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FROM THE EDITOR

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140/90 mm Hg is the target BP threshold for both diagnosis and treatment in the revised UK guidelines

IN THIS ISSUE

Dear ISH member,

The recently revised Hypertension guidelines in the UK (page 18) from the National Institute for Health and Care Excellence (NICE) differ from current American and European guidelines by retaining a target blood pressure (BP) threshold of 140/90 mm Hg (or 135/85 mm Hg for out-of-office recordings) for both diagnosis and treatment of high BP. This target is now equivalent for people with or without type-2 diabetes, providing a clear and consistent threshold.

People below 80 with stage-1-hypertension, however, are now offered treatment using a 10-year cardiovascular risk threshold of 10% instead of the previous 20%. The UK guidelines recognise the balance between benefit and harm when treating low-risk people with stage-1- hypertension and therefore give flexibility to patients and doctors in their choices, emphasising the importance of lifestyle changes. NICE continues to recommend starting with monotherapy, thereby excluding the results of the Pathway-1 trial (suggesting that BP control is attained faster with dual therapy), because the outcome in that trial was a surrogate marker. Finally, as before, drug treatment starts (step 1) with an ACE Inhibitor or an Angiotensin-II-receptor blocker (ARB) for younger patients or a Calcium channel blocker for those aged 55 and over. Beta-blockers (or alpha-blockers) come far down the drug list (step 4), and are recommended for patients with resistant hypertension and a blood potassium level above 4.5 mmol/L; spironolactone is recommended for those with lower potassium levels. In this issue of Hypertension News, Richard McManus and co-workers present a summary of the revised guidelines (page 18). NICE has kindly allowed us to republish two of their original charts (pages 20 & 21).

In this issue of the Newsletter, you will also find an elegant paper on the unresolved and controversial issue linking hypertension to cancer, written by Pavel Hamet and co-workers, which I strongly recommend you to read (page 14). The increased risk of cancer in people with high BP seems to be established in meta-analyses, but the relative risks vary and so do the organs affected. Pavel Hamet and co-workers conclude that *"We still don't have a clear picture of the mechanisms underlying the association between hypertension and cancer"*. Moreover, *"Today, technologies should help us to directly examine the genomic basis of the increased risk of cancer, particularly that of kidney cancer in hypertensive individuals".*

The "Learning the Ropes" section in this issue of the Newsletter is on the inclusion or not of Heart Failure in randomised controlled trials (RCT), where two "giants" in the field, Paul Whelton, US (page 9) and Bryan Williams, UK (page 12) have been asked to take different stands. Thomas Kahan from our Editorial team has written an Introduction to this section (page 8). We expect more comments on this in coming issues of HT News. Please, also note the advert for a new Editor of the Journal of Hypertension on page 7. If you want the job, now is the time to apply, if you haven't done so already!

Finally, my sincere thanks to our Editorial team, who spend more hours than you can imagine on giving you a Newsletter worth reading and to all authors who provide their texts *pro bono.*

Have a good read!

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Alta Schutte
ISH President 2018-2020

Dear Members,

With the Holiday Season around the corner, I cannot believe how quickly this year has run out! This is probably due to every month being packed with exciting activities and meetings!

One particular highlight worth sharing is that on 1 July 2019, the World Health Organization added **fixed dose combination therapy to the WHO Essential Medicines List.** This is a significant step forward as single-pill combinations (SPCs) is the emerging best practice for convenient hypertension control and improving patient adherence – aligned with the recommendations for SPCs in multiple national and international hypertension guidelines (Table republished with permission from *The Lancet*). As stated in a related Correspondence to The Lancet "countries must now implement policies that put single-pill combinations in the hands of the patients who need them".[1]

	ACC/AHA 2017	ESC/ESH 2018	India 2013	China 2010	Thailand 2015	LASH 2017	WHO HEARTS
When to use two blood pressure lowering drugs							
Not controlled on monotherapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Initial treatment for all individuals	No	Yes*	No	No	No	Yes	No
Initial treatment for selected individuals, eg, those who are >20/10 mm Hg from goal† or at high cardiovascular risk	Yes	Yes	Yes	Yes	Yes	Yes*	Yes
When to use single-pill combinations							
Recommended to substitute for separate pills to improve adherence	Yes	Yes	Yes	Yes	NR	Yes	NR

ACC=American College of Cardiology. AHA=American Heart Association. ESC=European Society of Cardiology. ESH=European Society of Hypertension. LASH=Latin American Society of Hypertension. NR=not reported. *Consider monotherapy in patients with low-risk grade 1 hypertension (systolic blood pressure <150 mmHg), or patients who are frail or aged >80 years. †Some referred to this as stage II hypertension or marked increased blood pressure. Adapted from Salam et al.[4]

Table: **Selected hypertension guidelines' recommendations for dual combination and fixed-dose combinations**

Please also take note of the following highlights and news bits:

• On 15 September 2019 abstract submission opened for the **Joint ESH-ISH Meeting** to be held in **Glasgow, Scotland from 29 May to 1 June 2020.** Abstract submission closes by **29 November**, so please save these dates carefully! Reduced registration fees are also available until 15 February – so register early here: https://www.hypertension2020.org.

With exciting speakers already confirmed, this event is one not to be missed. Stay updated by following the event on Twitter with #Hypertension2020. Highlights to look forward to are:

o The release of the **2020 ISH Global Hypertension Guidelines** catering for the needs of those in low resource settings and high resource settings, chaired by Thomas Unger. Watch this space!
o Recognising new investigators, life-time achievers, women scientists and those working in the developing world with **ISH awards**. In the coming months the Chair of the Awards Committee, George Stergiou, will invite you all to submit nominations for the various awards (http://ish-world.com/activities/awards-prizes.htm).
o For the first time, the ISH will also recognise and honour members of the Society who have distinguished themselves through excellence in clinical practice or research in the field of hypertension, by awarding "**Fellows of the International Society of Hypertension**" (FISH). FISH status will be a symbol of excellence, and will represent recognition by the ISH of our members's scientific and professional accomplishments in the field of hypertension. Members will be invited during the coming months to apply online.
o Sessions by the **Women in Hypertension Research Committee** and **New Investigator Committee** including several topics such as career planning.
o With the meeting being in the month of May, there will be specific activities on **May Measurement Month,** including scientific sessions where investigators from around the world will have the opportunity to share their experiences.

• Please note that the official journal of the Society, the Journal of Hypertension is advertising a Call for Applications for a new **Editor-in-Chief**. http://ish-world.com/data/uploads/Call_for_Editor_JH.pdf Applications should be submitted by 1 December 2019.
• The ISH Committee handling **bids for the 2024** ISH meeting is chaired by Fadi Charchar. Numerous applications were received, and applicants shortlisted will have the opportunity to present their bids at the ESH-ISH Joint Meeting in Glasgow. The winning bid will also be announced there, and I am very curious to know where we will all be going in 2024.
Finally, may every member have a peaceful Holiday Season – taking some rest and enjoying time with family and friends. I am greatly looking forward to encounter all of you during ISH events in the new year.

With my very best wishes,

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[1]Benjamin IJ, Kreutz R, Olsen MH, Schutte AE, Lopez-Jaramillo P, Frieden TR, Sliwa K, Lackland DT, Brainin M. Fixed-dose combination antihypertensive medications. Lancet 2019; 394: 637-638. http://dx.doi.org/10.1016/S0140-6736(19)31629-0

THE SECRETARY'S VOICE

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One of the major current tasks of our Society is the elaboration of a new ISH 2020 Global Hypertension Guidelines document.
In the recent past, several local Hypertension Societies have published their own Hypertension Guidelines, among others, the US-American AHA/ACC Guidelines or the Latin American Guidelines in 2017, followed by the European ESC/ESH Guidelines in 2018, the Japanese Hypertension Guidelines and the UK-NICE Guidelines in 2019.

All these documents have their own merits. They are based on extensive review of the current literature trying to extract as much scientific evidence as possible on which to base their preventive, diagnostic and therapeutic recommendations. They are usually written by a large panel of renowned experts and have undergone several stages of external review. Some of them like the European- and the US-American Guidelines are also quite voluminous

which may reduce their readability. While all of them bring together the best available knowledge to distill into recommendations, they address to a large extent their own local or regional clienteles. Most of these Guidelines stem from affluent countries or regions, in which optimal health care is possible if not comprehensively provided. Advanced, sophisticated diagnostic measures, expensive therapies are widely available and in many such countries also financially taken care of by social health providers or at least by private health insurances. However, in many regions of the world, in the less affluent, developing countries, the reality looks quite different. Little is covered by the local health system and one has to scale down expectations and performance from optimal to minimal.

When the idea came up within the council and executive committee of our International Hypertension Society to write our own updated 2020 Hypertension Guidelines, it was clear from the very beginning that we should not create just another guideline document copying in essence what has already been provided by others. We were captured by the thought that within the context of the society's mission to provide global assistance in combatting hypertension, we should generate a document which would take also into account the needs of the less affluent regions of the world, the so-called low- and middle income countries (LMIC). This appeared even more important in view of the fact that blood pressure trends show a clear shift of the highest blood pressures from high-income to low-income regions, with an estimated 349 million with hypertension in high income countries (HIC) and 1.04 billion in low- and middle-income countries (LMIC) in 2010, and that hypertension control is substantially lower in LMIC than in HIC.[1] In another survey, it had been shown that the number of adults with raised blood pressure substantially increased from 1975 to 2015, with the increase largely in low-income and middle-income countries.[2]

This in mind, our goal was to create guidelines as brief and concise as possible in order to facilitate readability. In addition, we wanted them to be to be of practical use especially in LMIC, and to be read and followed also by health care providers and medical assistants without an MD degree.

It became clear to us that, in order to allow specification of essential as opposed to optimal standards of hypertension management in LMIC, we would have to abandon a continuous, strict observance of scientific/clinical evidence in favor of expert opinion. To follow this strategy, we are dividing our recommendations whenever possible in two parts: essential and optimal. Whereas essential means a minimal standard of care based on expert opinion even in absence of clinical evidence, optimal describes evidence-based standards of care as summarized in recent guidelines, especially the opulent recent European and US-American documents. We are convinced that, following this avenue, we will reach out globally, providing assistance to hypertension management in many low-and middle income areas of the world in which resources are scarce and in which current guidelines, as excellent as they may be, are difficult to follow.

The ISH 2020 Global Hypertension Guidelines Committee consists of 12 members: Claudio Borghi (Italy), Fadi Charchar (Australia), Nadja Khan (Canada), Neil Poulter (UK), Dorairaj Prabhakaran (India), Agustin Ramirez (Argentina), Markus Schlaich (Australia), Aletta Schutte (South Africa), George Stergiou (Greece), Maciej Tomaszewski (UK), Thomas Unger (The Netherlands; Chair), Richard Wainford (USA), Bryan Williams (UK). We have met three times face-to face, and will have another session in December. A large group of international reviewers will be invited end of October making sure that parts of the world, especially also the LMIC, are represented and that their experts can contribute to the final document. We plan to have our Guidelines presented at the ISH/ESH/BIHS Congress in Glasgow (UK) end of May 2020 and have them published at the same time. We are convinced that with our new ISH 2020 Global Hypertension Guidelines we will make an important, practical contribution to reduce the global burden of hypertension.

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Who should be offered antihypertensive medication?

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The association between blood pressure and fatal cardiovascular complications is strong, and antihypertensive treatment reduces cardiovascular morbidity and all cause mortality. However, global cardiovascular risk determines the absolute benefit of antihypertensive treatment in reducing cardiovascular events. This would suggest a strategy to identify patients to be offered antihypertensive treatment based on cardiovascular risk superior to treating people based on threshold blood pressure values alone.

Recently, Herrett and colleagues[1] reported on the eligibility and outcomes of offering antihypertensive treatment based on cardiovascular risk, as compared to blood pressure values alone. The authors compared three strategies to define treatment eligibility: 1) a blood pressure of 140/90 mm Hg or more alone; 2) UK National Institute of Care and Excellence (NICE) guidelines on the management of hypertension (2011 and 2019); and 3) a strategy based on absolute risk strategy, using a QRISK2 cardiovascular risk score 10% or greater for a cardiovascular event within 10 years. The study[1] collected information in the UK from primary care and hospital based care, and mortality for 1 222 670 people aged 30-79 years with no prior cardiovascular disease. Outcome was a first diagnosis of coronary artery disease or cerebrovascular disease. Mean age at entry was 51 years, 57% were female, blood pressure 129/78 mm Hg, and 18% were on antihypertensive treatment. Median follow up was 4.3 years, and 7.1 events per 1000 person years were diagnosed.

More people were eligible for treatment with a strategy based on blood pressure alone (39%), as compared to a strategy based on NICE 2011 and NICE 2019 guidelines (22 and 27%, respectively) or a risk based strategy alone (29%). The efficiency of the strategies were different as 63% of the events occurred in patients eligible with a blood pressure strategy, while 47 and 56% occurred with a strategy based on NICE 2011 and NICE 2019 guidelines, and 68% with a risk based strategy. Thus, a strategy based on blood pressure alone would require treating 38 patients for 10 years to avoid one event, while treatment according to NICE 2011 and NICE 2019 guidelines would require 28 and 29 patients, and an absolute risk strategy would require 27 patients treated for 10 years to avoid one event.

These results suggest that a strategy based on absolute risk would prevent substantially more people from incident cardiovascular disease than a strategy based on NICE guidelines or blood pressure alone. This extends previous findings[2,3] and agrees with some guidelines on the management of hypertension[4]. Also, the study[1] provides indirect support to one key change in the latest NICE guideline to offer antihypertensive treatment to people with a QRISK2 10-year cardiovascular event risk of 10% [5], as compared to the previously (NICE 2011) recommended 20% threshold. However, some limitations of this study should be considered. While a risk-based strategy would make some people with normal or slightly elevated blood pressure eligible for treatment, the evidence for a reduction in cardiovascular events by starting antihypertensive treatment at blood pressure values below 140/90 mm Hg is unclear. Also, an achieved blood pressure below 120/70 mm Hg is may be associated with an increased risk. The current study did not investigate people 80 years or older, where the prevalence of hypertension is very high. Finally, other risk score systems use less background information and/or calculate 10-year cardiovascular mortality risk, which may not yield similar results. However, the present findings of antihypertensive treatment based on cardiovascular risk being superior to treatment based on blood pressure alone would most likely persist.

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Nitrosative stress drives heart failure with preserved ejection fraction

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Over the last several decades, the paradigm of heart failure (HF) has shifted from a disease caused by passive backup of venous pressures due to a reduction in left ventricular (LV) contractile function (i.e. HF with reduced ejection fraction – HFrEF), to one driven by an imbalance in complex neurohormonal mechanisms leading to vicious cycle of cardiac and vascular dysfunction. However, we have also learned that many HF patients have relatively normal contractile function, with HF resulting from an impairment in LV diastolic rather than systolic function, termed HF preserved ejection fraction (HFpEF), but our understanding of the mechanism underlying this condition has lagged behind. While drugs that target neurohormonal activation are now the cornerstone of the management of HFrEF, these targeted do not appear to provide similar benefits for HFpEF, and its treatment remains largely limited to fluid management. This is particularly a concern given that HFpEF is now recognized as the most common cause of HF affecting millions of people worldwide.[1] To date, progress in the field has been largely stymied by the lack of experimental models that faithfully reproduce the human syndrome.[2] In the April issue of Nature, Schiattarella and colleagues introduced (with extensive validation) a new model of HFpEF that seems to phenotypically and molecular recapitulate the human condition.[3]

HFpEF is characterized by impaired LV relaxation, and is often associated with and LV hypertrophy.[1,4] Systemic hypertension has consistently been identified as one of the most important risk factors for the development and progression of HFpEF, and is prevalent in up to 50-80% of patients. Schiattarella et al. generated a 'two-hit' model of HFpEF by combining mechanical (hypertension induced by endothelial NO synthase inhibition) and metabolic stress. Mice fed a high-fat diet and treated with Nω-nitrol-arginine methyl ester (L-NAME)) developed key features of HFpEF, including cardiac hypertrophy, diastolic dysfunction, exercise intolerance, and pulmonary edema. A unique feature of this model was the preservation of LV systolic function and a sustained suppression of the IRE1α–XBP1 axis, a novel molecular signature of HFpEF, for up to 12 months. Authors also provide convincing evidence that the commonly used aortic constriction model is a time-delineated model of HFpEF, which progresses to systolic dysfunction and loses this HFpEF molecular signature. This has important implications as humans with HFpEF rarely display any systolic dysfunction.

The authors then used their model to implicate, for the first time, nitrosative stress and suppression of the unfolded protein response (UPR) in the pathogenesis of HFpEF. They focused on the IRE1α–XBP1 axis, the most evolutionarily conserved branch of the UPR, which acts to mitigate cellular stress that can disrupt protein quality. This axis was significantly supressed in the myocardium of their high fat diet + L-NAME mice; findings that were also confirmed in human heart tissue from patients with HFpEF but not HFrEF. Furthermore, they demonstrated robust elevations in iNOS in HFpEF, which promotes S-nitrosylation of cysteine residues within multiple proteins, disturbing their function. This group hypothesized that one of these proteins was IRE1α, which when nitrosylated reduces Xbp1s transcript levels, and engenders the HFpEF phenotype. Finally, they demonstrated that pharmacologic inhibition, genetic suppression iNOS or cardiomyocyte-specific overexpression of XBP1s attenuated, but did complete abrogate, the pathological HFpEF phenotype.

The lack of a complete recovery of cardiac function with iNOS suppression may not be surprising. HFpEF is a multifaceted disease, and thus targeting a single pathway is unlikely to fully restore normal cardiac function and some pathological consequences of activation of this pathway may not be fully reversible (i.e. fibrosis). Nevertheless, iNOS represents a potential exciting therapeutic target. This animal model of HFpEF may also have broader implications if the mice progress to group II pulmonary hypertension and right ventricular dysfunction. HFpEF is the most common cause of group II pulmonary hypertension (PH), presence of which portends a poor prognosis.[5] Research into mechanisms of group II PH is hampered by the same limitations in availability of relevant animal models that have hindered innovation in the field of HFpEF. Therefore, we would like to commend this group for their significant contribution and for renewing hope in finding a effective therapy for patients with HFpEF. Their animal model will undoubtably equip us with new tools to explore disease mechanisms and novel treatment strategies.

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On the inclusion of heart failure as an outcome in hypertension studies

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You may be aware of this section to Hypertension News, which was introduced earlier this year. "To learn the ropes" means to find out how to do something, learning how a particular task or job is done, to acquire an expertise. The expression appeared in standard English some 200 years ago, and is most probably is of nautical origin, where basic skills handling the ropes on sailing ships were essential. We previously highlighted the possibilities and limitations of meta-analyses for the assessment of studies in cardiovascular medicine. Another critical issue is to decide on the proper outcome to choose for large studies. A conservative and robust outcome is all-cause mortality. It is well defined, easy to understand for both health care providers and lay people, and can be applied across different diseases and other risks. However, as all-cause mortality (by definition) eventually will be 100% the time of follow up is important in the evaluation of results from clinical studies[1].

Many hypertension and other cardiovascular trials also include acute non-fatal myocardial infarctions and non-fatal stroke into a composite endpoint. Both myocardial infarction and stroke are well defined, at least if subject to hospitalization. However, other cardiovascular events such as a transitory ischemic attack, angina pectoris, vascular procedures, or heart failure are more difficult to ascertain, in particular if there are no reliable objective biomarkers and/or a subjective evaluation and judgment included.

Hypertension is the most important attributable risk for incident heart failure. The prognosis for incident heart failure remains poor, with a 5-year mortality of approximately 50% from the first recorded diagnosis of heart failure[2]. Furthermore, heart failure patients are frequently hospitalized, with subsequent low quality of life and very high costs[3]. Of note, some patients with heart failure seem to be hospitalized very often, while others my have only few hospitalizations for their disease during the course of time, suggesting that the cumulative number of hospitalizations may be more important than the time to the first event in studies of cardiovascular outcomes[4]. More recently, similar observations have been made also for patients with coronary artery disease[5]. But recurrent events are not independent. They cluster in a subgroup with many more than the average number of hospitalizations during a given time period. These and other considerations invalidate standard statistical techniques.

Heart failure is a clinical syndrome characterized by typical symptoms that may be accompanied by signs caused by a structural and/or functional cardiac abnormality[6]. However, symptoms and signs may be difficult to evaluate in obese individuals, in the elderly, in people with lower limb venous circulation abnormalities, and in patients with respiratory tract disease. An electrocardiogram, echocardiography, and natriuretic peptides often add to the diagnostic accuracy, but the diagnosis of new onset heart often remains difficult as symptoms and signs are non-specific, and values of natriuretic peptides and echocardiography findings are sometimes inconclusive[7]. Thus, heart failure as an outcome in large cardiovascular outcome studies remains an issue for discussion. For arguments pro and con, please see the excellent contributions elsewhere in this issue.

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Heart failure as an endpoint in hypertension trials?

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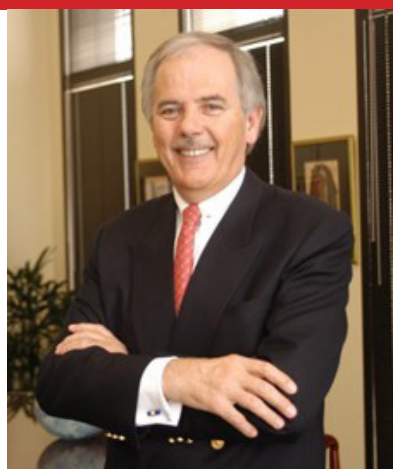

The importance of heart failure as a cardiovascular complication, the central role of blood pressure as the most important preventable risk factor for heart failure, and the demonstrated efficacy of antihypertensive drug therapy for prevention of heart failure combine to make a compelling case for inclusion of heart failure in antihypertensive therapy event-based trials, especially those conducted in older adults.

Prevalence and burden of heart failure

Heart failure is an increasingly common cardiovascular complication that has serious consequences for the individual and for society, especially in high-income countries like the United States (US). In contrast to the overall trend for a progressive decline in cardiovascular disease mortality among US adults, heart failure prevalence is increasing[1]. Based on data from the US National Health and Nutrition Examination Survey, approximately 6.2 million US adults had heart failure in 2013-2016. Heart failure is very age dependent, with lifetime risks varying from 20-45% in adults 45 years or older, depending on age and ethnicity. In Framingham Study analyses, heart failure has been about eight times more common in the eight compared to the fifth decade of life. Approximately 80% of the hospitalizations due to heart failure and 90% of heart failure-related deaths occur in adults aged 65 years or older. The US Census Bureau predicts this segment of the population will almost double in size, to approximately 80 million persons (about 20% of the population) by 2050. Because of this change in demography and better survival from incident heart failure as well as other diseases, the prevalence of heart failure is likely to increase substantially unless curbed by prevention interventions. Current estimates suggest an increase to more than 8 million US adults with heart failure by 20301. US population estimates identify current annual expenditure for heart failure to be between $30 to $40 billion. Much of the economic burden results from hospitalization expenses, followed by costs related to drug purchases, office visits and lost productivity. Worldwide heart failure annual costs have been estimated to approximate $110 billion but the financial burden is expected to increase substantially in future years.

Blood pressure and heart failure

High blood pressure is the most important modifiable risk factor for heart failure. In the Prospective Studies Collaborative meta-analysis of 61 cohorts (almost 1 million participants) there was a log-linear relationship between usual systolic as well as diastolic blood pressure and heart failure mortality, with no evidence of a threshold in risk down to at least 115/75 mm Hg[2]. Likewise, in a linked electronic health record study of approximately 1.25 million adults a 20/10 mm Hg higher level of systolic/diastolic blood pressure was associated with a heart failure events hazard ratio (95% confidence interval) of 1.27 (1.23 to 1.32)/1.23 (1.14 to 1.29), with no evidence of a threshold in risk[3]. In addition to this direct relationship, high blood pressure is the underlying cause of left ventricular hypertrophy and other heart failure risk factors such as ischemic heart disease[4].

Heart failure in clinical trials

Based on its epidemiology, lowering blood pressure should prevent heart failure, especially in older adults. Consistent with this expectation, there was no incident heart failure in the actively treated group compared to 11 such events in the placebo group in the 1970 Veterans Administration Cooperative Study Group trial of antihypertensive, despite the fact that their mean age was only 50 years[5]. One would expect heart failure to be a more prominent feature in trials with older adults. The heart failure experience in six trials of antihypertensive drug treatment conducted in older adults is displayed in the table. In each trial, heart failure was less common in the group assigned to more intensive blood pressure reduction. Consistent with biology, the reduction in heart failure was most prominent in HYVET (64% with a 95% CI 42-78%; $p<0.001$), a placebo-controlled trial conducted in a cohort with a mean age of 83 years at baseline[6]. However, even in the active treatment-controlled Systolic Blood Pressure Intervention Trial (SPRINT) more intensive antihypertensive drug treatment resulted in a 38% reduction in heart failure (hazard ratio 0.62 and 95% CI 0.45 to 0.84; $p=0.002$).

Heart failure is a very relevant trial outcome with serious health consequences. In the Systolic Blood Pressure Intervention Trial (SPRINT), diagnosis of new onset heart failure was associated with a 9.5 fold higher risk of death from any cause, a 26.8 fold increase in death from cardiovascular disease, a 15.7 fold increase in myocardial infarction, a 9.9 fold increase in non-myocardial infarction acute coronary syndrome, and a four-fold increase in stroke during the remainder of trial follow-up[7]. In addition, almost one-third (29%) of those with new onset ADHF had a second episode of heart failure during follow-up. Heart failure in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was also associated with a markedly increased risk of mortality, independent of treatment group allocation, both during the trial[8] and during extended follow-up for an average of 8.9 years (4.9 years of trial experience and 4 years of post-trial follow-up)[9]. The finding of higher mortality in trial participants with new-onset heart failure compared to their counterparts without heart failure was noted both in the context of preserved (>4 fold higher risk) and reduced (almost 6 fold higher risk) ejection fraction[10].

The heart failure diagnoses employed in trials such as SPRINT and ALLHAT have been based on use of rigorous, objective diagnostic criteria that have been validated in prior studies. For example, diagnosis of new-onset heart failure in SPRINT required 1) exclusion of chronic, stable heart failure, 2) fulfillment of multiple specific criteria including acute cardiac decompensation resulting in hospitalization or an emergency department visit with administration of intravenous diuretic or inotropic agents, 3) an appropriate response to treatment, and 4) adjudication by a committee blinded to treatment allocation and specifically trained to recognize the diagnosis. The ALLHAT diagnosis was validated against four other ALLHAT definitions with increasingly stringent requirements, two Framingham Heart Study definitions and a diagnosis made by 11 independent (non-ALLHAT) cardiologists who were blinded to the participant's treatment assignment. There was a high level of concordance between the various definitions, with each yielding similar treatment comparison heart failure results and similar heart failure risk consequences[8].

In a meta-analysis of 123 randomized controlled trials in which blood pressure was lowered with antihypertensive drug therapy, meta-regression identified a relative risk reduction for heart failure that was proportional to the magnitude of the achieved reduction in systolic blood pressure ($p<0.0001$)[11]. For a 10 mm Hg lower level of systolic blood pressure, the hazard ratio for heart failure was 0.72 (95% CI 0.67 to 0.78). This was independent of starting level of blood pressure and the presence or absence of cardiovascular disease at baseline. Diuretics were superior to all other drug classes for prevention of heart failure, with a hazard ratio of 0.81 (95% CI 0.75 to 0.88), independent of whether the trials included participants with or without heart failure at baseline.

Summary and conclusions

Heart failure is an increasingly common cardiovascular complication, especially in older adults. It is associated with substantial mortality/morbidity and cost. Blood pressure is the most important preventable risk factor for heart failure and is an underlying cause of other heart failure risk factors such as left ventricular hypertrophy and ischemic heart disease. Antihypertensive drug treatment trials have repeatedly demonstrated that lowering blood pressure prevents heart failure and meta-regression analysis identifies a strong dose-response relationship. Because of its high burden of illness, increasing prevalence, relationship to high blood pressure in observational studies and antihypertensive drug treatment trials, heart failure should be an outcome in event-based randomized controlled trials of blood pressure reduction., especially those conducted in older adults.

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Figure legend: Risk of all-cause mortality and selected cardiovascular disease complication during trial follow-up in Systolic Blood Pressure Intervention Trial (SPRINT) participants with and without incident heart failure (HF). CV = cardiovascular; MI ACS = myocardial acute coronary syndrome. Adapted, with permission, from Upadhya B et al. Clin Heart Fail. 2017;10:e003613.

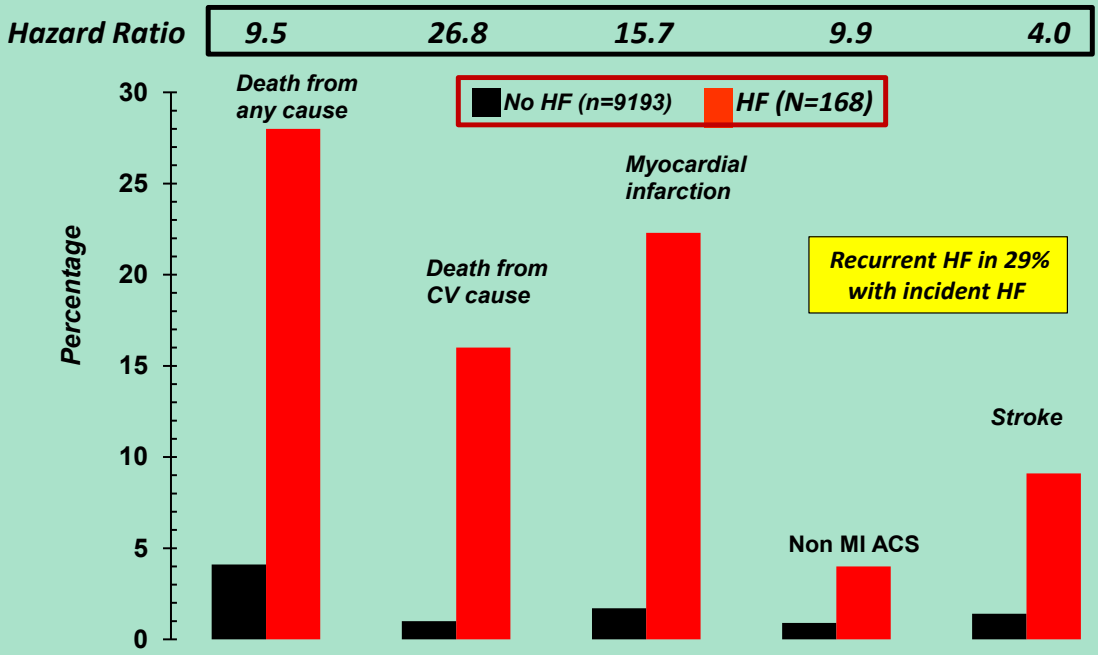

Table. Heart failure experience in six trials of antihypertensive drug treatment

Trial*	Year	Size	Design**	Active	Control	Age, years (mean)	Heart failure (active vs. control)
(active vs. control)							
EWPHE	1985	840	DB	HCTZ***	Placebo	≥60 (--)	-63%
SHEP	1991	4736	DB	Chlorthalidone	Placebo	≥60 (72)	-49%
Syst-Eur	1997	4695	DB	Nitrendipine	Placebo	≥60 (70)	-29%
Syst-China	1998	2394	Alternative	Nitrendipine	Placebo	≥60 (66)	-58%
HYVET	2008	3845	DB	Indapamide	Placebo	≥80 (83)	-64%
SPRINT	2015	9361	Open	Intensive	Standard	≥50 (68)	-38%

***EWPHE=European Working Party on high Blood Pressure in the Elderly Trial; SHEP=Systolic Hypertension in the Elderly Program; Syst-Eur=Systolic Hypertension in Europe Trial; Syst-China=Systolic Hypertension in China Trial; HYVET=Hypertension in the Very Elderly Trial; SPRINT=Systolic Blood Pressure Intervention Trial.**
****DB=double-blind; Alternative=alternative allocation to active treatment or placebo; Open=random allocation to more intensive (Intensive) or less intensive (Standard) treatment**
*****Hydrochlorothiazide combined with triamterene**

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Heart Failure as an end-point in hypertension trials
Challenges in interpretation of mechanisms of benefit

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Heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) are a common consequence of longstanding uncontrolled hypertension. Moreover, since 1990, the prevalence and years living with disability due to hypertensive heart disease, has increased much more than other consequences of hypertension such as ischaemic heart disease or stroke [1]. The latter no doubt reflects the fact that the gestation of heart failure in hypertensive patients is a long process and has become a more prominent consequence of hypertension increased survival of hypertensive patients and population ageing. Heart failure is also associated with significant morbidity and increased risk of hospitalisation all of which contribute to a substantial disease burden in hypertensive patients. For all of these reasons, it is both logical and important to consider heart failure as an important clinical outcome in hypertensive patients and important to consider whether treatment can prevent this outcome or its consequences. There have however, been a number of challenges with the inclusion of heart failure as an end-point in hypertension trials, not least of all, with the validation of the end-point. This was perhaps best exemplified with the controversy around the discontinuation of the doxazosin arm of the ALLHAT trial in 2000 due to an apparent doubling of additional treatment or hospitalisation due to heart failure, relative to treatment with chlorthalidone [2]. Interestingly, this difference between treatments emerged very early and was associated with no apparent increase in mortality. This raised a number of questions at the time, which are still relevant in the discussion of the interpretation of the heart failure end-point in hypertension trials today. First and most importantly, diuretic therapy is very effective at masking or reducing the signs and symptoms of heart failure and in reducing the risk of hospitalisation due to HFrEF in hypertensive patients. Second, most patients entering trials are already treated for their hypertension and in many cases that treatment will involve a diuretic. Often these treatments are stopped as patients change over to a new treatment regimen. For example, in the era of ALLHAT, many patients were treated with diuretic therapy and discontinuation of that therapy and a switch to doxazocin in that study could easily have resulted in an unmasking of pre-existing HFrEF, precipitated not by treatment with doxazocin but diuretic withdrawal. Third, some studies have not included detailed validation of heart failure as an end-point and the fact that treatments such as vasodilators, or calcium channel blockers can cause fluid retention and peripheral oedema creates the potential for the erroneous diagnosis of heart failure. I concede that this is less likely today where the use of natriuretic peptides and echocardiography are more common to validate the diagnosis of heart failure in a clinical trial setting.

The effectiveness of diuretic-based treatments at preventing the signs and symptoms of HFrEF and heart failure hospitalisation has in my view, been greatly understated in the discussion of major clinical trials. This is often due to a desire to imply that the benefit is related to either blood pressure lowering in the case of hypertension trials, or a specific drug action in other trials. First let us consider the SPRINT study as the paradigm for the hypertension trial [3]. In that study, the conclusion was that more intensive blood pressure lowering resulted in a reduction in major cardiovascular events and mortality. In fact, the most dramatic and significant benefit was on mortality and heart failure hospitalisation. This has led to the conclusion that the benefit was due to more intensive blood pressure lowering. But in the case of heart failure hospitalisation, let us consider the comments I made above about the ALLHAT study. First, diuretics were extensively used in SPRINT, especially in patients requiring more intensive therapy when randomised to achieve the more intensive blood pressure goal. This was usually chlorthalidone (a drug shown to be highly effective at reducing heart failure hospitalisation in ALLHAT) or spironolactone (another diuretic that has also be shown to be effective at reducing heart failure hospitalisation or mortality in patients with HFrEF [4]). Indeed, in SPRINT approximately 50% more diuretic was used in patients randomised to more intensive BP lowering than less intensive BP-lowering [3]. Thus, can we conclude that a major component of the benefit of more intensive BP lowering in SPRINT was due to the more intensive BP lowering, or the more extensive use of diuretic driving a reduction in heart failure hospitalisation independent of the BP lowering? Second, just as in ALLHAT, most patients randomised into SPRINT were previously treated for their hypertension. In SPRINT, for those randomised to the less intensive BP goal, in some cases, their baseline treatment was reduced and I suspect in many cases, this would have led to

withdrawal of diuretic therapy in the less intensively treated group. Could this have less to an unmasking of heart failure in some of these patients, thereby contributing to the difference in heart failure between the more versus less intensively treated groups? A difference that would have had less to do with the difference in blood pressure and more to do with the differences in drug treatment, especially the use of diuretic therapies. These are very important considerations when interpreting the results of trials and their impact of guideline recommendations.

The powerful effect of diuretic-based treatments on the heart failure end-point in trials other than hypertension has in my view, also been consistently downplayed in favour of espousing a whole variety of drug specific benefits. Consider the very impressive data with spironolactone or eplerenone in reducing mortality in patients with HFrEF [4,5]. Consider also the data with the ARB/NEP inhibitor also providing benefit beyond the standard of care in patients with HFrEF [6]. Although numerous mechanisms have been evaluated with regard NEP-inhibition in this context, it seems most likely once again that the key benefit derives from the natiuretic effect of NEP inhibtion.

We should also reflect on the data with SGLT-2 inhibitors in patients with diabetes. These drugs have shown benefits in reducing major cardiovascular events in diabetes, but especially heart failure [7]. I have listened to numerous extravagant ideas and complex explanations as why this benefit might have accrued with few acknowledging some key facts; (i) heart failure is very common in patients with diabetes; (ii) diabetes is a volume expanded state; (iii) SGLT-2 inhibitors are osmotic diuretics that offload sodium, an effect that can be especially potent when combined with other diuretic therapies. In my view, this is another example of a diuretic-based treatment leading to outcome benefits for hospitalised heart failure but without recognition of this potential mechanism. It was no surprise therefore, when SGLT-2 inhibitors were also recently shown to be beneficial in reducing heart failure hospitalisation in patients without diabetes [8]. A key question is why the beneficial effects in reducing heart failure hospitalisation of additional diuretic therapy in its many guises, has been overlooked or down-played in all of these settings? The answer rests with the perception that, thiazide-like diuretics, aldosterone antagonists, NEP-inhibition or even SGLT-2 inhibitors, are weak diuretics that would be incapable through this mechanism alone, of modifying heart failure outcomes. This perception in my view, is wrong, because these “diuretics” are often given on a background of other diuretics acting through different mechanisms and the combination of two or more dissimilar diuretics acting at different parts of the nephron is a very potent natriuretic strategy, often deployed in patients with advanced heart failure.

Thus, my concern about heart failure as an end-point in clinical trials, is not about its validity as an end-point but rather, a failure to recognise or acknowledge the independent power of the diuretic action of a variety of different drugs, in a number of trials, to drive their major benefit through a reduction in hospitalisation for heart failure via their diuretic action. This is likely to be of special importance in hypertension trials in older patients who are most at risk of heart failure and in whom it is difficult to differentiate whether the beneficial effects of treatment are being driven by diuresis or BP-lowering, especially when the composite outcome measure of benefit is primarily driven by a reduction in heart failure hospitalisation, like it often is.

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Hypertension and cancer: an update to an unresolved issue

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At the onset the word "cancer "was invariably absent from the glossary of hypertension literature until 1974, when a warning against rauwolfia derivative, particularly reserpine, was issued for its potential of increasing the risk of breast cancer[1-3]. In the following years, a series of articles were published concerning kidney cancer risk in users of diuretics[4].

Noticeably, these were all retrospective observations. The first careful prospective analysis on that subject was performed by Dyer[5] who demonstrated in a 14-year prospective follow-up, the association of several types of cancer with systolic and diastolic blood pressures, independently of therapy. Several prospective studies [6-9] subsequently demonstrated that hypertension per se, may be a culprit of cancer, as we have summarized previously[10]. Then, came out the calcium channel blockers accusation, a retrospective evidence collected from registries and published in important journals [11,12], without any mention of the existing prospective evidence. In our mind, the major weakness of these analyses, was the neglect of indication bias: as usually a novel class of antihypertensive medication is used in the most severely affected subjects, and since hypertension levels appears to be an independent risk of cancer, those subjects are logically at higher risk, independently of their antihypertensive treatments. Notwithstanding the above, it seems that our field has a short memory: Repeatedly, the notion that calcium channel blockers increase the risk of cancer, particularly of breast and kidney cancers emerges in the literature[13] and was disputed [14-15] and revived very recently[16]. It is important to note that when such risk factors as obesity and diabetes are being factored in, the evidence that hypertension is a risk of cancer, and more importantly that a decrease in blood pressure can attenuate that risk is rather convincing[17].

The strongest level of evidence to the debate is contributed by systematic reviews and meta-analyses. Thus, Han et al[18] presented in 2017, thirty studies that were separated according to their prospective or retrospective design. While the retrospective studies presented a relative risk (RR) of 1.29 (95%CI: 1.14-1.47), the prospective ones, that were more homogenous, and weighted for random effect, yielded a RR of 1.15 (95%CI: 1.08-1.22). The significant association was restricted to post-menopausal woman who had a RR of 1.19 (95%CI: 1.09-1.31). A more recent meta-analysis performed in 2019 by Seretis et al[19] reported a positive and significant association between blood pressure and renal cancer specifically, in both sexes, with a RR of 1.5 (95%CI: 1.31-1.75). A significant association was also reported in the prospective studies, for breast, stomach and colon cancers, even when multivariate adjustment was included.

We still do not have a clear picture of the mechanisms underlying the association between hypertension and cancer. The meta-analyses described above concluded to the need for Mendelian randomisation methodology to assess the potential causal role of hypertension in the incidence of cancer. We have initially proposed abnormalities of proliferation/apoptosis that are present in both cancer and hypertension, as a potentially shared mechanism[10,20]. Massive progress in Genome wide Association studies (GWAS) offers the opportunity to analyse shared genomic pathways and to develop polygenic risk prediction models.

As a first step we conducted a gene-centric look-up of genomic loci that were found to be associated to both, breast cancer and hypertension. Data for breast cancer were published in 2019, and a polygenic risk score for prediction of breast cancer and breast cancer subtypes was developed using data from 79 studies conducted by the Breast Association Consortium. The best polygenic risk score included 313 SNPs21. The most comprehensive GWAS of blood pressure was reported by Mark Caulfield and Paul Elliott and their coworkers who identified 535 novel loci of blood pressure in 201822. The table below lists the 24 genes in common between the two studies as well as their main characteristics. Several of these genes were already known as being involved in the pathophysiological mechanisms of hypertension. Thus we previously demonstrated that proliferative and apoptotic anomalies throughout the life cycle of genetically hypertensive rats and mice include such genes as TGFB, FGF, p53 as well as genes regulating telomere homeostasis which led us to propose "Hypertension as a case of accelerated aging"[23]. We also demonstrated anomalies in the transcription of several members of the heat shock genes family in organs of genetically hypertensive rodents and even in circulating cells of humans and proposed hstf1 as the responsible gene[24] . We discovered a gene which is more expressed in several organs of genetically hypertensive rats and whose expression is negatively regulated by calcium levels.

Overexpression of this gene, named Hypertension-related, calcium regulated gene (HCaRG) protects the kidney from ischemic injury[25]. In the context of this discussion, it is noteworthy that this gene, has been recently involved in renal carcinoma and may be a potential prognostic marker for this type of kidney cancer[26,27].

Today technologies should help us to directly examine the genomic basis of the increased risk of cancer, particularly that of kidney cancer in hypertensive individuals. This information will be useful for the early identification of at-risk individuals and for prevention of this additional risk in subjects with hypertension.

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For full references click here

Gene	Annotation	Location	Summary
MDM4	MDM4 regulator of p53	1q32.1	Binds the p53 tumor suppressor protein and inhibit its activity and have been shown to be overexpressed in a variety of human cancers.
ATXN7	Ataxin 7	3p14.1	The encoded protein is a component of the SPT3/TAF9/GCN5 acetyltransferase (STAGA) and TBP-free TAF-containing (TFTC) chromatin remodeling complexes, and it thus plays a role in transcriptional regulation.
TGFBR2	Transforming growth factor beta receptor 2	3p24.1	Mutations in this gene have been associated with Marfan Syndrome, Loeys-Deitz Aortic Aneurysm Syndrome, and the development of various types of tumors.
LRBA	LPS responsive beige-like anchor protein	4q31.3	Implicated in renal and colon cancer.
AHRR	Aryl-hydrocarbon receptor repressor	5p15.33	Involved in regulation of cell growth and differentiation.
TERT	Telomerase reverse transcriptase	5p15.33	Telomerase expression plays a role in cellular senescence resulting in progressive shortening of telomeres. Deregulation of telomerase expression in somatic cells may be involved in oncogenesis.
HSPA4	Heat shock protein family A (Hsp70) member 4	5q31.1	HSPA4 (Heat Shock Protein Family A (Hsp70) Member 4) is a protein coding gene involved in hypertension and cancer.
EBF1	EBF transcription factor 1	5q33.3	Gene ontology annotations related to this gene include DNA-binding transcription factor activity and C2H2 zinc finger domain binding.
CDKAL1	CDK5 regulatory subunit associated protein 1 like 1	6p22.3	The protein encoded by this gene is a member of the methylthiotransferase family. Genome-wide association studies have linked single nucleotide polymorphisms in an intron of this gene with susceptibility to type 2 diabetes.
SMOC2	SPARC related modular calcium binding 2	6q27	The encoded protein may serve as a target for controlling angiogenesis in tumor growth and myocardial ischemia.
LINC00536	Long intergenic non-protein coding RNA 536	8q23.3	Implicated in bladder and breast cancer and orthostatic intolerance.
FAM208B (TASOR2)	Transcription activation suppressor family member 2	10p15.1	Transcription Activation Suppressor Family Member 2 is a Protein Coding gene.
FGFR2	Fibroblast growth factor receptor 2	10q26.13	The extracellular portion of the protein interacts with fibroblast growth factors, setting in motion a cascade of downstream signals, ultimately influencing mitogenesis and differentiation.
LSP1	Lymphocyte specific protein 1	11p15.5	Its rs3817198 T>C polymorphism contributes to increased breast cancer risk.
TBX3	T-box 3	12q24.21	T-box genes encode transcription factors involved in the regulation of developmental processes. Identified for genome-wide significant associations with blood pressure in several ethnic groups.
RPS27P25	Ribosomal protein S27 pseudogene 25	12q24.31	Pseudogene of unknown function.
RIN3	Ras and Rab interactor 3	14q32.12	The protein encoded by this gene is a member of the RIN family of Ras interaction-interference proteins, which are binding partners to the RAB5 small GTPases.
RBFOX1	RNA binding fox-1 homolog 1	16p13.3	Associated with blood pressure and cancer.
CDYL2	Chromodomain Y like 2	16q23.2	Gene ontology annotations related to this gene include methylated histone binding.
ATAD5	ATPase family AAA domain containing 5	17q11.2	Involved in a RAD9A-related damage checkpoint, a pathway that is important in determining whether DNA damage is compatible with cell survival or whether it requires cell elimination by apoptosis.
AQP4-AS1	AQP4 antisense RNA 1	18q11.2	AQP4-AS1 was identified as gene whose expression levels may contribute to the pleiotropy of complex traits involved in cardiovascular health and blood pressure regulation.
SETBP1	SET binding protein 1	18q12.3	The encoded protein has been shown to bind the SET nuclear oncogene which is involved in DNA replication.
ELL	Elongation factor for RNA polymerase II	19p13.11	ELL is elongation factor component of the super elongation complex (SEC), a complex required to increase the catalytic rate of RNA polymerase II transcription by suppressing transient pausing by the polymerase at multiple sites along the DNA.
GIPR	Gastric inhibitory polypeptide receptor	19q13.32	This gene encodes a G-protein coupled receptor for gastric inhibitory polypeptide (GIP), which was originally identified as an activity in gut extracts that inhibited gastric acid secretion and gastrin release, but subsequently was demonstrated to stimulate insulin release in the presence of elevated glucose.

Table 1: Genes associated to hypertension and breast cancer in large GWAS studies.

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Why we should focus more on protective factors than risk factors in cardiovascular prevention

DOI: 10.30824/1911-11

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Ingress

For decades researchers have focused on cardiovascular risk factors, including hypertension, and complications to understand mechanisms and treatment opportunities to prevent cardiovascular disease. More recently it has been proposed to focus more on subjects escaping age-related and risk factor-related complications in a search for protective factors. Even if these "escapers" are not many in absolute terms, they could represent extremes for finding biological targets for further mapping of protecting genes and mechanisms. If such preventive and causal mechanisms could indeed be defined they could eventually be developed into new drug targets for cardiovascular protection.

For a long time the focus in preventive cardiology has been on individual risk factors and disease progression, and guidelines reflect the accumulated evidence to treat risk factors including hypertension [1]. In my opinion, this is not enough for two reasons. First of all many risk factors act within a socio-cultural context that has to be addressed on a societal level, for example taxation and regulation of salt consumption and drugs like tobacco and alcohol. Secondly, we know that in spite of effective drugs, now often used in combination therapy, the cardiovascular risk can only be reduced to a certain level, not eliminated. This calls for new ways of thinking, and one such way to find new drug targets for prevention would be to study "the epidemiology of anomalies" - i.e. the cases when we expect the worst due to a heavy risk factor burden but no disease manifestation is seen, or otherwise substantially delayed. Here a few examples are given and discussed.

The search for protective mechanisms

In the clinical perspective, the treatment of conventional risk factors makes sense in order to reduce risk and treat disease manifestation[1-3], but from another perspective it instead could be worth pursuing to find protective mechanisms. The ultimate reason for this is to find biomarkers (including genes) associated with protection from clinical complications in order to map protective mechanism as these one day could turn into novel drug targets. The well-known residual risk in spite of treatment calls for new treatment targets, for example based on a novel understanding of protection. If new targets could be defined, leading to novel therapies, such alternatives could hopefully be combined with the well-established drugs to control hypertension, hyperlipidemia and hyperglycemia for synergistic effects to further reduce the residual risk, maybe in the format of a poly-pill. This is a strategy recently shown to provide benefits in the PolyIran study, published in the Lancet[4].

Clinical examples of unexpected protection from complications

A few clinical models exist to illustrate cardiometabolic protection, to be further explored. For example, in long-standing type 1 diabetes of more than 40 to 50 years duration and daily insulin regimen, there is a minority of patients who seem to escape major cardiovascular complications even if minor complications such as simplex retinopathy or mild microalbuminuria are present. This has been shown in the Joslin Medalist Cohort in the US[5], as well as in the Golden Year´s cohort in the UK[6], but lately also in the National Diabetes Register from Sweden[7]. Previous studies have tried to map protective factors in these patients, but so far no conclusive genetic findings have been presented. Thus, only descriptive data are available, showing for example a favourable lipid profile in these survivors of complications. As pointed out by the former Editor of Diabetologia, Edwin Gale, these patients with type 1 diabetes can be subdivided into *survivors* (who had an event but survived for a long time), *delayers* (who had to wait for a long time but finally experienced a complication), and the true *escapers* of complications[8].

Another model of protection is the so-called metabolically healthy obesity (MHO), a disputed condition normally defined by absence of variables linked to the metabolic syndrome[9]. An alternative way to define these rare subjects is to find individuals with high body mass index, but escaping hospitalization during long periods of mid-life, as was recently documented in Swedish subjects with body mass index (BMI) >35 kg/m^2 from a population-based study[10]. Even if MHO exists, such individuals will probably not remain free of complications in the long perspective, but such events may be postponed until a higher age.

A third model is represented by patients with chronic kidney disease (CKD) on peritoneal dialysis for a number of years but not harmed by cardiovascular complications[11] in spite of the fact that CKD in most patients is associated with a pronounced increased risk of atherosclerosis as well as media sclerosis of large arteries [12].

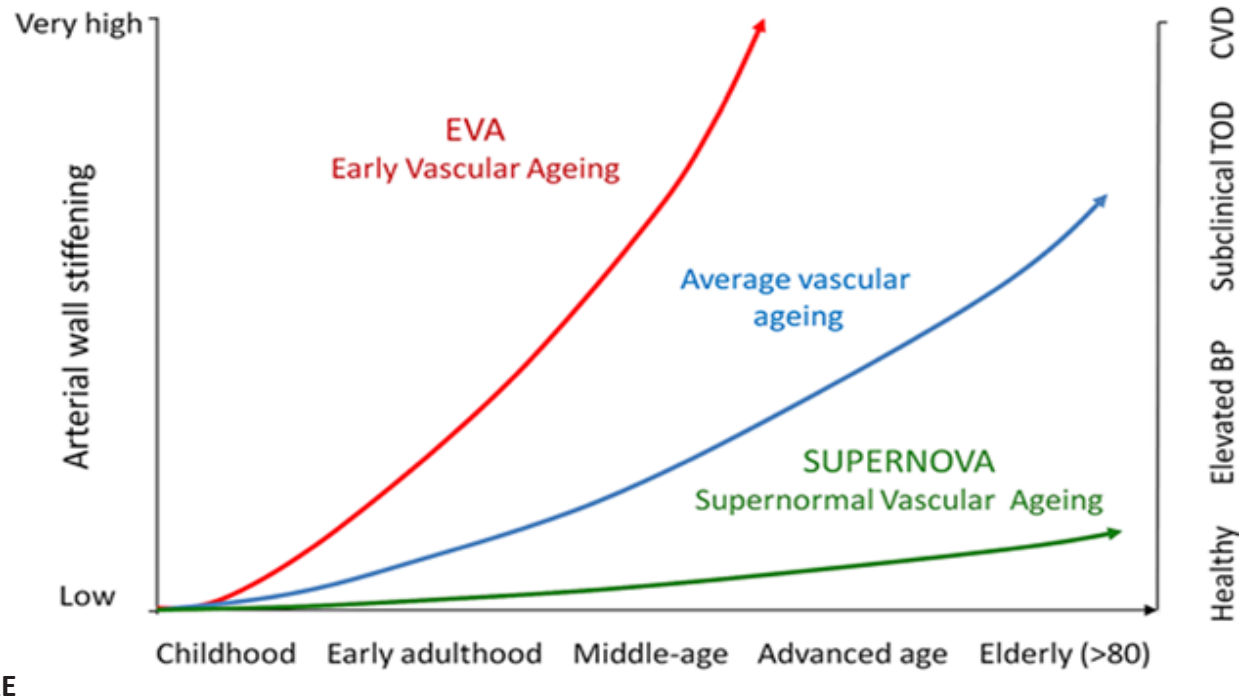
Ethnic differences in susceptibility to blood pressure increase

There may even be other suitable models to explore linked to blood pressure regulation. Why do not all patients with diabetes have elevated blood pressure, even if hypertension is the expected phenotype linked to diabetes? In one study comparing immigrants from Iraq with native Swedes in the city of Malmo, it was revealed that the former exhibited many features of the metabolic syndrome, including hyperglycaemia, dyslipidaemia and increased waist circumference, but the blood pressure were not as elevated as expected [13]. A similar phenomenon has been described among Pima Indians, also selected to survive in hot climates. This could mean that the renal function is differently regulated in subjects exposed to such climates when water and sodium balance has to been well preserved and regulated by genetic factors. In fact, when Pima Indians were examined for sympathetic nervous system (SNS) activity versus Caucasian[14], the latter were characterized by an upregulated SNS, a possible implications of increased energy production as a consequence for evolutionary selection to survive in colder climates. Thus, such geographical and ethnic comparisons could provide new insights into the regulation of blood pressure in relation to kidney function and energy production.

Whether these models simply represent an extreme at the lower end of the normal distribution of risk factors or clinical parameters, or they really represent a specific protective (genetic) causative mechanism is still an open question that further epidemiological and mechanistic studies should try to explore. In addition, pure random effect and play of chance could also influence the distribution of "extremes". As far as genetics are explored the quest for a true protective mechanism may also involve the application of mendelian randomization as a way to dissect causality, as was shown for uromodulin, a factor related to blood pressure lowering in a causal way when extremes from the blood pressure distribution were compared[15].

The SUPERNOVA concept for escaping arterial stiffness

Finally, a recent review on supranormal vascular ageing (SUPERNOVA) in Hypertension by Stéphane Laurent et al.[16] proposed that some people escape the age-related increase in arterial stiffness as measured by carotid-femoral pulse wave velocity (c-f PWV), see Figure. We now try to further map these "extreme" subjects in a joint French-Swedish collaborative project, aiming for deep phenotyping using genomics, proteinomics and other measures, but also to study the long-term prognosis of the SUPERNOVA subjects, that are even more extreme than the subjects with so called Healthy Vascular Ageing (HVA) representing simply the lower 10% of the c-f PWV distribution [17, 18].



FIGURE

Super Normal Vascular Aging (SUPERNOVA) as an extreme phenotype to understand protection from age-related increase of arterial stiffness in elastic arteries as measured by carotid-femoral pulse wave velocity, c-f PWV (modified from reference 16).

Summary

In summary, if cardiovascular prevention should be able to explore new avenues of research and clinical applications it could be of value to use extremes in the way that protective factors could be defined and mapped [19].

Even examples from the animal world can be used, for example why hibernating bears with high LDL cholesterol levels do not develop atherosclerosis [20]. The goal is to find such causal protective mechanisms that could one day turn into new drug targets. If so, traditional drugs to lower risk factors could be combined with true protective drugs that enhance protective mechanism - a new polypill to be tested!

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A summary of the NICE 2019 Hypertension guidelines DOI: 10.30824/1911-12

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In August 2019, the National Institute for Health and Care Excellence (NICE) published a new clinical guideline on the diagnosis and management of hypertension in adults.[1] A new guideline was needed to reflect the findings from a number of important research studies since the last NICE Hypertension guideline [CG127] was published in 2011.[2] The results of these studies has seen a shift in the American College of Cardiology/ American Heart Association (ACC/AHA) guidelines towards diagnosing hypertension at the lower blood pressure threshold of 130/80 mmHg, though only initiating treatment for people with a blood pressure between 130/80 mmHg and 140/90 mmHg who are deemed at 'high risk' of cardiovascular disease.[3] These recommendations have been controversial, given the prevalence of hypertension is predicted to rise by around 15% due to this threshold reclassification, despite many of those newly diagnosed not needing treatment.[3] How have NICE interpreted the same data and how does the latest guideline differ from 2011?

Key recommendations that remain unchanged

The threshold for diagnosing and treating hypertension recommended by NICE remains unchanged, at 140/90mmHg for clinic readings or 135/85mmHg for average home blood pressure measurement (HBPM) or daytime ambulatory blood pressure monitoring (ABPM). The threshold for stage 2 remains the same at 160/100 mmHg but stage 3 or 'severe hypertension' has a new diastolic cut off 180/110 mmHg. Diagnosing hypertension should not rely on single clinic readings, but instead use either HBPM or ABPM. Whilst ABPM remains the gold-standard there are resource and cost implications associated with its uptake. HBPM is a cost-effective and well tolerated alternative.

Treatment targets and diagnostic thresholds remain equivalent. The landmark SPRINT study, a randomised controlled trial of intensive versus standard blood pressure control, reported that treating to a lower target of 130/80 mmHg

led to reductions in cardiovascular events and mortality, improvements supported by the results of a subsequent meta-analysis.[4 5] However, in considering the applicability of these results to UK recommendations, NICE took account of potential limitations in the SPRINT study design and generalisability, particularly to primary prevention across populations with hypertension. For example, SPRINT involved higher risk groups, (including people with cardiovascular disease, chronic kidney disease or a 10-year cardiovascular risk score >15%) and also reduced the dose of medication, particularly diuretics, in the 'usual care' arm. A further meta-analysis including trials of primary prevention failed to show benefit of reduction below 140mmHg systolic.[6]

Furthermore, the SPRINT trial used 'unattended', automated blood pressure measurements, which typically result in significantly lower readings, perhaps as much as 10mmHg.[7] Applying these results directly to healthcare settings where titration is based on routine clinic measurements may risk over treatment and the results themselves may reflect under treatment in the control arm (if the target was more akin to <150 mmHg systolic). Lower target treatment thresholds also led to higher rates of adverse events, including hypotension, syncope, electrolyte imbalance and acute kidney injury.[5 8] Maintaining a single diagnostic and treatment threshold was felt to have the additional benefit of offering a clear, unambiguous recommendation. There were limited data meeting the NICE guideline inclusion criteria as to the relative merits of starting treatment in confirmed hypertension with either a single antihypertensive medication or dual therapy. The Pathway 1 trial, which suggested dual therapy may help achieve target blood pressure control more quickly, was excluded because the outcome was a surrogate marker.[9] As a result and in the absence of other evidence, NICE continues to recommend starting with monotherapy treatment.

Key changes in the 2019 guideline

A lower QRISK2 threshold for treatment in stage 1 hypertension

The change that has captured the most attention in the latest NICE guideline is the move to offer people aged below 80 years with stage 1 hypertension treatment using a 10-year cardiovascular risk (QRISK2) threshold of 10% instead of the previous 20%. There is clear evidence that people with stage 2 hypertension benefit from blood pressure lowering treatment in terms of a reduction in both cardiovascular events and mortality.[6] However, the evidence is more limited for people with stage 1 hypertension who do not have diabetes, renal disease, cardiovascular disease or target organ damage and so NICE undertook a health economic analysis to inform their recommendation on this question. They assessed threshold cardiovascular risk levels of 5%, 10%, 15% and 20%. For people aged 60 years, treatment was cost-effective at the 10% threshold but not at the 5% threshold. For people younger than 60, a lower risk threshold of 5% may be cost-effective, so consideration should be given to treatment in this group based on patient preference. The guideline recognises the balance between benefit and harms when treating low-risk people with stage 1 hypertension and therefore gives flexibility to patients and professionals in their choices, emphasising the importance of lifestyle change.[8] Despite these apparently modest changes, NICE recognise that these recommendations would mean over 500,000 people becoming eligible for treatment with around £10m net impact in the first five years if only a quarter of these take up long term treatment.

New advice on taking blood pressure measurements

NICE continue to recommend that blood pressure should be measured in both arms at the time of diagnosis but suggest a difference of 15 mmHg should now be considered significant, compared to the previous 20 mmHg.[10] Subsequent blood pressure readings should be measured from the arm with the higher reading and patients informed which this is. This reflects the fact that even small differences in blood pressure between arms can indicate a significant increase in cardiovascular risk. A standing blood pressure should be measured in people with diabetes, symptoms of postural hypotension or aged over 80 years. If there is a significant postural drop (>20 mmHg systolic), blood pressure treatment should be based on the standing reading.

Accelerated and severe hypertension

Differentiating accelerated from severe hypertension is difficult and there is limited evidence on this topic. NICE have clarified clinical signs consistent with accelerated hypertension that may help guide clinicians in deciding which patients need urgent assessment, to avoid unnecessary emergency referrals to hospital on the basis of very high single blood pressure measurements alone. These include retinal haemorrhage, papilloedema or life-threatening symptoms. In the absence of these features, it is recommended clinicians arrange urgent investigations for end-organ damage, including urine dipstick, blood tests and an electrocardiogram. Such patients should be reviewed and have their blood pressure repeated within a week.

Inclusion of diabetes

People with diabetes are now included in the NICE 2019 hypertension guidance and their target blood pressure thresholds are now equivalent to those without diabetes, i.e. 140/90 mmHg on clinic readings or 135/85 mmHg on ABPM or HBPM. The previous recommendation was a consensus opinion based on the Hypertension Optimal Treatment (HOT) trial.[11] However, this was prior to the ACCORD study, which found treating to a target of 120 mmHg compared to 140 mmHg systolic in people with type 2 diabetes did not reduce the composite primary outcome of fatal and non-fatal major cardiovascular events.[12]

Conclusion

The new NICE guideline differs from American guidelines and retains target blood pressure thresholds of 140/90 mmHg or 135/85 mmHg out-of-office measurement for both diagnosis and treatment. This target is now equivalent for people with or without type 2 diabetes, providing a clear and consistent threshold. The major change has seen the QRISK2 threshold for treatment in stage 1 hypertension reduced to 10%. There are also changes to help clinicians identify high risk patients based on between arm blood pressure difference and clinical signs relevant to severe hypertension.

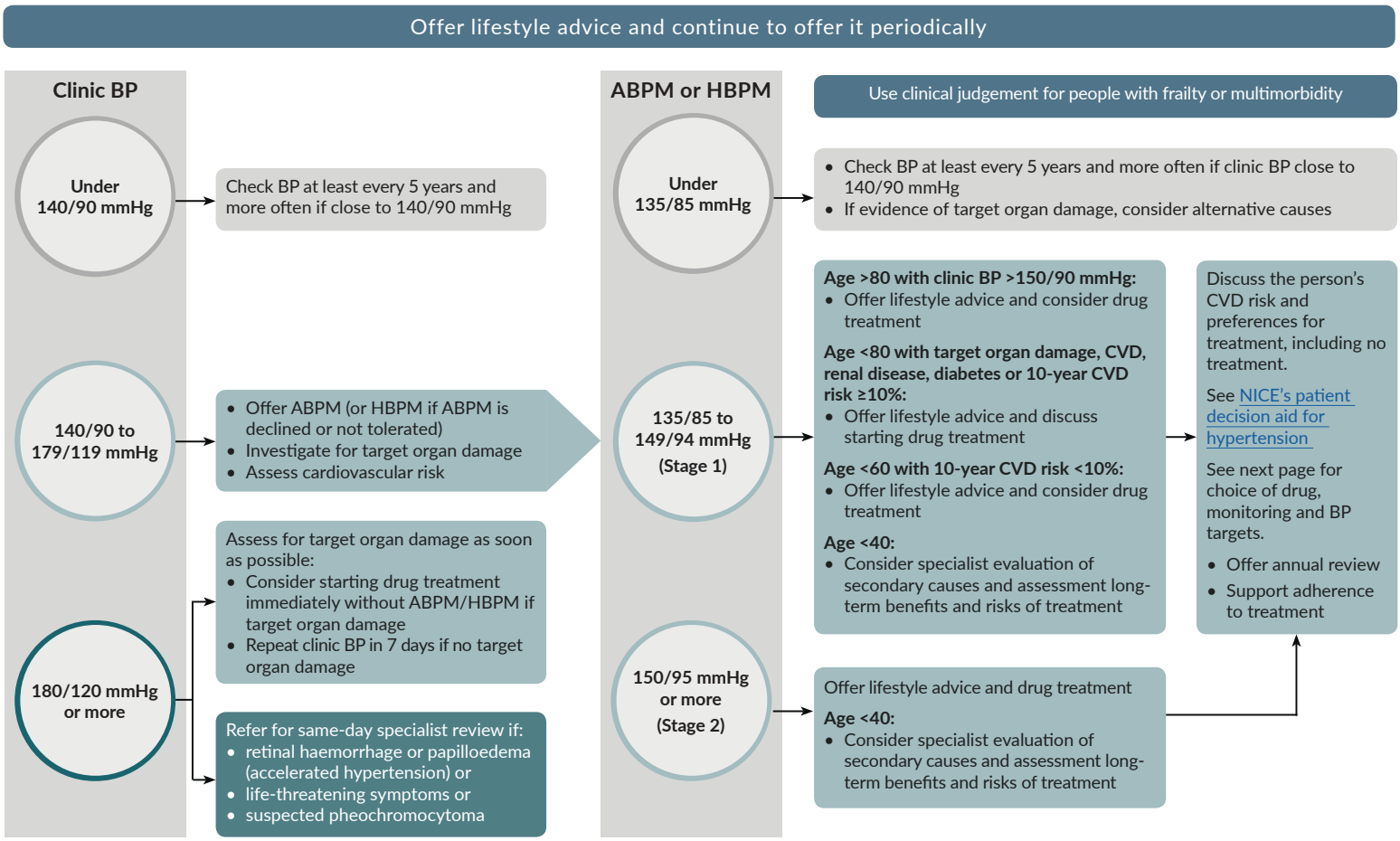
Disclaimer

The NICE guideline referred to in this article was produced by the National Guideline Centre for the National Institute for Health and Care Excellence (NICE). The views expressed in this article are those of the authors and not necessarily those of NICE.

National Institute for Health and Care Excellence (2019) Hypertension in adults.
Available from https://www.nice.org.uk/guidance/ng136

Hypertension in adults: diagnosis and treatment

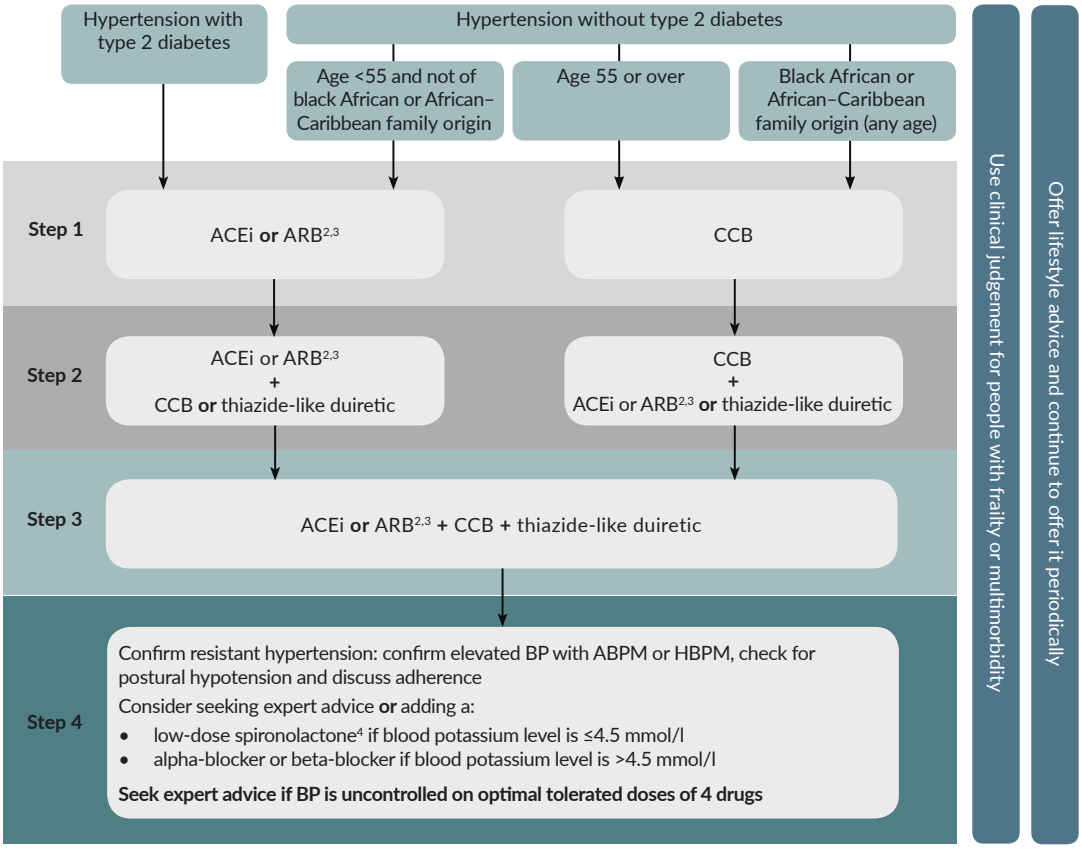
NICE National Institute for Health and Care Excellence



Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CVD, cardiovascular disease; HBPM, home blood pressure monitoring.

This is a summary of the recommendations on diagnosis and treatment from NICE's guideline on hypertension in adults. See the original guidance at www.nice.org.uk/guidance/NG136

Choice of antihypertensive drug[1], monitoring treatment and BP targets



Monitoring treatment

Use clinic BP to monitor treatment.

Measure standing and sitting BP in people with:

- type 2 diabetes **or**
- symptoms of postural hypotension **or**
- aged 80 and over.

Advise people who want to self-monitor to use HBPM. Provide training and advice.

Consider ABPM or HBPM, in addition to clinic BP, for people with white-coat effect or masked hypertension.

BP targets

Reduce and maintain BP to the following targets:

Age <80 years:

- Clinic BP <140/90 mmHg
- ABPM/HBPM <135/85 mmHg

Age ≥80 years:

- Clinic BP <150/90 mmHg
- ABPM/HBPM <145/85 mmHg

Postural hypotension:

- Base target on standing BP

Frailty or multimorbidity:

- Use clinical judgement

[1] For women considering pregnancy or who are pregnant or breastfeeding, see NICE's guideline on hypertension in pregnancy. For people with chronic kidney disease, see NICE's guideline on chronic kidney disease. For people with heart failure, see NICE's guideline on chronic heart failure

[2] See MHRA drug safety updates on ACE inhibitors and angiotensin-II receptor antagonists: not for use in pregnancy, which states 'Use in women who are planning pregnancy should be avoided unless absolutely necessary, in which case the potential risks and benefits should be discussed', ACE inhibitors and angiotensin II receptor antagonists: use during breastfeeding and clarification: ACE inhibitors and angiotensin II receptor antagonists. See also NICE's guideline on hypertension in pregnancy.

[3] Consider an ARB, in preference to an ACE inhibitor in adults of African and Caribbean family origin.

[4] At the time of publication (August 2019), not all preparations of spironolactone have a UK marketing authorisation for this indication.

BIHS British and Irish Hypertension Society
Committed to preventing cardiovascular disease

This visual summary builds on and updates previous work on treatment published by the BIHS (formerly BHS)

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEi, ACE inhibitor; ARB, angiotensin-II receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; HBPM, home blood pressure monitoring.

Published: August 2019

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 DOI: 10.30824/1911-13

May Measurement Month 2019 (MMM19) breaks the ONE MILLION screening milestone for the third year in a row

In May 2019, thousands of volunteers from across the globe came together for the third year running to carry out our annual synchronised and standardised blood pressure screening campaign. Since the end of July this year, May Measurement Month (MMM) volunteer statisticians have been tackling the long task of cleaning and analysing the data collected during MMM19, with a view to submitting the results by the end of the year for publication in a leading global journal. Although final numbers have not been confirmed at the time of going to press we are pleased to announce that the number of countries taking part in MMM19 is similar to the number that took part in 2018. Once again those involved have comfortably exceeded targets, by collectively screening **in the region of 1.5 million people**.

This continued momentum shows the strong global appetite for, and commitment to, increasing awareness of the issues surrounding high blood pressure via MMM.

New Data in MMM19

MMM19 saw a few changes compared with previous years. Firstly, we were delighted to welcome a number of new countries who joined MMM for the first time, including Afghanistan, Algeria, Bulgaria, Japan, Kyrgyzstan, Mongolia, Saint Lucia, South Korea, Sri Lanka and Tunisia.

Following feedback from previous MMM campaigns, a number of amendments were made to this year's questionnaire. Four new questions were added to the questionnaire as follows. For those participants who reported taking prescribed medication to treat high blood pressure; we added:

1. How many drug classes do you take for your blood pressure?
2. Do you take a statin?
3. Do you take aspirin?

We also asked:

4. If female, have you had raised blood pressure in a previous pregnancy?

Question 1 will help us to see how frequently monotherapy is successful at controlling BP, whilst questions 2 and 3 will advise on how closely good practice is followed regarding other frequently recommended concomitant medication.

Question 4 will confirm or refute the data suggesting that previous pregnancy associated hypertension is linked with higher BP in later years.

To ensure that the questionnaire was not lengthened, the following questions were removed to make room for the new questions:

1. Time of measurement
2. Temperature at the site of screening
3. What type of BP machine is being used to take the readings? (automated / not automated)
4. Which arm is being used to take the blood pressure? (left / right)

MMM Publications

Following the MMM publications in the run up to MMM19**, plans are in the pipeline for a further supplement of national papers from MMM18, as well as the MMM19 global paper both to appear before May 2020. For some analyses we may also combine the data from MMM17, '18 and '19, to provide insights from over 4 million screenees.

The accuracy of MMM data submitted via the MMM app and Excel spreadsheets has significantly improved over the last 3 years. Whilst the MMM app remains the fastest way for us to collect clean data, at the time of going to press, indications show that whilst the percentage of data submitted via the MMM app has increased it was still disappointingly low at around 15% or 16% of data in 2019 compared to 8% in 2017. Increased app usage in future years would facilitate earlier analysis and therefore potentially allow earlier publication.

Once again, the MMM team would like to thank everyone who has been involved. That MMM helps to save and improve lives was strongly supported by a recent BMJ article (BMJ 2019; 366: L4064) which showed community-based screening in China carried out in a very similar fashion to MMM was associated with a large significant benefit on systolic BP levels. However, the MMM campaign cannot be carried out without the dedication and support of the thousands of volunteers who contribute all over the world and without whom there would be no MMM.

If you would like to learn more about future plans for MMM, or would like to get involved in 2020, please contact the MMM Project Manager: manager@maymeasure.com

A Simple Measure to Save Lives
Be part of it!
www.maymeasure.com

NOTE:
May Measurement Month is an initiative of the International Society of Hypertension launched in 2017 to build upon and extend WHL's World Hypertension Day.

** Published papers in 2019:
- MMM17 39 national papers supplement https://academic.oup.com/eurheartj/article/40/25/2006/5481538
- MMM18 global analysis https://academic.oup.com/eurheartj/article/40/25/2006/5481538

Judith Bunn and Lisa Woodward, MMM Project Manager and MMM Communications Manager
MMM Project Manager - manager@maymeasure.com

"DDD": DYLAN'S DISTRIBUTION DATA

The July 2019 issue of Hypertension News maintained strong readership, albeit somewhat lower than our peak readership with the March 2019 issue. Part of this may be attributed to summer holiday which inevitably leads to reduced readership and engagement.

Dylan's Distribution Data (July-September 2019)	
Total Estimated Readership	**3524**
Accessed via Twitter	184
Accessed via Facebook	155
Accessed via DOI	2611
Accessed via Web Site	574

Dylan Burger- dylburger@hotmail.com

Dear Colleagues,

It is our great pleasure to invite you to attend the next Joint Meeting of the European Society of Hypertension (ESH) and the International Society of Hypertension (ISH) in collaboration with the British and Irish Hypertension Society, to be held in Glasgow, UK, from May 29 to June 1, 2020.

The meeting will not only cover the latest science across the whole spectrum in the field of hypertension, including diagnostics, therapeutics, novel mechanisms, digital health, co-morbidities and epidemiology, but will also focus on other related conditions, such as diabetes, dyslipidemias, obesity and metabolic syndrome, and other more recent topics, such as cardio-oncology and cardio-immunology.

These are only few examples of the wide-ranging topics included in the stimulating scientific programme. Please visit the congress website: www.hypertension2020.org/topics/ for further information on topics.
The European and International Society of Hypertension meetings are the largest and most significant scientific events in hypertension worldwide. Attracting delegates from around the world and world-leading authorities in the field of hypertension and related diseases, this event is the most appropriate forum for reporting and discussing emerging important diagnostic and therapeutic approaches with experts from around the world. Top speakers confirmed so far: www.hypertension2020.org/scientific-programme/

We take this opportunity to remind you of the final deadline to submit your original abstract - November 29, 2019. We invite you to do so now via the congress website:
www.hypertension2020.org/abstracts/

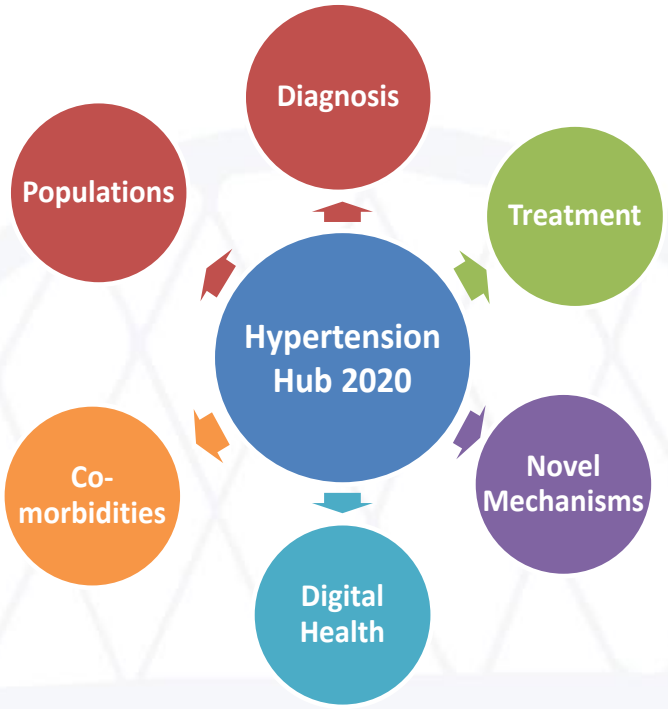
The meeting will take place at the Scottish Event Campus, which comfortably accommodates the large number of participants and diversified scientific and educational activities that characterise ESH-ISH Joint Meetings, and also offers excellent exhibition space for industry. The Scottish Event Campus is located only 15 minutes from Glasgow International Airport and 5 minutes from the heart of the city centre.

We look forward to welcoming European and International experts in hypertension and related conditions to Glasgow next May together with the many investigators and clinicians to contribute together to the success of the next Joint Meeting: ESH-ISH 2020 Glasgow.

A.F. Dominiczak	***R. Kreutz***	***A.E. Schutte***	***U. Martin***
ESH ISH 2020	President ESH	President ISH	President BIHS

JOINT MEETING ESH-ISH 2020

ESH-ISH 2020 Glasgow scientific programme – High Impact Science & Clinical Practice



Co-morbidities, e.g.

- ***Hypertension in elderly patients with multi-morbidity***
- ***Atrial fibrillation***
- ***Hypertension meets cardio-oncology***
- ***Pulmonary co-morbidities and treatment of hypertension***
- ***Hypertension and diabetes*** *- shall we treat differently?*
- ***Hypertension in rheumatology*** *- shall we treat differently?*
- ***Cognitive impairment in hypertension*** *– how to prevent?*

Novel mechanisms, e.g.

- ***Mechanistic lessons from genetic studies***
- ***Microbiome, metabolism and salt***
- ***Inflammation and immune system***

Diagnosis, e.g.

- ***Ultrasound / MRI / CT*** *in hypertensive pathology and risk evaluation*
- ***Can we go beyond ABPM?*** *- How to measure blood pressure in the future - novel wearables*
- ***Artificial Intelligence and Machine Learning*** *in predicting hypertension and its outcomes*
- ***Multiplexing of biomarkers*** *- composite approaches to stratification/prediction*
- ***Cardiovascular risk assessment*** *in hypertensive patient - the same or different to general population?*

Treatment, e.g.

- ***How to reconcile European and American guidelines***
- ***Developing the new and remembering the old therapeutic options for resistant hypertension*** *- from pharmacological approaches to novel devices*
- ***Metabolic interventions*** *in hypertension - SGLT-2 inhibitors in HTN and beyond*
- ***Precision medicine or polypill?*** *- what is the best approach for my hypertensive patient?*
- ***Device based approaches***

JOINT MEETING
ESH-ISH
2020
Glasgow

May 29 - June 1, 2020
Scottish Event Campus
Glasgow, United Kingdom
www.hypertension2020.org

European Society of Hypertension
International Society of Hypertension
BIHS

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@ESH_Annual / @ISHBP / @BIHSoc_Events
@ESHAnnualMeetings / @ISHBP / @bihsocevents

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Report on the 2nd International Congress of Hypertension in Children and Adolescents (ICHCA)

Ruan Kruger (Chair: New Investigators Committee)
Centre of Excellence: Hypertension in Africa Research Team (HART)
MRC Research Unit for Hypertension and Cardiovascular disease
North-West University

For those working closely in childhood and adolescent hypertension, this congress should be on your bucket list of meetings to attend in 2020!

Growing evidence indicates the importance of identifying and managing childhood and adolescent hypertension, since early vascular aging and related cardiovascular disease originates as early as infancy. Along with the recent advances in paediatric hypertension, with reference to 2016 and 2017 evidence-based hypertension guidelines,[1,2] the International Congress of Hypertension in Children and Adolescents (ICHCA) showcases cutting-edge research on the key contributors and implications of high blood pressure in children from developing and developed countries.

The Congress Committee, Professors Brian Rayner (South Africa), Mieczysław Litwin (Poland), Empar Lurbe (Spain), and Daniel Feig (USA), hosted the second successful congress in the sprawling capital of Poland on 24–26 May 2019. The 2019 ICHCA meeting involved an outstanding faculty from fifteen countries amongst others, Prof Joseph Flynn (USA), Prof Krzysztof Narkiewicz (Poland), Prof Tomas Seeman (Czech Republic), Prof Janusz Feber (Canada), Prof Paolo Palatini (Italy), and Prof Elke Wühl (Germany). The scientific programme captured numerous themes amongst others the epidemiology and pathogenesis, target organ damage, risk profiling, secondary causes and treatment guidelines/updates of paediatric and adolescent hypertension.

Some interesting topics included the links of early life stress or childhood adversity with oxidative stress promoting pro-inflammatory phenotypes in children with subsequent cardiovascular risk in adulthood (by Jennifer Pollock, USA); renal compromise in terms of salt intake and ethnic-specific physiological phenotypes (by Prof Brian Rayner, South Africa, and Prof Stella Stabouli, Greece); echocardiographic interpretations and target organ damage in childhood hypertension (Prof Elaine Urbina, USA); and how to apply fuzzy logic to predict blood high pressure in children (Prof Janusz Feber, Canada). The congress also included a small selection of e-Posters and short scientific communications from peer-reviewed abstracts and young investigators.

The third ICHCA meeting will be hosted in Warsaw, Poland in 2020. The exact dates are being discussed and will be announced by the end of 2019.

References:

1. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016;34(10):1887-920.
2. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics. 2017;140(3):e20171904

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3rd Summer School of the Asian Pacific Society of Hypertension/International Society of Hypertension (Ayutthaya, Thailand 22nd – 26th July)

Dean Picone[1], Rachel Climie[1,2]

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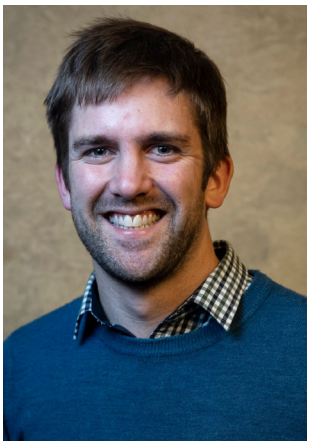
[2]Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia



The 3rd Summer School of the Asian Pacific Society of Hypertension in collaboration with the International Society of Hypertension (ISH) was held in Ayutthaya, Thailand from the 22nd to 26th July 2019. The summer school was successfully organised by Professor Trefor Morgan and the Thai Hypertension Society, where 29 scholars and 10 faculty from 16 countries in the Asia-Pacific region and beyond enjoyed stimulating scientific discussion and wonderful hospitality.

The first requirement of the summer school was a group photo **(Figure 1)**. After this task each summer school scholar presented an abstract within themes including hypertension epidemiology, prevention or treatment, blood pressure measurement or secondary hypertension. Scholars were also given the opportunity to present their current research findings which included novel interventions for the treatment of hypertension and blood pressure measurement issues.

Figure 1. Summer school scholars & faculty members.

Faculty members gave lectures on a variety of topics including the role of the sympathetic nervous system and renin angiotensin system in hypertension, and resistant hypertension and presented fascinating case studies which were a highlight for many scholars.

The summer school scholars and faculty were also treated to an afternoon social activity exploring the historic sights of Ayutthaya -which was Thailand's capital city until 1767. Highlights included the amazing Arts of the Kingdom Museum (Figure 2) and Wat Mahathat's Buddha Head.

Ruan Kruger (ISH-New Investigators Committee lead) represented the ISH on the faculty and he shared interesting insights on paediatric hypertension and promoted the New Investigator Network of the society. Other ISH representatives included Thomas Unger and Markus Schlaich.

Overall, the 3rd Summer School was a great learning and networking experience for all. Indeed, the scholars are already continuing discussions with the aim to establish enduring collaborations. The 4th iteration of the summer school is planned for 2021 and new investigators from the Asian-Pacific region should keep an eye out for future details. All scholars were extremely grateful for the support of their national hypertension societies which provided financial assistance to attend the summer school.

Figure 2. Summer school scholars and faculty on their way to Arts of the Kingdom Museum.

British and Irish Hypertension Society Annual Scientific Meeting 2020

28th – 29th May 2020

Queen Elizabeth Teaching and Learning Centre, Glasgow

KEY DATES:

Abstract Submission Deadline:	**29th November 2019**
Notification to Authors:	**14th February 2020**
Early Registration Closes:	**13th March 2020**

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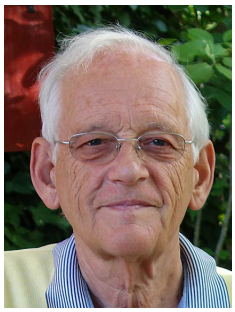
ISH Hypertension News Team



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