic measurements and if needed, revascularization could be performed immediately.	Use of iodinated contrast and ionized radiation. Invasive modality. Pre- or posthydration when eGFR < 30 ml/min.1.73m^2

Adapted from Bavishi et al.[2] eGFR: estimated glomerular filtration rate.

that the included studies demonstrated a low-to-moderate risk of bias, high heterogeneity and limited overall quality.

It is striking that almost all authors who have criticized the trials for methodological reasons state that the number of patients with advanced disease are underrepresented in these trials while in their opinion such patients are likely to benefit most of angioplasty. This is a rather curious reasoning. It makes much more sense to suppose that PTRA will help patients with less advanced disease. Indeed, already from an early phase of stenosis intrarenal abnormalities develop.[5] Unfortunately, no trials have examined the effect of angioplasty specifically in patients with low-grade renal artery stenosis.

Currently, there is a tendency to restrict a dilation procedure to patients who exhibit a significant pressure gradient across the stenosis, either at baseline or after a hyperemic stimulus.[6] It should be stressed, though, that there is no evidence yet for better outcome when treatment decisions are based on functional measurements such as pressure gradients or fractional flow reserve.[7]

In a joint venture, a consensus panel of the Society for Cardiovascular Angiography and Interventions (SCAI), the American Heart Association (AHA) and the American College of Cardiology (ACC) has formulated criteria for 'appropriate use' of angioplasty in patients who are most likely to benefit from this procedure.[8] Cardiac destabilization syndromes, rapidly deteriorating renal function or stage IV chronic kidney disease in patients with treatment-resistant hypertension and bilateral renal artery stenosis or stenosis in a solitary kidney are considered appropriate indications. Newly discovered hypertension or asymptomatic ARAS are not. In all other cases, it should be left to the professional judgement of the clinician. It should be stressed, though, that these recommendations are based on expert opinion and not on hard evidence. Irrespective of whether angioplasty is considered or not, in patients with ARAS cardiovascular risk management (statins, antiplatelet therapy) is always indicated.

In patients with FMD, the therapeutic approach is a little different. In the absence of concurrent atherosclerotic lesions, anti-atherosclerotic measures are not useful in FMD. Especially in patients younger than 50 years, one may consider angioplasty[9] but there have been no randomized trials of PTRA in FMD.

We must conclude that we can still not make recommendations for the diagnosis and treatment of renal artery stenosis that are based on sound and irrefutable clinical evidence. Probably our best options today are to screen for a stenosis with CTA, to confirm the diagnosis with DSA and to base the decision to do angioplasty on individual clinical grounds.

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PERSPECTIVES IN HYPERTENSION

Taking the bull by the horn – efforts at addressing hypertension and related diseases in Africa with focus on Ghana




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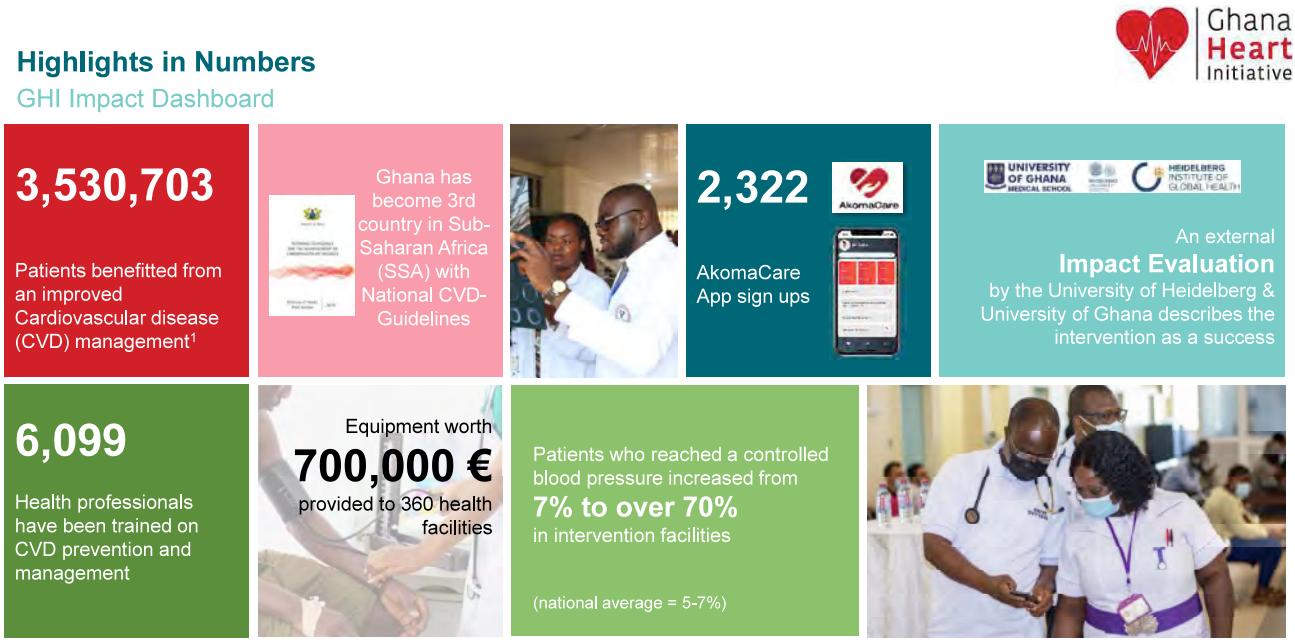
Hypertension in Africa: A Growing but Invisible Epidemic

The number of people living with hypertension is estimated at 1.3 billion with more than three-quarters (75%) of adults with hypertension living in low-and middle-income countries including those in Africa.[1] Regrettably, hypertension cases in Africa rose from 54.6 million in 1990 to 130.2 million in 2010, representing a 138.5% increase, and are projected to reach 216.8 million by 2030, a further 66% rise.[2] Yet, the bigger challenge lies not in the numbers alone, but in the invisibility of the disease, often undetected until it causes fatal complications.

Hypertension in Ghana: The Unseen Health Crisis

Ghana is experiencing a steady increase in hypertension cases, fueled by rapid urbanization, sedentary lifestyles, and unhealthy diet.[3,4] Worryingly, 70% of hypertensive individuals in Ghana are unaware of their condition, and just 5% of those on treatment have their blood pressure adequately controlled.[5] Hypertension has remained a major cause of hospital admissions and deaths, mainly driven by late detection and poor management.[3,6] Despite national efforts by the Ministry of Health, nearly half of individuals show signs of end-organ damage at the time of diagnosis, a chilling reminder of how long

Figure 1: Diagrammatic presentation of the key successes of GHI.



hypertension can go unnoticed and a reflection of fragmented health systems, limited screening, low awareness, poor access to care, and missed opportunities for prevention, particularly in rural areas where significant portions of the population reside.[7,8,9]

Bridging the Gaps: Strengthening Systems for Hypertension Control

Amidst challenges facing hypertension control in Africa, Ghana is making significant strides in tackling hypertension and other cardiovascular diseases through concerted efforts to strengthen health systems and improve care delivery. An example that stands out is the Ghana Heart Initiative (GHI), which we launched in 2018 as a flagship program to enhance cardiovascular health by improving hypertension prevention, diagnosis, and management, especially at the primary care level where the majority of Ghanaians first engage with the health system[9] (**figure 1**).

One of the most transformative components of the initiative has been the development of a national guideline for cardiovascular disease (CVD) care, which has promoted standardized evidence-based treatment across all levels. To ensure its widespread adoption, the AkomaCare digital app was introduced, enabling providers to access and apply the guidelines easily.

To address capacity gaps and maldistribution of health staff, selected staff were trained and facilities equipped with digital blood pressure monitors, electrocardiograms, defibrillators, clinical guidelines, and job aids to ensure early detection and standardized treatment of hypertension. Through these coordinated interventions, blood pressure control rates in participating facilities improved dramatically from just 7% at baseline to 70%, far exceeding the national average of 5–9.5%.[4,5]

To ensure integration into local structures, ownership, and continuity, the project was implemented through a partnership between the Ghana Health Service, Ministry of Health and Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ), with enormous funding support from Bayer AG. GHI exemplifies how targeted, collaborative efforts can overcome barriers to hypertension care.

Consolidating Gains and Expanding Impact

Building on the success of the Ghana Health Initiative, the AYA Integrated Healthcare Initiative, funded by three pharmaceutical companies and one foundation, is adopting a modular, systems-based approach to scale-up efforts at reducing the burden of non-communicable diseases by strengthening care integration within primary

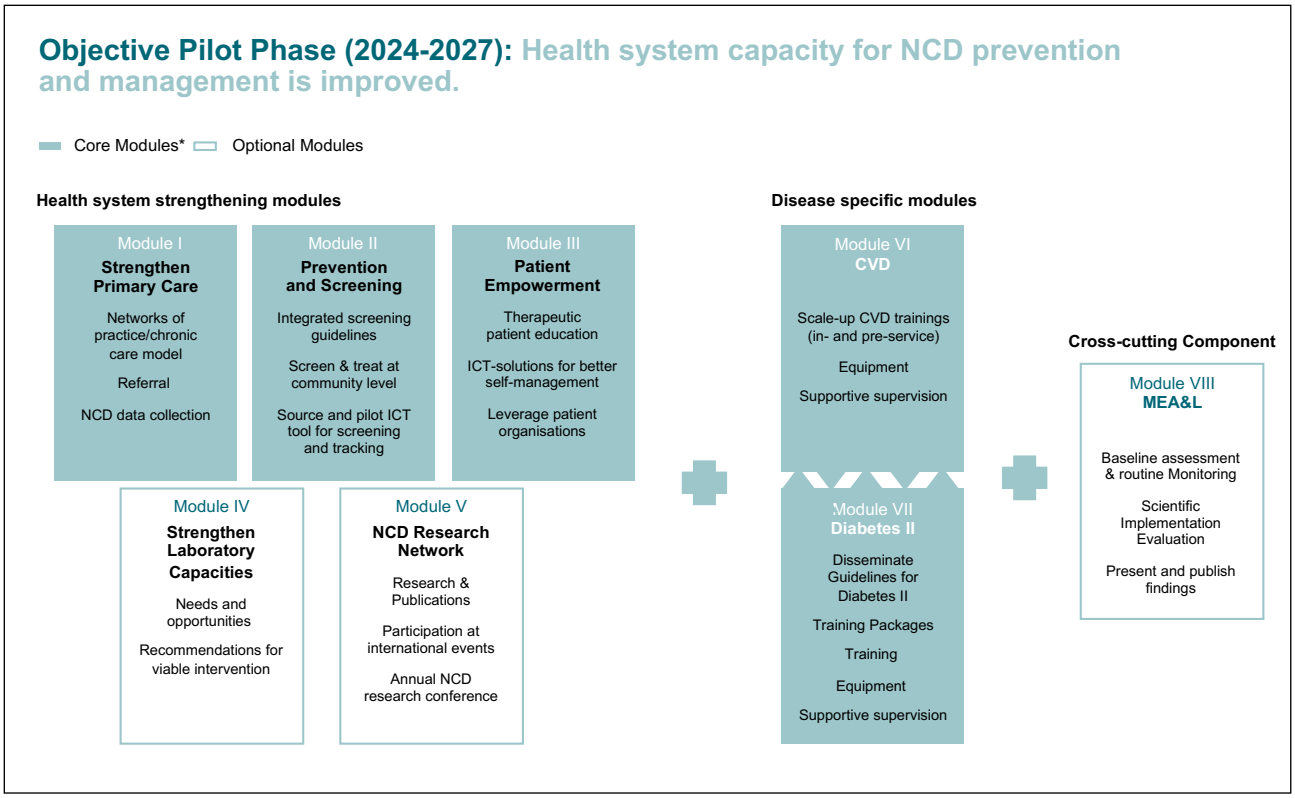
healthcare systems (**figure 2**). Through AYA, we are expanding our focus beyond hypertension and related CVDs to include obesity and type 2 diabetes, which are high impact NCDs that often coexist, share common risk factors, and act synergistically to worsen health outcomes.

To ensure that our health services are responsive and community-centered, primary level facilities will be equipped and referral systems streamlined to support seamless patient referrals across different levels of care. Primary health care facilities constitute the backbone of Ghana's health infrastructure and serve as the first point of contact for the majority of the population. However, prescription restrictions and limited capacity have long hindered access to timely quality care at the community level, particularly at B1 facilities (health centers without a resident medical doctor). To address these systemic barriers, the initiative is investing in the capacity building of non-physician providers, such as physician assistants through hands-on mentorship, digital decision-support tools, and structured supervision. Enabling them to manage cases locally, bringing much needed care to underserved populations and reducing long distance referrals.

To maximize reach, we will leverage locally available resources such as community pharmacies, community health nurses, and volunteers by equipping them with the skills and tools needed to conduct community-level screening and raise awareness among over 150,000 individuals. Our decentralized community-based approach will ease facility burden, enable early detection, and reduce complications, especially in underserved areas.

Additionally, a cohort of 2,800 healthcare providers (HCPs) will be trained to identify, manage, treat, and support patients with hypertension and CVDs. Through task-shifting, HCPs will offer contextually relevant and culturally sensitive therapeutic education, fostering trust and enabling patients to adopt healthy lifestyle changes and self-management. To further support this effort, an ICT tool will also be developed to provide patient reminders, educational content, and facilitate communication between patients and caregivers, enhancing continuity of care.

Figure 2: Concept and modules of the AYA Integrated Healthcare Initiative.



A Defining Moment for Health Systems and Development in Africa

Now more than ever, we must move beyond rhetoric and commit to bold, coordinated, and sustained action on the prevention and control of hypertension as a development imperative.

Hypertension is no longer a silent killer; it is a loud and urgent call for systemic change. In Ghana and across Africa, the growing tide of cardiovascular disease threatens to reverse decades of health and development progress. But it also presents an opportunity, a point of inflection, to reimagine healthcare as not just a curative service but a proactive, preventive, people-centered system.

Every missed opportunity to prevent or control hypertension is a life cut short in the prime of productivity, a blow to families, communities, and overall development. Delaying action means accepting preventable deaths of millions in their most productive years, an inexcusable failure that costs far more than prevention ever will. This is a defining moment.

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PERSPECTIVES IN HYPERTENSION

Early detection of pre-heart failure in hypertension: bringing cardiac biomarkers and echocardiography into everyday practice

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Hypertension is the leading cause of heart failure worldwide, yet most of our clinical effort is spent on treating blood pressure numbers rather than looking for the silent cardiac damage that builds up over years. As preventive cardiologists, we are often struck by how frequently routine clinic visits overlook hidden structural or biochemical changes in the heart. By the time symptoms appear, opportunities for prevention of heart failure have often passed.

That's why we and our colleagues have been exploring how simple tools we already have, namely serum cardiac biomarkers and echocardiography, can help us identify "pre-heart failure" in people with elevated blood pressure or hypertension before they develop symptoms.

From Numbers to Phenotypes

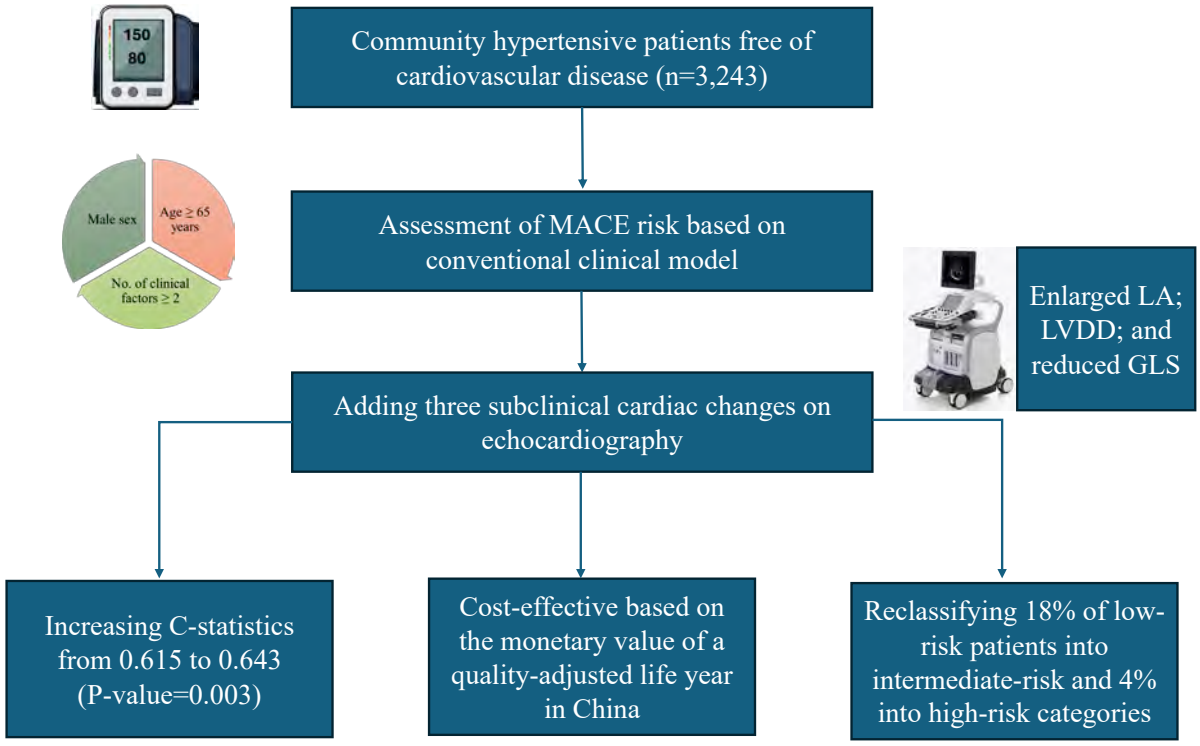
Contemporary hypertension care relies on office and/or home blood pressure readings plus conventional risk factors such as smoking and dyslipidemia. But these measures tell us little about what's actually happening in the heart. Over the past decades, robust evidence has demonstrated that natriuretic peptides such as NT-proBNP and high-sensitivity cardiac troponins rise in response to subclinical myocardial stress or injury. In large population-based studies, elevated levels of these cardiac biomarkers are common even in stage 1 hypertension and strongly predict future heart failure and cardiovascular events.[1,2]

At the same time, echocardiography, especially when we look beyond ejection fraction to parameters such as left ventricular mass, left atrial diameter, and diastolic function, can reveal structural and functional changes long before symptoms appear. Put together, cardiac biomarkers and echocardiography provide a much richer picture of heart health than blood pressure alone.

Pre-Heart Failure Is Real and Detectable

The universal definition and classification of heart failure specifically define pre-heart failure, that is individuals with risk factors such as hypertension plus abnormal cardiac structure or function or elevated cardiac biomarkers, but no heart failure symptoms.[3] This stage is common in hypertensive populations. For example, in a nationally representative hypertension survey, we found that the weighted prevalence of pre-heart failure was 42.8%.[4] In addition, our recent work showed that pre-heart failure defined by age-specific NT-proBNP cutoffs in the general population approaching 17.1%.[5] We further

Figure 1A



Risks of ASCVD and HF associated with the three echocardiographic measures

	Hazard ratio (95% CI)		
	Enlarged LA	LVDD	Reduced GLS
ASCVD	1.95 (1.38, 2.75)	1.80 (1.39, 2.33)	1.51 (1.22, 1.87)
HF	3.85 (2.27, 6.55)	5.72 (2.64, 12.39)	4.15 (2.63, 6.53)
P-value*	0.035	0.005	<0.001

ASCVD, atherosclerotic cardiovascular disease; HF, heart failure; CI, confidence interval; LA, left atrium; LVDD, left ventricular diastolic dysfunction; GLG, global longitudinal strain

ASCVD included coronary heart disease, myocardial infarction, and stroke

*indicated comparison of hazard ratio between ASCVD and HF

Figure 1B

demonstrated the potential of echocardiography for risk reclassification and cost-effectiveness in cardiovascular primary prevention among hypertensive individuals in China (**Figure 1A**; In Press in the Journal of Hypertension). Notably, conventional echocardiographic parameters, such as left atrial enlargement, were found to confer a higher risk of heart failure than heart attack or stroke (**Figure 1B**).

Detecting pre-heart failure matters because it identifies hypertensive patients who derive the greatest absolute benefit from intensive blood pressure lowering. For example, in post-hoc analyses of the SPRINT trial, participants with elevated biomarkers saw far larger reductions in heart failure and death than biomarker-negative individuals.[6]

Why Hypertension Guidelines Should Catch Up

Heart Failure guidelines and American Diabetes Association consensus statement already recommend cardiac biomarker screening for high-risk, asymptomatic individuals. But hypertension guidelines have been slow to follow,[7,8] perhaps due to a lack of randomized trials or cost-effectiveness data. Yet the science is clear: elevated NT-proBNP or cardiac troponin in a hypertensive patient signals a malignant cardiac phenotype and should prompt closer monitoring, imaging assessment, and potentially earlier or more intensive therapy.

From our perspective, biomarkers and imaging should be viewed as complementary ones. Post-hoc analysis of the SPRINT trial showed that left ventricular hypertrophy carries very different prognostic meaning depending on whether cardiac biomarkers like NT-proBNP or cardiac troponin are elevated; a malignant phenotype that carries four-fold higher risks of heart failure and death.[9] This tells us that while cardiac biomarkers can efficiently flag many apparently "low-risk" individuals, echocardiography remains critical for identifying those with structural remodeling who are at especially high risk. A pragmatic 'biomarker-first, imaging-second' approach could therefore maximize efficiency while still capturing the hidden malignant cases that matter most for heart failure prevention.

Looking Ahead: Pragmatic and Equitable Solutions

Moving from evidence to implementation will require pragmatic trials of biomarker-guided hypertension management, cost-effectiveness analyses, and simplified algorithms for use in primary care. Point-of-care NT-proBNP testing, portable echocardiography and integration of artificial intelligence may all help us tailor screening to individual risk profiles while keeping it affordable in the future.

A Call to Action

As clinicians, we can begin now. Consider ordering NT-proBNP or high-sensitivity cardiac troponin in your hypertensive patients with other risk factors, unexplained symptoms, or poor blood pressure control. Use echocardiography proactively, not just when ejection fraction falls. Start thinking of hypertension not simply as a number to control, but as a continuum of cardiac risk we can intercept.

If we embed cardiac biomarker and imaging assessment into hypertension care pathways, we can shift from reactive treatment of overt heart failure to proactive prevention of its earliest stages, and ultimately improve outcomes for billions worldwide.

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PERSPECTIVES IN HYPERTENSION

When sodium meets potassium: a systems model of blood pressure control

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Sodium and potassium are often discussed separately when we think about blood pressure regulation, but in physiology, they are constant partners. Their interplay shapes renal handling of electrolytes, extracellular fluid volume, and ultimately arterial pressure. In our recent paper "Modulation of blood pressure by dietary potassium and sodium: sex differences and modeling analysis" (Stadt & Layton, 2024),[1] we developed a computational model that brings these elements together in a single, integrated framework. By linking sodium and potassium homeostasis with fluid balance, hormonal regulation, and blood pressure control, and by incorporating sex-specific physiology,[2,3] we can explore how dietary changes in sodium and potassium intake interact to influence blood pressure.

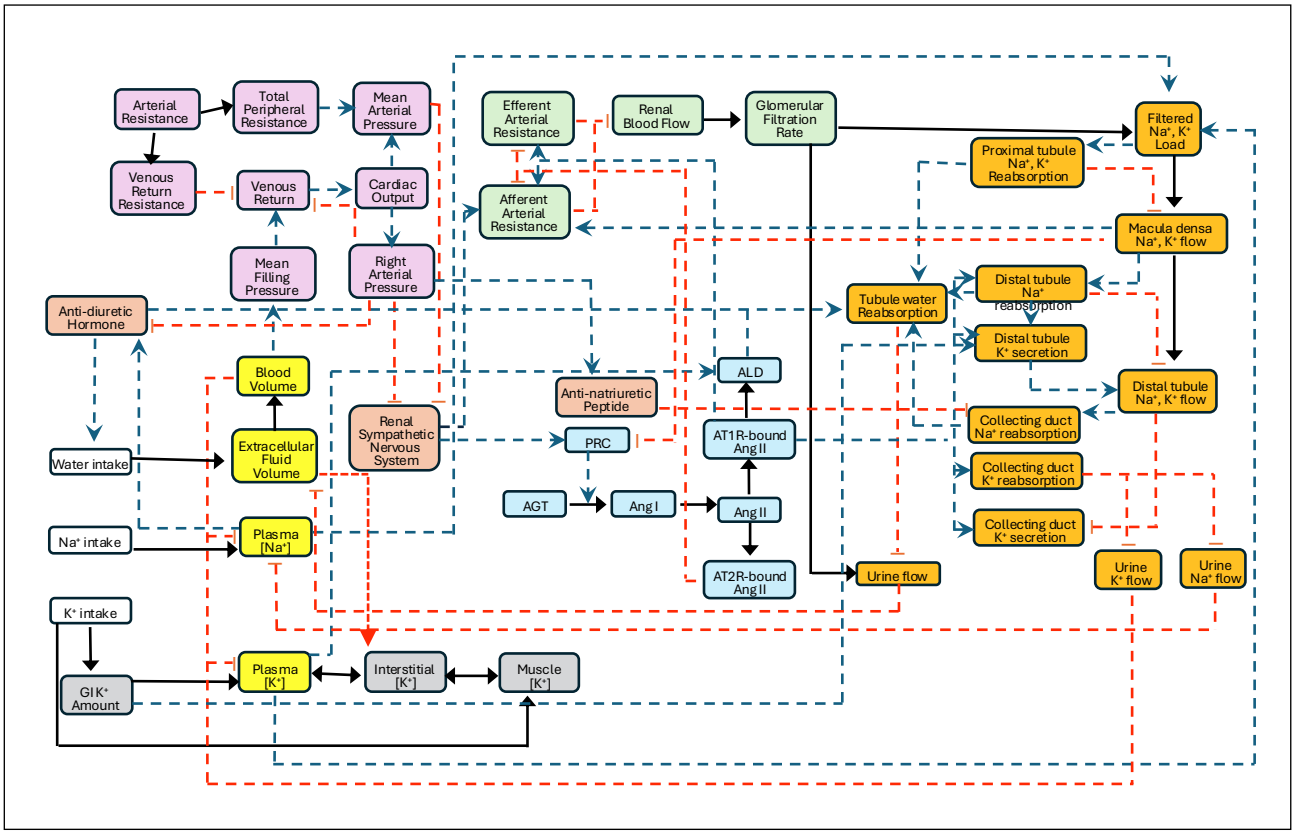
Overview of the Model

The model is a whole-body, sex-specific representation of sodium, potassium, and fluid homeostasis, linked to blood pressure. Its goal is to capture the integrated physiology of kidney function, hormonal control, and cardiovascular response so that we can examine how changes in dietary sodium and potassium intake affect blood pressure.

At the renal level, the model represents glomerular filtration, tubular reabsorption and secretion of sodium and potassium along multiple nephron segments, and their regulation by hormones such as aldosterone and angiotensin II. It also includes gastrointestinal feedforward control of potassium excretion – signals that are activated by oral potassium intake before plasma [K^+] rises significantly – which helps prevent large postprandial fluctuations. The cardiovascular component links extracellular fluid volume to arterial pressure, allowing us to capture the long-term blood pressure effects of altered sodium and potassium handling. Importantly, the model incorporates male–female differences in renal transporter abundance and hormone levels, which enables simulations of sex-specific responses.

How does one build a computational model to describe the interactions among these regulatory processes? **Figure 1** shows a schematic diagram of how the model represents physiological feedback/feedforward mechanisms that regulate blood pressure and potassium homeostasis. The model diagram is highly intricate and not easy to untangle, not unlike the underlying physiological system, with many interacting components. There are positive and negative feedback signals (denoted by blue and red dashed lines) going in all kinds of directions, linking the renal system (orange boxes), cardiovascular system (purple boxes), gastrointestinal system (a grey box), renal sympathetic nervous system (a beige box), and renin-angiotensin-aldosterone system (blue boxes). The complexity of the system is precisely why computational modeling is an asset in data interpretation.

Figure 1. Model schematic diagram depicting physiological feedback/feedforward mechanisms that regulate blood pressure and potassium (K+) homeostasis. Box colors indicate processes or variables that are more closely related to each other. Solid arrows show the sequence of steps in a process, or one variable that turns into another. Blue and red dashed lines indicate simulating or inhibiting actions. Modified from Ref.[1] with permission.



This model is the result of integrating two lines of previously published work. The first is the series of computational models we published on sodium, fluid, and blood pressure regulation.[4,5] These models represent the renin-angiotensin-aldosterone system, pressure natriuresis, and the links between sodium balance, extracellular volume, and arterial pressure. The second body of work is our models of potassium homeostasis,[6–8] which represent dietary intake, gastrointestinal feedforward signals, cellular uptake (via insulin- and aldosterone-sensitive Na^+-K^+-ATPase), and renal potassium excretion, including both feedback and feedforward regulation.

By combining these two frameworks, we were able to represent not only the regulation of sodium and potassium individually but also their physiological interactions. This integration was essential, because potassium intake does not simply alter plasma [K^+], it also affects sodium handling, extracellular volume, and ultimately blood pressure.

Sex differences were incorporated based on experimental data for transporter expression and hormone levels, providing separate male and female parameter sets.

Simulation Results, Key Findings, and Implications

We used the model to simulate a range of dietary scenarios: high and low sodium intake, high and low potassium intake, and combinations of the two. Several consistent patterns emerged. High sodium intake predictably increases extracellular fluid volume and raises arterial pressure, whereas high potassium intake has the opposite effect: it stimulates kaliuresis but also promotes natriuresis by reducing proximal tubular sodium reabsorption and enhancing distal sodium delivery. The resulting natriuresis reduces extracellular fluid volume and lowers blood pressure. Combined high sodium and high potassium intake demonstrates that the potassium effect is robust – potassium supplementation attenuates or even reverses

sodium-induced blood pressure elevations. Finally, sex differences were apparent: female transporter patterns produced a blunted hypertensive response to sodium loading and slightly different patterns of kaliuresis and natriuresis with potassium supplementation. These results are summarized in **Figure 2**.

These findings align with clinical and experimental evidence that dietary potassium can mitigate the hypertensive effects of sodium[9,10] and support recommendations to increase potassium intake (e.g., through fruits and vegetables) as part of blood pressure management strategies.

Here are a few clinical implications of our findings:

- Potassium supplementation is an effective antihypertensive strategy even in the presence of high sodium intake, not only because of direct kaliuresis but also because of its secondary natriuretic effect.
- Sex differences matter. Women may have a more attenuated blood pressure response to sodium load, which has implications for dietary guidelines and for interpreting clinical studies.
- Integrated modeling is powerful. By linking renal transport, hormonal regulation, and cardiovascular responses, we can explore "what-if" scenarios that are difficult to test experimentally.

Limitations and Next Steps

As with any model, there are limitations. Human data for some parameters – particularly transporter abundances and hormonal regulation in females – remain sparse. Some regulatory mechanisms, such as gut-to-kidney signaling of potassium intake, are incompletely characterized experimentally. In addition, the model is designed for long-term (hours to days) regulation and does not represent rapid, minute-to-minute changes, nor does it yet include pathological states such as chronic kidney disease.

Future work could expand the model to include disease conditions, aging, circadian variation, and inter-individual variability. Such refinements could make it even more useful for predicting blood pressure responses to dietary interventions in specific patient populations.

Conclusion

This work shows what happens when sodium meets potassium – not just in the nephron, but across the whole system. By integrating sodium and potassium handling with fluid and blood pressure regulation, our model highlights how these two ions jointly shape long-term cardiovascular outcomes. The simulations reinforce what clinical data have suggested: raising dietary potassium can offset the hypertensive effects of sodium, and sex-specific physiology

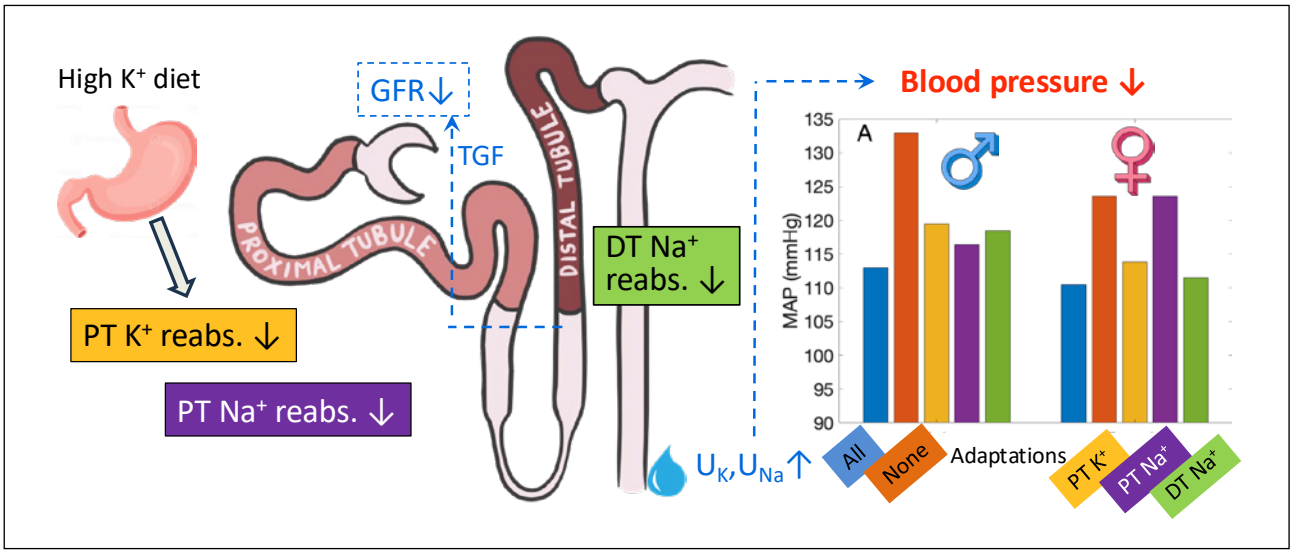


Figure 2. High potassium (K+) intake lowers blood pressure by suppressing renal K+ and sodium (Na+) reabsorption. In males, reduction in proximal Na+ transport has the largest effect. In females, where Na+-Cl- cotransporter activities are higher, reduction in distal Na+ transport has the largest effect. PT, proximal tubule; GFR, glomerular filtration rate; TGF, tubuloglomerular feedback; DT, distal tubule; UK, urinary K+ excretion; UNa, urinary Na+ excretion. Reproduced from Ref[1] with permission.

matters for understanding blood pressure responses. Bringing sodium and potassium into the same modeling framework gives us a clearer, mechanistic picture of blood pressure control, one that can inform future research, refine dietary recommendations, and ultimately improve patient care. Last but not the least, this work underscores the value of computational modeling as a tool for exploring complex, multiorgan physiology and for generating mechanistic insights that can inform dietary recommendations and guide future research.

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PERSPECTIVES IN HYPERTENSION

Call to incorporate potassium-enriched salt into hypertension guidelines

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High sodium (salt) is a well-known risk factor for elevated blood pressure, cardiovascular disease, and premature death.[1] Despite decades of global efforts, including the WHO's SHAKE package, progress has been limited - no country is currently on track to meet the 2025 WHO salt reduction target, nor the 2030 goal.[2] Reducing sodium consumption remains challenging because sustained behaviour change is difficult to achieve. The primary barrier is public resistance to foods with a less salty taste, making it hard to shift both individual dietary habits and food industry practices.

Low potassium intake is a less widely recognised but equally important risk factor for high blood pressure. The global average intake is only 2.25 g/day, far below the WHO's recommended minimum of 3.5 g/day, primarily due to inadequate consumption of fresh fruits and vegetables.[3]

Potassium-enriched salts, also known as salt substitutes, reduced-sodium salts, or low-sodium salt alternatives, replace a portion of sodium chloride in regular salt with potassium chloride. These products can be used as a direct one-to-one switch for regular salt in seasoning, food preservation, and food manufacturing, with the key advantage of retaining the same salty taste.[4] A key benefit of switching to potassium-enriched salt is that it lowers blood pressure through the joint effects of reducing sodium intake and supplementing potassium intake. Common brands typically include "Lo Salt," "Lite Salt," and "Heart Salt."

Strong evidence supports a like-for-like switch from regular salt to potassium-enriched salt for blood pressure reduction and cardiovascular benefits,[5,6] including the landmark Salt Substitute and Stroke Study6 (SSaSS, published in NEJM). In 2025, the WHO Global report on hypertension recommended potassium-enriched salt to control blood pressure.[7]

However, the adoption of potassium-enriched salt in place of regular salt remains limited.[4] Our 2024 review highlighted that only 4 out of 32 hypertension guidelines mentioned the use of potassium-enriched salt.[4] Nevertheless, recognition is growing, with salt substitutes now explicitly recommended in the 2024 European Society of Cardiology Hypertension Guideline[8] and the 2025 American College of Cardiology and American Heart Association Hypertension Clinical Practice Guideline.[9]

A concern regarding potassium-enriched salt is the potential risk of hyperkalemia in people with chronic kidney disease (CKD).[4] No trial to

date has shown an increased risk of adverse clinical outcomes from hyperkalemia associated with potassium-enriched salt, although most trials excluded patients at risk of hyperkalemia. One trial that included CKD patients reported a higher incidence of biochemical hyperkalemia, but there was no evidence of clinical harm, and participants still experienced overall cardiovascular protection.[10] The summary recommendation for the safe use of potassium-enriched salt in the **Box** highlights the importance of excluding those at risk. The **Table** provides some practical advice for healthcare practitioners when considering potassium-enriched salt for a patient.

The recent incorporations of the recommendation to switch from regular salt to potassium-enriched salt in hypertension guidelines would support clinicians in promoting practical lifestyle strategies for optimal blood pressure control. For patients with hypertension who have no contraindications, this switch can lower blood pressure and reduce the risk of serious cardiovascular complications. Population-wide adoption of potassium-enriched salt could yield substantial public health benefits. Our modelling study estimates that global implementation could prevent approximately 3 million deaths annually, highlighting the significant potential impact on cardiovascular disease prevention and global health outcomes.

Box. Recommendation for the safe use of potassium-enriched salt*

If patients add salt to their food, they should make a 1:1 switch from regular salt to potassium-enriched salt with a composition of approximately 75% sodium chloride and 25% potassium chloride, unless they are at risk of hyperkalaemia because of kidney disease, use of a potassium supplement, use of a potassium sparing diuretic or another reason.

*According to Xu et al's review[4]

Table. Practical advice for clinicians and other health professionals

Safety considerations when starting potassium-enriched salt	Advice for patients when recommending potassium-enriched salt
• Check kidney function if a recent test result is available.	• Potassium-enriched salt will help control your blood pressure and should add to the benefits of any mediations you are using.
• Consider kidney function screening if a patient has any risk factors for kidney disease.	• Use potassium-enriched salt as a one-for-one switch for regular salt.
• Don't recommend potassium-enriched salt if moderate or severe kidney disease is present (Stage 3 or above).	• Try to eat a healthy diet with lots of fresh fruits and vegetables.
• Screen for contraindicated medications –potassium supplements or potassium-sparing diuretics. NOTE – concurrent use of renin-angiotensin-aldosterone system (RAAS) inhibitors with potassium-enriched salt, in the absence of kidney disease, does not appear to increase the risk of hyperkalaemia.	• If you have mild kidney disease (Stage 1 or 2) you are very unlikely to get hyperkalaemia or any other side effects. But stop using potassium-enriched salt if you become seriously unwell and re-start only when you have recovered.

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PERSPECTIVES IN HYPERTENSION

Full-spectrum CBD oil: a promising ally against hypertension?

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Introduction

Hypertension is a chronic, multifactorial condition marked by persistently high blood pressure, influenced by genetic and lifestyle factors such as smoking, obesity, and inactivity. It often progresses silently but can cause serious damage to vital organs, contributing to cardiovascular and renal diseases. Its global prevalence has doubled from 2009 to 2019, now affecting around 1.2 billion adults (World Health Organization, 2019).

Treatment involves lifestyle changes and antihypertensive medications, but long-term effectiveness can be limited due to tolerance and the need for combination therapies. Although 82 natural compounds have been FDA-approved for hypertension, many patients fail to achieve full blood pressure control. Incomplete understanding of the disease mechanisms highlights the need for further research and innovative therapies (World Health Organization, 2019).

Cannabis-Derived Phytocannabinoids: Historical Use and Cardiovascular Therapeutic Potential

Phytocannabinoids from the Cannabis plant, used medicinally since ancient times in civilizations like China, Egypt, and Greece, are now being investigated for their therapeutic potential. (Rock & Parker, 2021)

Among over 100 phytocannabinoids, cannabidiol (CBD) and Δ9-tetrahydrocannabinol (Δ9-THC) are the most abundant and active. Δ9-THC is psychoactive, while CBD is non-psychoactive, well-tolerated, and predominant in Cannabis sativa. These compounds act via cannabinoid receptors CB1 and CB2, which are part of the endocannabinoid system (ECS), a homeostatic regulator involving endogenous ligands like anandamide (AEA) and 2-AG (Jarvis et al., 2017).

CBD, a lipophilic molecule, crosses biological barriers efficiently and exhibits strong antioxidant and anti-inflammatory properties. Studies have also demonstrated its vasodilatory and hypotensive effects, highlighting its potential for treating cardiovascular diseases (Stanley et al., 2015).

Early Evidence from Cardiovascular Studies

Research on the cardiovascular effects of Cannabis compounds began in the 1970s. Early studies showed that Δ9-THC and CBD could reduce blood pressure in animal models. These findings raised interest in the role of the endocannabinoid system in cardiovascular regulation (Adams et al., 1977). Anandamide, an endogenous cannabinoid, was found to induce complex cardiovascular responses and lower blood pressure and heart contractility in hypertensive rats, effects mediated by CB1 receptors (Malinowska et al., 2001; Varga et al., 1995). Anandamide also reduced blood pressure in angiotensin II-induced hypertension, suggesting ECS interaction with hormonal (Bátkai et al., 2004).

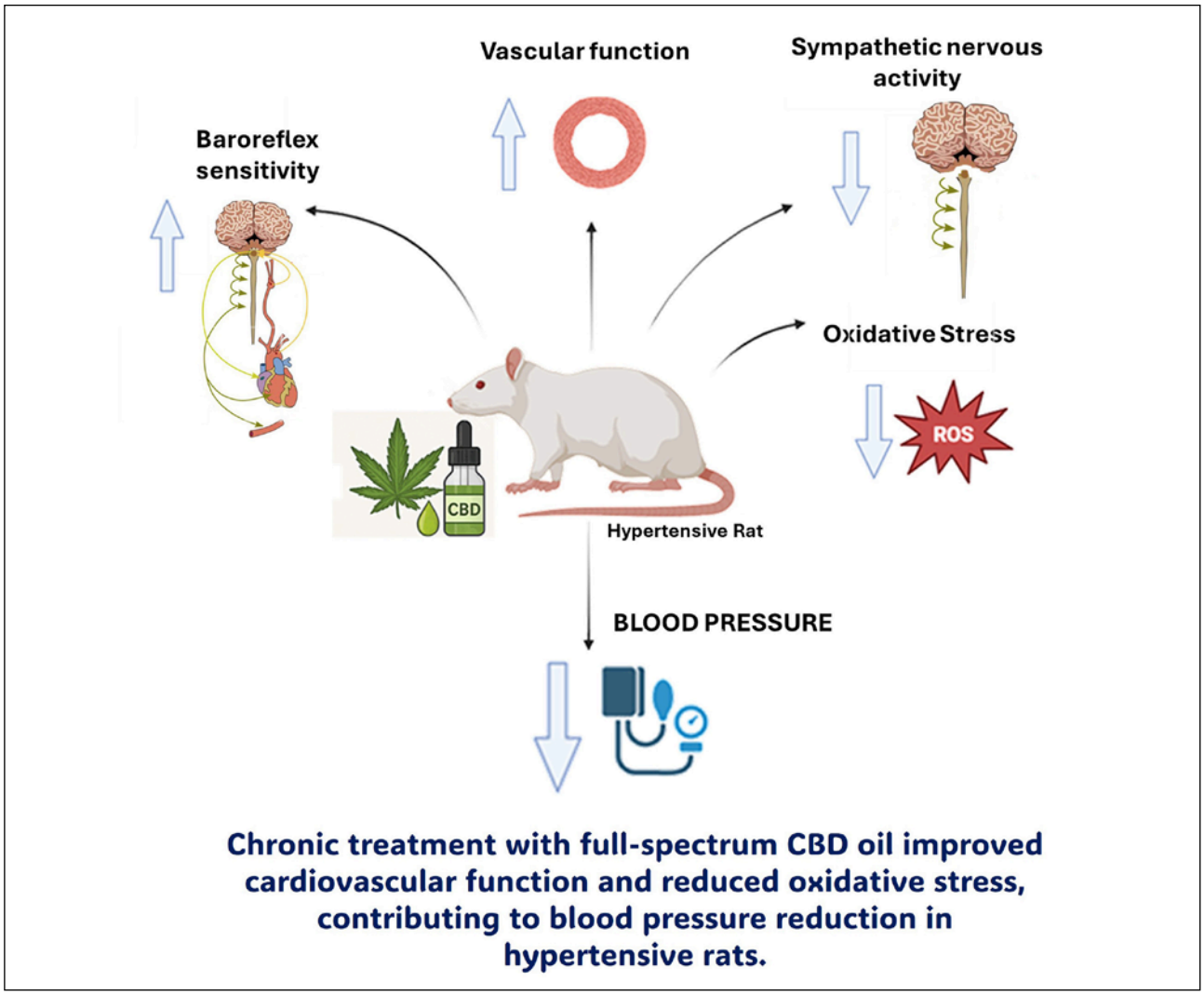
Fitocanabinoide such as Δ9-THC also lowers blood pressure, however its therapeutic use is limited by rapid tolerance. CBD, on the other hand, is non-psychoactive, well tolerated, and does not induce tolerance. In humans, a single 600 mg dose of CBD reduced both systolic and diastolic blood pressure and blunted the response to stress, supporting its potential as an antihypertensive agent (Jadoon et al., 2017).

Our Study: CBD in Renovascular Hypertension

In our study, we evaluated the chronic effects of full-spectrum CBD (a cannabidiol rich extract that also contains a variety of other naturally occurring compounds from the Cannabis sativa plant) in the 2-kidney, 1-clip (2K1C) model of renovascular hypertension, a condition caused by reduced blood flow to the kidneys and driven by high levels of angiotensin II vasoactivity hormone. Male Wistar rats underwent either 2K1C or SHAM surgery. Six weeks later, they received chronic oral treatment with cannabis oil containing CBD (20 mg/kg, administered every 12 hours for 14 days by intragastric gavage). A combination of in vivo, in vitro, and ex vivo techniques was used to assess cardiovascular outcomes.

The results were promising. chronic full-spectrum CBD oil treatment significantly reduced blood pressure, improved vascular function, and decreased oxidative stress in the arterial wall, factors strongly linked to hypertension progression. Furthermore, CBD enhances baroreflex sensitivity, a brain-controlled mechanism that helps the heart and blood vessels respond to changes in blood pressure, and reduces sympathetic nervous system overactivity, which is commonly elevated in hypertensive states (Flôr et al., 2024).

These findings suggest that full-spectrum CBD oil possesses multi-target antihypertensive properties, contributing to blood pressure reduction through mechanisms involving improved autonomic regulation, vascular tone, and oxidative balance. Although further clinical investigations are needed to confirm these effects in humans, our results support the therapeutic potential of full spectrum CBD oil in hypertension management, particularly in cases resistant to conventional treatment.



Chronic treatment with full-spectrum CBD oil improved cardiovascular function and reduced oxidative stress, contributing to blood pressure reduction in hypertensive rats.

Importantly, our study was made possible through collaboration with ABRACE, a nonprofit association that produces cannabis oil at low cost, thereby ensuring accessibility for the Brazilian population. This partnership underscores the vital role of community-based organizations in advancing scientific research and promoting equitable access to emerging therapies.

By bridging scientific innovation with social commitment, this research highlights CBD's therapeutic promise and advocates for broader public and governmental engagement in the discussion around medicinal Cannabis. Such efforts are essential to expand access and improve outcomes for the millions of individuals affected by hypertension in Brazil and globally.

Final remarks

Chronic full-spectrum CBD oil treatment demonstrates significant antihypertensive effects by enhancing baroreflex sensitivity, improving vascular function, reducing sympathetic nervous system activity, and mitigating arterial oxidative stress. These findings position CBD as a promising candidate for the treatment of renovascular hypertension and its associated cardiovascular complications.

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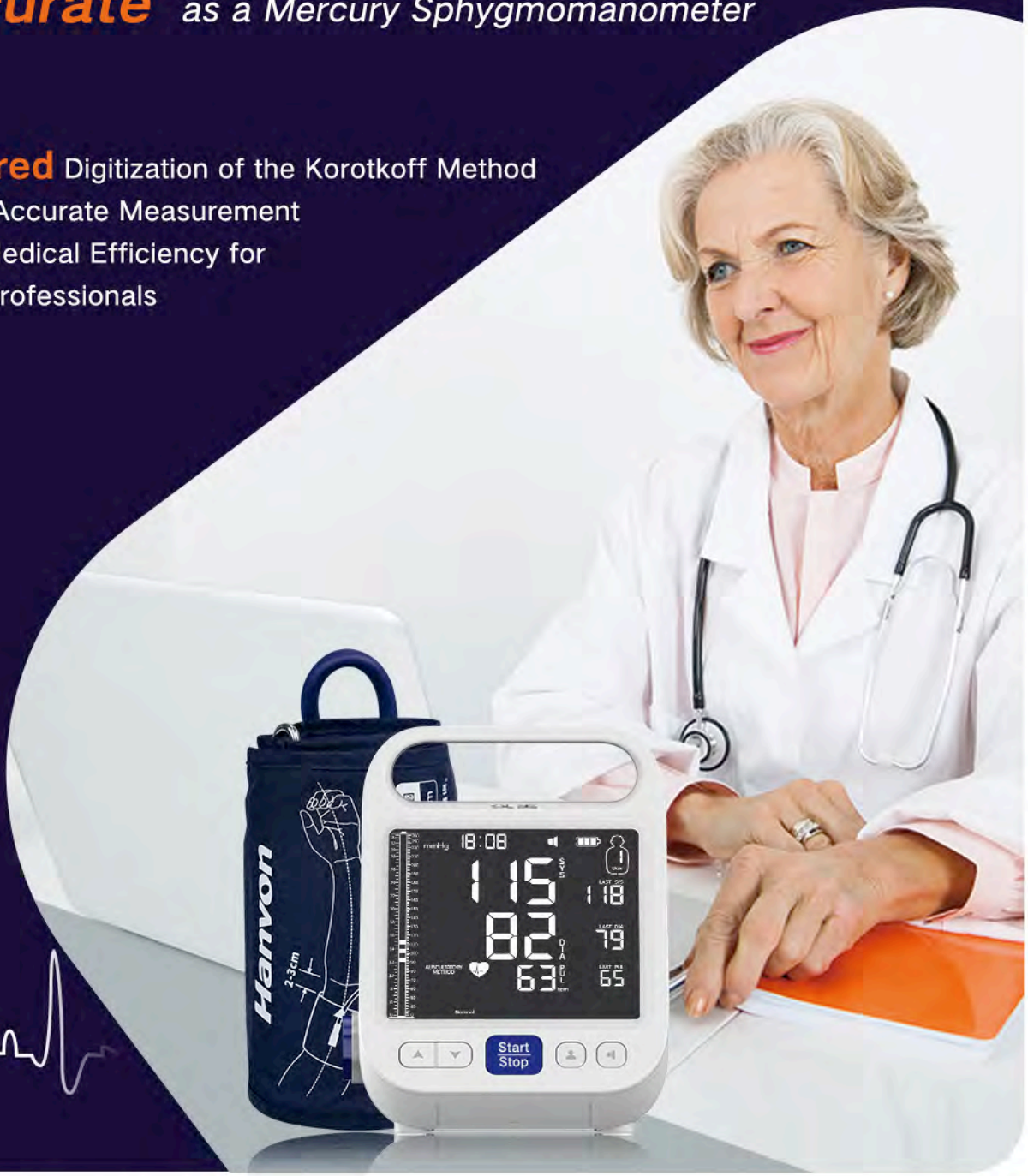

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ADHERENCE IN HYPERTENSION

PART 1: WORLD ADHERENCE DAY – THE CAMPAIGN

Adherence strategies in arterial hypertension: The ISH call to action

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Poor adherence to antihypertensive therapy remains one of the major barriers to achieving optimal blood pressure (BP) control globally. The ISH and other like-minded medical, scientific and patient societies, launched World Adherence Day in March 2025 to raise awareness, promote effective strategies, and engage multidisciplinary teams in tackling non-adherence as a major global health issue. This initiative, rooted in the ISH Cartagena Declaration,[19] seeks to catalyze a shift from awareness to action – through patient empowerment, digital innovation, and community-based care models. This article reviews the cornerstones of an adherence strategy in hypertension, emphasizing the role of task-shifting, health worker engagement, and digital monitoring to improve health outcomes and reduce cardiovascular risk.

1. Introduction: The Adherence Gap in Hypertension

Hypertension is the leading modifiable risk factor for cardiovascular morbidity and mortality worldwide. Despite the availability of effective and affordable pharmacological treatments, global control rates remain below 25% – largely due to suboptimal adherence to therapy.[1,2] Studies show that nearly 50% of patients discontinue antihypertensive medication within one year of initiation, driven by factors such as lack of awareness, side effects, complex regimens, and limited follow-up.[3,4] In this context, the launch of World Adherence Day represents a milestone. It positions adherence as a critical pillar of global cardiovascular prevention – emphasizing that innovation in drug discovery must be matched by innovation in patient engagement and care delivery models. The initiative recognizes that adherence is not merely a patient behavior but an outcome, influenced by health literacy, social support, and access to consistent care.[5] The Cartagena Declaration, announced at the ISH 2024 Congress, reaffirmed this vision by calling adherence a global priority to prevent premature cardiovascular deaths.[19]

2. The Cartagena Declaration: A Global Call to Action

The ISH Cartagena Declaration,[19] issued during the ISH's 2024 Scientific Meeting in Colombia, recognized the global challenge of improving adherence and transformed it into a unified international agenda and call to action to enhance therapeutic adherence in the treatment of hypertension worldwide. It called for a renewed commitment to strengthen adherence as a central determinant of blood pressure control, declaring March 27th, 2025, as the first World Adherence Day.

The joint launch of World Adherence Day aims to promote a culture of adherence through global advocacy and evidence-based implementation. Our society emphasized adherence as a "fourth cornerstone" of hypertension management – complementing accurate measurement, risk-based stratification, and guideline-directed treatment. The Cartagena Declaration[19] framed this initiative as a unified call to action, urging collaboration between health professionals, researchers, policymakers, and patients to improve adherence at every level of care. By aligning these efforts with Sustainable Development Goal (SDG)[3,4,5] reducing premature mortality from noncommunicable diseases – the initiative transforms adherence from a clinical challenge into a global health priority.

3. Adherence Strategies: Multi-Dimensional and Patient-Centered

Adherence in hypertension is a complex behavioral and structural phenomenon. Effective strategies operate at multiple levels.

3.1 Patient-Level Interventions

Educational programs that enhance disease understanding and self-efficacy are fundamental. Evidence demonstrates that simplified regimens – such as fixed-dose combinations – significantly increase adherence rates.[6] Behavioral approaches, including motivational interviewing and feedback-based coaching, foster self-monitoring and accountability. Mobile health technologies, such as SMS reminders and app-based medication trackers, have shown up to 20–25% improvement in adherence.[7,8]

3.2 Health System-Level Interventions

Health system redesign is essential to sustain adherence. Task-shifting and task-sharing – delegating routine functions from physicians to trained nurses, pharmacists, and community health workers (CHWs) – have demonstrated strong impact on adherence and BP control, especially in low- and middle-income countries.[9-11] In Brazil, Peru, and Mexico, CHW-led interventions improved adherence and reduced systolic BP by 10–15 mmHg. Supervision and integration of these workers into multidisciplinary teams are key to maintaining quality and consistency of care.

3.3 Community and Policy-Level Interventions

Community engagement and public awareness campaigns can modify social norms around medication-taking and lifestyle changes. Policies that ensure the availability of low-cost medications, adherence counseling, and continuous care follow-up are essential to sustain these gains.[12] In this sense, World Adherence Day and the ISH Cartagena Declaration together act as catalysts for advocacy – stimulating government accountability and investment in community-based solutions.[19]

4. Task-Shifting and the Role of Health Workers

Task-shifting and task-sharing have emerged as pivotal strategies to close the adherence gap in chronic diseases, including hypertension. The delegation of responsibilities from physicians to CHWs enables more frequent contact, improved patient education, and timely detection of non-adherence or side effects. The WHO recognizes this model as a sustainable response to workforce shortages and as a mechanism to extend the reach of primary care.[13] In Latin America, programs integrating CHWs have reported adherence improvements of 20–30%, with significant gains in BP control and reductions in hospitalizations.[9,10] In sub-Saharan Africa, CHW-based models reduced healthcare costs by up to 40%, primarily through prevention of avoidable complications and hospital admissions.[14–16] Training programs for CHWs should emphasize patient communication, home BP monitoring, early detection of treatment side effects, and coordination with physicians for therapy adjustments.

5. Digital Health and Innovation for Adherence

Digital health solutions enhance the reach and precision of adherence interventions. Smartphone applications and wearable devices allow remote BP tracking, medication reminders, and feedback loops between patients and healthcare teams. Artificial intelligence–driven analytics can identify adherence patterns and trigger tailored interventions.[17,18] Integrating these tools with CHW outreach maximizes impact – combining human empathy with technological precision.

6. Perspectives and Future Directions

The ISH Cartagena Declaration and World Adherence Day together represent a turning point in global hypertension management. For hypertension, adherence must be viewed not only

Table 1. Multilevel Strategies to Improve Adherence in Arterial Hypertension

Level	Strategy	Key Components	Evidence/Impact
Patient	Education & Simplification	Fixed-dose combinations, tailored counseling, reminders	20–30% improvement in adherence [6,7]
Health Worker (CHW/Nurse)	Task-shifting and follow-up	Training in communication, BP monitoring, supervision	10–15 mmHg BP reduction; cost savings up to 40% [10,14]
System	Integration & Team-based care	Multidisciplinary teams, clinical protocols, performance indicators	Sustained control rates in primary care [11]
Technology	Digital Adherence Tools	mHealth apps, wearables, AI-based analytics	Real-time feedback; scalable population impact [17,18]
Community/Policy	Awareness & Access	Medication affordability, adherence campaigns, supportive environments	Strengthened public engagement [12]

as a treatment issue but as an indicator of system performance and patient trust. Strengthening adherence requires a paradigm shift: from acute care to continuous engagement, from physician-centric to team-based care, and from passive monitoring to proactive empowerment. Scaling up CHW-led models, leveraging digital ecosystems, and embedding adherence metrics in national quality frameworks will be essential to sustain progress and realize the vision outlined in Cartagena.

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ADHERENCE IN HYPERTENSION

PART 1: WORLD ADHERENCE DAY – THE CAMPAIGN

Improving medication adherence and hypertension control: the essence of a global movement

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There are some simple facts about hypertension that bear repeating. Hypertension remains the leading risk factor for non-communicable disease mortality, responsible for 11 million deaths in 2021.[1] Treatment is affordable, cost-effective, and can be integrated into primary care with relative simplicity. Finally, less than half of adults with hypertension globally are receiving treatment, and fewer than 20% of people with hypertension have their condition under control.[2] These simple and seemingly incongruous facts reveal a complex reality; one where the policies and systems needed to implement hypertension care are lacking, and where barriers to initiating and sustaining treatment pose significant challenges to patients.

Failure to initiate or sustain pharmacological treatment, known as medication non-adherence, is common. Although rates vary across studies and settings, the proportion of people not adhering to antihypertensive medication in the first year after starting treatment often ranges from 50-80%.[3,4] It is also one of the major drivers of the high rates of uncontrolled hypertension observed globally. Of the approximately 630 million people treated for hypertension worldwide, only 320 million have their condition under control. As of 2024, 99 countries have control rates below 20%. In addition to significant mortality and morbidity, uncontrolled hypertension causes massive expense due to the costs of managing myocardial infarction and stroke, and resulting productivity losses. These losses are greatest in low- and middle-income countries, where most people with hypertension live and where hypertension control rates are often lower.[2]

The question, therefore, is clear; how do we intervene to increase medication adherence in people with hypertension? We need to act on multiple fronts and with tailored interventions. Adherence may seem like the simple matter of helping individual patients remember to take their pills, and we are fortunate to have several evidence-based approaches in our toolbox to help achieve this. Patient education and motivation

interventions, medication reminders and clinical pharmacist consultations for example have been shown to improve adherence in several trials.[5] However, we also need to ensure that our health policies and systems make these interventions feasible, and do not present additional roadblocks to medication adherence. Hypertension medications must be affordable and available to the entire population. Treatment protocols should appropriately address medication adherence, and primary care teams must be trained, equipped and ready to implement these protocols in their practice. Policies to improve health literacy and public awareness of the risks of hypertension and non-adherence should be pursued.[6]

As a global advocacy organization representing over 200 scientific and advocacy societies worldwide, World Heart Federation (WHF) is working to promote such policies and awareness. We recognize that these interventions must be driven at national level and be context appropriate. But we also recognize such national action can be inspired and shaped by the power of global campaigns. Improved hypertension detection, treatment and control rates were central to WHF's advocacy at the recent UN High Level Meeting on Non-Communicable Diseases. The resulting draft UN Declaration contains a target of 150 million more people having their hypertension under control by 2030. Although less ambitious than the 500 million target advocated by WHF, this sets countries with a clear goal towards which they now must work.[7] Policies to improve adherence to hypertension medications must naturally be a part of this, and WHF will work to support implementation of such policies at national level. WHF's Hypertension Roadmap provides a useful guide for this work, and improving medication adherence is one of the priority solutions it calls on countries to implement. Specific policy approaches presented in the Roadmap include steps to reduce patient out-of-pocket costs for medication, improve care coordination and patient-centredness, and reduce the burden of renewing and refilling prescriptions.[6]

The use of single-pill combination therapies (SPCs) has also proven effective in improving medication adherence. Leading hypertension treatment guidelines now give preference to these medications and several combination therapies are included in the WHO Essential Medicines List.[6] However, barriers to implementation of SPCs, including complex regulatory pathways and challenges to procurement, persist. WHF's recent Roadmap on SPCs again presents several policy approaches to overcoming these barriers that can be implemented at national level.[8] The Pan American Health Organization's HEARTS in the Americas programme provides a useful case study. SPCs for hypertension treatment have been integrated into the programme's standard treatment protocols, and a centralized pooled procurement mechanism ensures the availability of affordable SPCs in several countries in Latin America.[8,9]

Although advocacy and technical guidance are key to policy change, a major shift in adherence rates to hypertension treatment will also require the momentum and impetus of a global movement. Recently, WHF initiated World Adherence Day to unite civil society, healthcare professionals and other actors behind this cause every year on 25th March.[10] Thanks to a wealth of educational and communication resources and the engagement of partners, including the International Society of Hypertension, events were organized internationally to educate health professionals and patients. News stories and social media raising awareness about the importance of adherence reached over half a million people worldwide. Going forward, World Adherence Day offers an excellent opportunity to build momentum and harness further action on adherence at national level. Ultimately, it should be the engine that drives the machine of improved awareness and policy.

While the need to act on hypertension may seem self-evident, and the challenge of adherence straightforward, the solutions are complex and require a thoughtful and holistic response. This response relies on the energy of an array of stakeholders, working nationally and internationally to highlight the significant health gains to be made by tackling uncontrolled hypertension and non-adherence. Global advocacy, awareness campaigns and policy guidance are an important part of this, and WHF is committed to this work. We count on your support.

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ADHERENCE IN HYPERTENSION

PART 2: ADHERENCE – THE SCIENTIFIC EVIDENCE

Through the CAT's eye: seeing non-adherence clearly

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Non-adherence: the Oldest Problem in Medicine

"Keep a watch on the faults of the patients, which often make them lie about the taking of things prescribed," wrote Hippocrates. Two and a half millennia later, the sentiment remains painfully relevant. Despite the availability of safe, effective antihypertensive drugs, **non-adherence persists in 30–50% of patients**, contributing to a **twofold higher cardiovascular risk** and a **fourfold increase in stroke**.

As C. Everett Koop, the former U.S. Surgeon General, put it bluntly: "Drugs don't work in patients who don't take them."

Why Is Adherence Still So Poor?

We clinicians are trained to diagnose and prescribe – but not necessarily to ask. In a multinational survey of more than 3,000 primary care professionals, only half routinely asked about adherence.[1] Even when they did, responses were often unreliable. Some patients genuinely believe they take their medication correctly; others may feel embarrassed to admit lapses.

Traditional approaches – pill counts, refill checks, or self-reports – are **imprecise and often misleading**. The result? Escalation of therapy, unnecessary investigations, and mutual frustration.

The challenge is simple to describe but hard to solve: **how do we know whether a patient is truly taking their medicine?**

A New Lens: The Chemical Adherence Test (CAT)

In 2014, we developed a new way to see adherence objectively – **the Chemical Adherence Test (CAT)**. This laboratory test uses **liquid chromatography–tandem mass spectrometry (LC-MS/MS)** to detect traces of prescribed cardiovascular drugs in a simple spot urine sample.

CAT can currently detect around 60 commonly used medications with high sensitivity and specificity. It is relatively inexpensive (about £45

per sample), robust, and practical – samples can even be mailed to the testing centre. Today, the **National Centre for Adherence Testing (NCAT)** in Leicester, UK, receives specimens from more than 50 centres across the UK and Europe.

When and How to Test

Adherence testing is especially valuable for:

- **Patients with apparent resistant hypertension:** non-adherence increases in a near-linear manner with the number of prescribed medications and reaches around 30–40% in those on three drugs.
- **Unexpected treatment failure**
- **Within the first here months of treatment change**
- **Younger patients** as they are more likely to be non- adherent
- **Clinical trials,** where verifying medication exposure strengthens validity

Testing is straightforward. We obtain verbal consent, explaining that the test is now part of routine assessment for patients on multiple drugs. The urine sample is collected on the same day, and results are typically available within days.

Discussing the Results

This is the crucial moment- and the one that often worries clinicians, especially as we are not formally trained in this area. But with the right framing, CAT results can enhance trust rather than undermine it.

A simple opening line that we use and which has worked well is: "Your urine test did not detect some of your medications. It's difficult for all of us to remember pills every day – does that happen with you?"

Such an approach invites honesty rather than defensiveness. The next step is to explore barriers and provide tailored interventions:

- **Forgetfulness or disrupted routines:** Use dosette boxes, reminder alarms, and involve family members or partners.
- **Side effects or complex regimens:** Consider switching medications or using fixed-dose combination pills, which are effective but still underused.
- **Lack of understanding:** Often, the term hypertension is misinterpreted as "tension" or stress, and patients are unaware that lifelong treatment may be necessary.
- **Cost or access issues:** Identify and address financial or logistical barriers.

Understanding Behaviour: The COM-B Model

Adherence is not just a pharmacological issue; it's a behavioural one. We use the **COM-B model of behaviour change**, proposed by Michie et al.[6]

- **Capability** – Does the patient have the knowledge and skills to adhere?
- **Opportunity** – Are medications accessible and affordable?
- **Motivation** – Does the patient see a clear reason to continue long-term therapy?

By addressing these dimensions, clinicians move from blame to collaboration – helping patients succeed.

What the Evidence Shows[2-5]

Real-world observational data demonstrate CAT's power to clarify uncertainty:

- Non-adherence was identified in approximately 25% of referred patients.
- Guided interventions improved clinic systolic blood pressure by about 20 mmHg and avoided unnecessary drug escalation.
- CAT pinpointed which agents were most often omitted, enabling targeted counselling.
- High rates of non-adherence were seen among patients attending TIA, renal, diabetes, and heart failure clinics.
- A single CAT measurement predicted long-term adverse outcomes.
- The test is cost-effective, saving approximately £500 per patient with apparent resistant hypertension.

Beyond routine care, CAT has strengthened major clinical trials – **PATHWAY-2**, **ORBITA**, and **RADIANCE-HTN** – by objectively verifying that participants were truly taking their assigned medications.

Limitations and Lessons Learned

No test is perfect, and CAT has its limitations:

- **Trust:** Some worry that objective testing could erode the doctor–patient relationship. In practice, most patients appreciate the clarity and respond positively when the discussion is handled with empathy.
- **Pharmacokinetics:** Drug half-life and timing of the last dose can affect detection, but studies show minimal impact overall.
- **Accessibility:** CAT currently requires LC-MS/MS equipment and trained personnel. A useful guide for those looking to t up the method is our paper by Lane D, et al.[7] Efforts are under way to automate analysis and reduce costs tenfold.
- **Evidence gap:** While observational data are strong, randomised trials proving that CAT improves adherence and outcomes remain limited.

The Way Forward: Making Adherence Testing Routine

Hypertension care should include adherence assessment just as naturally as we measure blood pressure, kidney function, or lipids. Integrating CAT or other objective adherence checks can transform care pathways, guiding rational therapy and avoiding unnecessary polypharmacy.

Other priorities include greater clinician awareness and training and embedding adherence checks into digital health systems and remote monitoring

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Take-Home Message

Treating hypertension without checking adherence is like treating anaemia without measuring haemoglobin. Let's make adherence conversations as routine and compassionate as any other part of care, and remember to:

Ask – Check – Chat

- Ask about adherence
- Check with pharmacy records or CAT
- Chat about barriers, without judgement

Through the CAT's eye, we can finally see the unseen – and give our patients the best chance to benefit from the therapies we prescribe.

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ADHERENCE IN HYPERTENSION

PART 3: HOW TO ACHIEVE ADHERENCE

Is my patient ready for antihypertensive medication?

A paradigm shift in medication implementation and adherence

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The Old Assumptions

We physicians were trained to prescribe, and to believe that patients would simply follow our instructions. The old paternalistic model of medicine assumed compliance as a given: the physician prescribed, and the patient obeyed. Reality tells a different story. In hypertension and other chronic diseases, between 20% and 50% of patients do not take their medications as prescribed.[1] What's worse, most physicians don't even suspect it.[2] Both doctor and patient believe that prevention is in place, when in fact, it's not. It's the perfect storm for a silent disaster.

When non-adherence is finally discovered, most of us are not prepared to address it.[2] We may try persuasion through fear, blame the patient's "lack of discipline," or shrug and say, "it's their choice." But behavioral science shows that none of these work.[3] It's time to move from prescription as reflex to prescription as partnership.

Borrowing Lessons from Other Fields

Our colleagues in bariatric surgery won't operate unless a multidisciplinary team (psychiatrists, nutritionists, social workers) confirms that the patient is psychologically and socially ready.[4]

Tobacco cessation therapy also follows a clear logic: pharmacological intervention begins not when the patient wants to quit, but when they are ready to quit.[5]

> ***"Perhaps the next revolution in hypertension care won't come from a new drug, but from learning to ask: Is my patient ready?"***

So why should hypertension be different? Before prescribing, shouldn't we ask: Is my patient ready for this intervention? And if not – how can I help them get there?

The Science of Readiness: Behavioral Frameworks

Behavioral science offers several frameworks for understanding and improving adherence (**Table 1**).[3] No single model fits all patients, but each helps us see the main drivers of adherence and how to intervene.

Social Cognitive Theory (SCT)[6] emphasizes self-efficacy, the patient's belief in their ability to manage their disease. Without it, adherence rarely happens. The COM-B model identifies three core components of behavior: Capability, Opportunity, and Motivation. If one is missing, adherence will fail. The Health Belief Model focuses on perceived risk, benefits, and barriers, showing that patients act when they believe the benefits outweigh the costs. The Transtheoretical Model (TTM) reminds us that change is a process, not an event – patients move through stages from precontemplation to action and maintenance. Self-Determination Theory (SDT) adds an essential dimension:

autonomy. When motivation comes from within, because the patient feels in control, adherence becomes sustainable.

These frameworks teach us that adherence is not binary; it evolves through stages and depends on dynamic interactions between personal capability, motivation, and the environment.

From Initiation to Maintenance

Adherence unfolds in stages: initiation, maintenance, and discontinuation, each with its own vulnerabilities.

Initiation: Readiness and self-efficacy are essential. If a patient is not ready, starting medication too early can backfire.

Maintenance: Social and environmental factors, family support, stigma, and cultural norms strongly influence persistence. The support of an integrative health system that retains the participants is highly important.

Discontinuation: Motivation wanes over time. Addressing doubts and side effects early can prevent dropout.

Across all stages, motivation and capability form the core. Social networks, health literacy, and system support build the scaffolding that sustains adherence.

The Socioeconomic Dimension

Beyond psychology, social determinants of health (education, income, housing, food security) shape adherence profoundly.[7,8] For many patients, the daily decision is not whether to take a pill, but whether to afford one. Education and income affect understanding of disease, perceived control, and the ability to prioritize treatment. Patients facing social vulnerability such us migrants, displaced persons, or those in crisis, may experience barriers that no amount of counseling can fix without structural support.

Mental health adds another invisible layer. Depression, anxiety, or cognitive decline may appear as "noncompliance" but in fact reflect diminished motivation or memory. Addressing mental health may be the first step toward adherence.

Family and community values are equally critical. When aligned around prevention and wellness, they amplify adherence; when stigma or fatalism dominate, they erode it.

Health Systems and Scientific Societies: The Bigger Picture

Adherence is not a private issue between patient and doctor – it's a systemic challenge.

Health systems can foster or frustrate adherence through access, affordability, and continuity of care. Simplified regimens, like single-pill combinations, have shown clear benefits. Lowering medication costs, ensuring consistent supply chains, and engaging community health workers are proven strategies.

Scientific and professional societies also play a crucial role. The World Heart Federation roadmap, the International Society of Hypertension (ISH) initiatives, and the ISH Cartagena Declaration all emphasize adherence as a cornerstone of global cardiovascular prevention. The Heart program from the Pan-American Health Organization (PAHO) is an extraordinary example of how scientific and public health organizations can develop implementation programs to decrease the gap in blood pressure control.[9]

Training healthcare professionals to recognize behavioral and social barriers is essential. Public health authorities and scientific organizations must collaborate to develop national programs that support clinicians and empower patients, going beyond reminders and apps to build true self-efficacy and readiness.

Practical Recommendations for Clinicians

Before writing a prescription, start a conversation. Explore the patient's beliefs, fears, and motivation.

> ***"Empowering patients is not just ethical – it's efficient."***

Use one of the frameworks – SCT, COM-B, or SDT – to identify gaps in readiness. If a patient lacks capability or motivation, focus on empowerment before adding pills.

This preparatory phase naturally aligns with the lifestyle modification period recommended by hypertension guidelines. It transforms that window into an opportunity for psychological and behavioral preparation.

Table 1

Model	Focus	Key Mechanism	Evidence in Medication Adherence
Health Beief Model	Perceptions of risk and benefits	Perceived threat and barriers	Moderate
Social Cognitive Theory (SCT)	Learning, self-efficacy	Skill-building, reinforcement	Strong
Trans theorectical Model (TTM)	Readiness to change	Stage-matched strategies	Moderate–Strong
Theory of Planned Behavior	Intention & perceived control	Norms and attitudes	Moderate
Common-Sense Model (CSM)	Illness beliefs	Cognitive/emotional representation	Moderate
COM-B / Behavior Change Wheel	Capability, Opportunity, Motivation	Systems-level integration	High (modern, adaptable)
Self-Determination Theory (SDT)	Intrinsic motivation	Autonomy support	Strong (sustained behavior)

Also, remember to suspect non-adherence in any patient with uncontrolled blood pressure despite two medications. As highlighted by Gupta et al. in this issue of *Hypertension News*, chemical adherence testing (CAT) should become part of standard hypertension evaluation.

Where testing is unavailable, a structured behavioral assessment – based on readiness, motivation, and opportunity – can guide clinical reasoning. Data strongly indicate that, in most cases, non-adherence is more common than true resistant hypertension.

The New Prescription

Medication adherence is not a matter of willpower. It is a behavior, one influenced by beliefs, emotions, environment, and systems. Understanding these factors moves us from command to collaboration.

Perhaps the next great advance in hypertension management won't come from a new molecule, but from a new mindset, one that treats prescribing as the beginning of a shared journey, not the end of a consultation.

So before you reach for your pen or click "send to pharmacy," pause for a moment and ask yourself: Is my patient ready?

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ISH COMMITTEE, PARTNER AND AFFILIATED SOCIETY REPORTS

ISH global career journeys: transitioning to independence and the role of mentorship

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The International Society of Hypertension (ISH) Global Career Journeys video series was an initiative of the Mentorship and Training Committee (MTC), recorded by Dr. Mariane Bertagnolli, who served as a committee member from 2022 to 2024. The goal of this series was to provide a resource of personal narratives from ISH early-career researchers across diverse regions, sharing their experiences during the transition to independence and their reflections on how mentorship supported, or could have better supported, their journey. The series also aimed to raise awareness among ISH members about significant cultural differences and inequities in academia, the various barriers faced by early-career researchers, and the vital role of international societies such as ISH, as sources of confidence and support throughout this process.

Through interviews recorded during the 2024 ISH World Congress in Cartagena, Colombia, featuring scientists from Mozambique, the UK, Greece, Chile, Australia, and Brazil, the series published on the ISH YouTube channel (https://www.youtube.com/@ISHBP) explored the transition from MD/PhD training to independent research careers. It highlighted the barriers and facilitators encountered along the way, and emphasized the critical role of mentorship in shaping these journeys. This report seeks to synthesize those narratives, focusing on key challenges, facilitators, and the impact of mentorship across different global contexts.

Transitioning from MD/PhD to Independent Scientist

The transition from MD/PhD training to becoming an independent scientist varies significantly across global contexts, as illustrated by the experiences of six researchers interviewed in 2024. In resource-limited settings like Mozambique, Brazil, and Chile, Drs. Neusa Jessen, Michele Mazzaron de Castro, and Patricio Araos Salas faced structural challenges such as limited funding, infrastructure, and institutional support. Their paths were shaped by the need to balance clinical or teaching duties with research ambitions, and both emphasized the critical role of international mentorship and collaboration in overcoming local constraints. Similarly, Dr. Konstantinos Kyriakoulis in Greece encountered bureaucratic and financial hurdles despite strong academic preparation, relying on global networks to guide and advance his career.

In contrast, researchers in more structured environments like the UK and Australia, represented by Drs. Karla Neves and Dean Picone, benefited from clear postdoctoral pathways, national funding schemes, and supportive institutional cultures.

Their transitions were facilitated by strategic planning and access to mentorship, although they still faced pressures related to publishing and grant acquisition. Dr. de Castro's experience in Brazil highlighted a hybrid reality: institutional instability and funding limitations were offset by resilience and international engagement. Across all cases, mentorship and global networking emerged as common facilitators, while disparities in infrastructure, funding, and systemic support defined the challenges unique to each region.

Transition Barriers and Facilitators

The recordings reveal that while all participants faced barriers in their transition to independent research careers, the nature and intensity of these challenges varied significantly by region. In countries like Mozambique, Greece, Chile, and Brazil, funding limitations were a major obstacle, often added by institutional instability and frequent policy shifts. These conditions created uncertainty and hindered long-term planning, making it difficult for early-career researchers to secure stable research positions and structure or to launch independent projects. Additionally, a lack of local mentorship in these regions, particularly where research or academic cultures are still developing, left many scientists without the guidance needed to navigate complex academic systems. In contrast, researchers in the UK and Australia experienced more structured and supportive environments. Institutional frameworks, clear career pathways, and access to national funding schemes facilitated smoother transitions. However, even in these contexts, the pressure to publish and secure competitive grants remained a significant stressor.

Across all regions, international collaboration emerged as a vital facilitator, providing access to mentorship, resources, and visibility. Personal resilience, adaptability, and strategic networking were consistently highlighted as essential traits for overcoming systemic barriers. Regional differences also flag the uneven trajectories to independence in global research environments and the critical role of international networks in bridging gaps for scientists, particularly in under-resourced settings.

Figure 1

The Role of Mentorship

Mentorship played a pivotal role in shaping the career trajectories of all the researchers interviewed, serving not only as a source of strategic guidance but also as emotional and professional support. Generally, participants agreed that mentors helped clarify research goals, navigate complex funding landscapes, and build visibility through international networks. This support was especially crucial during moments of uncertainty or institutional instability, offering reassurance and direction. For example, Dr. Neusa Jessen from Mozambique highlighted how mentorship helped her overcome professional isolation and connect with global collaborators, while Dr. Karla Neves in the UK benefited from mentors who helped her align with institutional expectations and refine her research focus.

Differences in Mentorship Culture

Our recordings showed that mentorship cultures varied widely across regions, reflecting broader disparities in academic infrastructure. In the UK and Australia, mentorship was formalized through institutional programs, regular evaluations, and integration into career development frameworks. These systems provided consistent guidance and accountability. In contrast, Mozambique and Brazil relied heavily on informal mentorship, often facilitated through international networks due to a lack of mentorship among senior researchers locally. Greece and Chile occupied a middle ground, where mentorship was valued but lacked consistent structure, prompting many researchers to seek support through global initiatives like ISH or professional societies.

Across all interviews, the concept and role of mentorship varied significantly across academic cultures. In the UK and Australia, trainees and early-career investigators are often supported by formal mentorship programs that operate independently of their research teams or supervisors. In contrast, in Mozambique, Chile, Brazil, and Greece, mentorship is still closely tied to supervision, typically provided by clinical or research supervisors. These disparities reflect a broader lack of consensus on the definition and value of mentorship globally, highlighting the need for clearer frameworks and culturally responsive approaches in international mentorship initiatives.

Common Supportive Aspects of Mentorship

Despite these cultural differences, the core functions of mentorship were generally appreciated. Across all narratives, mentors played a crucial role in career guidance, helping mentees set strategic goals and navigate complex academic systems. They also supported skill development in areas such as grant writing and publishing, while fostering professional networks and providing emotional encouragement. Mentors were often described as role models who inspired confidence and ambition, highlighting the multiple nature of effective mentorship.

The interviews also underscored several key elements that make mentorship impactful in shaping global research careers. Accessibility and responsiveness were vital, ensuring mentees felt supported and guided. Strategic insight into the research landscape helped mentees make knowledgeable decisions, while empowerment through encouragement of independence and leadership fostered long-term growth. Importantly, mentors who facilitated global networking opened doors to international collaborations and resources. Programs like the ISH MTC were especially valuable in bridging gaps for researchers in low-resource settings, offering structured support and enhancing outreach on the global stage.

Conclusion

The ISH Global Career Journeys video series offered a rich exploration of the diverse pathways researchers navigate in their transition to independence. By capturing voices from across continents, the series highlighted both shared challenges such as the pressure to publish and secure funding, and region-specific barriers like institutional instability and limited mentorship access. These insights emphasise the global importance of mentorship, international collaboration, and personal resilience in overcoming systemic hurdles and building sustainable research careers.

Importantly, the series provides valuable guidance for shaping future international mentorship programs and ISH initiatives. By identifying the structural disparities and showcasing the transformative impact of global networks and

mentorship, it offers a roadmap for targeted support as described in Figure 1. The experiences shared by participants reinforce the need for inclusive, accessible, and strategically designed mentorship frameworks, particularly for early-career researchers in low-resource settings where global organizations like ISH can play a pivotal role in fostering equity, outreach, and long-term success for emerging scientists worldwide.

Acknowledgements

I would first like to thank all ISH members who participated in this initiative for their honest narratives and their willingness to contribute to the series and strengthen mentorship efforts within ISH: Drs. Neusa Jessen (Mozambique), Michele Mazzaron de Castro (Brazil), Patricio Araos Salas (Chile), Konstantinos Kyriakoulis (Greece), Karla Neves (The UK), and Dean Picone (Australia). A special thank you to the members of the MTC from the 2022–2024 and 2024–2026 mandates, especially the Chairs Drs. Francine Marques, Augusto Montezano, and Lebo Gafane-Matemane, who contributed to the conception of the video series. Another special thank you to the ISH communication and media advisors, Matt Chorley and Julia Calvino, for their support in recording and editing the videos during the 2024 ISH World Congress in Cartagena, Colombia. Finally, I thank ISH Executive Assistant Helen Horsfield and ISH President Prof. George Stergiou for their support in the publication and dissemination of this report.

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ISH COMMITTEE, PARTNER AND AFFILIATED SOCIETY REPORTS

Navigating career challenges for women in hypertension research

A REPORT FROM THE ISH CAPACITY BUILDING NETWORK

A recent ISH webinar brought together three leading women in hypertension research – Tammy Brady (USA), Azra Mahmud (Pakistan), and Joanne O'Donnell (Australia) – to discuss how they have navigated career challenges, and their advice for career progression.

In the excerpts from the webinar that follow – lightly adapted from the session – ISH members Tammy, Azra and Joanne reflect on the value of supportive colleagues and networks, the importance of saying yes to opportunities, and how a career path doesn't need to be linear.

The webinar, which took place in September, was moderated by Jennifer Cluett (USA) and Debora Colombari (Brazil) both pictured below.

ISH members can watch the full webinar on demand from within the ISH Members' Area.

Joanne O'Donnell

'Find the right people to work with'

"Working in science can be tough. From the outside it can look like constant success, but behind the scenes it can be exhausting, you never have enough time, and you feel guilty that you can't do everything at home as well as work. The only reason I have stayed in science is because I found supervisors who were kind, understood that life happens, and supported me with children in tow. My advice is: don't just choose a lab or a project. Choose the people. A supportive supervisor can matter more than the research topic. And the right team makes a massive difference."

'Your career does not have to be linear'

"My background is in a completely different field, working on cell death and inflammation - I only transitioned later into hypertension. I've also had three children during my career, and taken a year of maternity leave with each, and returned to work in a different job every time. At times it has been chaos.

"So my career has been anything but linear. Success in academia is not a straight upward curve - there are dips, pauses, relaunches. But that's not failure - that's reality."

Joanne O"Donnell (Australia) is an NHMRC Research Fellow, Group Leader and co-deputy lab head in the Hypertension Research Laboratory at Monash University, Australia.

Tammy Brady

'Say yes to opportunities'

"My career is an example of the importance of saying yes. For example, early in my career, a mentor asked if I could attend an FDA (US Food and Drug Administration) meeting as a pediatric voice, representing the American Society of Pediatric Nephrology. I wasn't sure at the time why they needed me there, but I said yes, and went to the meeting.

"I sat at the table, made sure to speak, and at the end someone pointed to me and said: 'We need you on our committee.' That moment changed my trajectory. I went on to co-chair that group - which oversees validation protocols for blood pressure devices - for ten years. And that role has opened countless doors since."

'Step forward before you feel ready'

"Confidence doesn't magically appear - sometimes you have to speak up or step forward before you feel ready. I tell my mentees: do you think Tom Brady walks into a game saying 'I hope I win'? No - he says, 'I'm going to win.' So even if you don't feel ready for something, you try to put yourself into the right mindset, and do it anyway.

And never be afraid to ask for what you want. If you don't ask, the answer is no. Even when the answer is no, people remember that you spoke up. And the next time an opportunity comes, your name comes to mind. So much of leadership and moving forward in your career is simply being willing to step forward when others hesitate."

Tammy Brady is Professor of Pediatrics and Epidemiology at the Johns Hopkins University School of Medicine, USA.

Azra Mahmud

'Build your own support network'

"Sometimes it can be hard to find environments that genuinely back women when pressures rise. So instead of waiting for perfect systems, I tell young researchers: build your own safety net. Find one or two people you trust completely - even if they're outside your institution - and let them be your sounding board. You don't need dozens of mentors. You just need one person who will tell you the truth. Don't be discouraged if the structure around you isn't built for you - build your own structure."

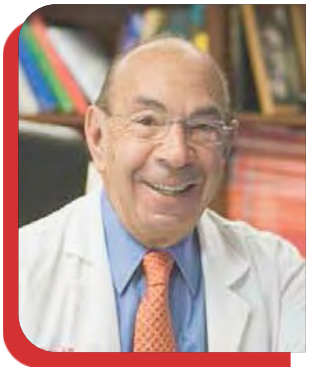
'Taking on challenges helps you grow'

"Like Tammy, I've said yes to many opportunities – maybe more than I should have over my career. And sometimes this stretches you thin. But every yes has widened my world. Saying yes to new opportunities led me from Ireland to Pakistan. Saying yes also got me into work around equity in healthcare, and improving access to healthcare in low-resource settings in Pakistan. This became a grassroots campaign. Saying yes to taking on new challenges doesn't mean you're always ready - but it means you're willing to grow, and the challenge will help you grow."

Azra Mahmud is Professor of Clinical Research at Shalamar Īnstitute of Health Sciences, Pakistan.

ISH COMMITTEE, PARTNER AND AFFILIATED SOCIETY REPORTS

The Inter-American Society of Hypertension (IASH). Yesterday and today



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Program-Chair, XX2nd Biennial Scientific Sessions, IASH, Guatemala City, Guatemala, January 15 – 17, 2026

MARIELA GIRONACCI

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Like the legendary Phoenix rising from the ashes, the Inter-American Society of Hypertension (IASH) has been reborn—stronger, brighter, and more determined than ever to champion the control of hypertension across the Americas. This renewal symbolizes not only the Society's resilience but also its unwavering commitment to lead the region in advancing research, elevating clinical practice, and shaping public health strategies. Just as the Phoenix transforms through fire to soar higher, the IASH will stand as a powerful champion for hypertension control, driving scientific discovery, advancing clinical excellence, and inspiring collaboration among nations, particularly throughout Latin America and the Caribbean basin. With renewed vision and vitality, the IASH has recommitted to becoming a guiding force, uniting professionals and communities in the fight against cardiovascular disease and inspiring a healthier future for generations to come.

The story of IASH began in August 1974, when under the venerable leadership of Juan Fasciolo, MD, Chair of the Department of Physiology, Mendoza, Argentina and Merlin F Bumpus, PhD, Chair of the Research Division Cleveland Clinic Foundation, a small but visionary group of scientists came together in Mendoza, Argentina, during the World Congress of Cardiology for the first Pan American Symposium on Vasoactive Peptides and Hypertension.[1] That meeting planted the seed of what would one day grow into a formal society dedicated to advancing hypertension research and care across the Americas. That vision became a reality with the incorporation of the Inter-American Society of Hypertension as a tax-exempt organization in the state of Ohio, USA in 1980. From the beginning, our Society has been about people – about creating opportunities to learn, connect, and inspire one another. Every biennial meeting was more than just a scientific gathering; it has been a place where young investigators found mentors, where collaborations began, and where ideas grew into lifelong commitments. Over 21 biennial meetings across North, Central, and South America, IASH helped establish regional and national societies and supported the training of many scientists in top laboratories in the USA and Canada.

In 2016, many of us came together in Orlando, FL, with a shared purpose: to imagine what IASH could become in the new millennium. Out of those conversations, we shaped a vision that still inspires us today: "The Americas will have the best blood pressure control and the lowest prevalence

IASH Executive Committee members define the mission and objectives of the Society in Orlando, FL 2019.

of cardiovascular disease in the world." We also defined our mission: to improve hypertension control and reduce the toll of cardiovascular disease by fostering communication, education, and research across our continent. We set clear priorities for ourselves: to help scientists and clinicians learn from one another, to challenge traditional models of hypertension management, to collaborate with other organizations working on cardiovascular and metabolic diseases, and to close the care gaps that leave too many people unprotected. That commitment is renewed today with the organization of the upcoming International Scientific Sessions of the IASH, to be held under the Chairmanship of Fernando Wyss, MD, in Guatemala City, Guatemala, on January 15-17, 2026 (registration and abstract submission available at www.iashonline.org).

Our journey has always been about more than meetings or milestones. It has been about us — a community of colleagues, friends, and partners working together to transform hypertension care across the Americas. From the beginning, our Society has been about people — about creating opportunities to learn, connect, and inspire one another. Every biennial meeting was more than just a scientific gathering; it was a place where young investigators found mentors, where collaborations began, and where ideas grew into lifelong commitments. In Guatemala, we will renew our commitment to collaborating with the International Society of Hypertension to implement new strategies for the effective management of high blood pressure and its cardio-renal metabolic consequences in the Caribbean Basin and Latin American countries, based on documented evidence of underutilized healthcare services due to discrimination based on sex, socioeconomic status, and ethnicity. To this end, our new partnership with the International Society of Hypertension Americas Regional Advisory Group (RAG) and the World Hypertension League, to be showcased at the Guatemala meeting, lays the foundation for achieving these goals.

We appreciate the opportunity to communicate with our colleagues through this *Hypertension News*letter and extend to all of you our cordial invitation to join us in Guatemala on January 15 -17, 2026.

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Opening Ceremony, 2018 IASH Scientific Sessions in Guayaquil, Ecuador.

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