British Heart Foundation

Easing the pressure

Impact of British Heart Foundation (BHF) support for high blood pressure research

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Impact thematic review

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Impact of BHF support for hypertension research

1) Introduction

Hypertension, or high blood pressure, is a condition in which the force of the blood against the artery walls is consistently too high. It is a major risk factor for cardiovascular diseases, such as heart attack, stroke, and heart failure, as well as other health conditions including kidney disease. Hypertension affects over one billion people worldwide and is responsible for 10 million deaths every year. It is the number one risk factor for death globally[1, 2]. In the UK, it is estimated that around one third of adults have hypertension, but many are unaware of their condition or do not receive adequate treatment[3].

Blood pressure (BP) is expressed as two numbers: the systolic pressure, which is the pressure when the heart contracts and pumps blood, and the diastolic pressure, which is the pressure when the heart relaxes and fills with blood. The unit of measurement is millimetres of mercury (mmHg). High BP is considered to be 140/90 mmHg, where 140 is the systolic (upper) number and 90 is the diastolic (lower) number. For individuals over 80, high BP is considered 150/90 mmHg or above. The higher the BP, the more serious the condition and the more urgent the need for treatment. Hypertension without a known cause is called primary (essential) hypertension. In contrast, secondary hypertension has a known cause, for example, kidney disease.

The causes of hypertension are complex and multifactorial, involving genetic, environmental, and lifestyle factors. BP is regulated by various systems and networks in the body, such as the nervous system and the renal system. Any dysfunction or imbalance in these systems can lead to increased BP. Some of the common risk factors for hypertension include obesity, physical inactivity, smoking, excessive alcohol consumption, stress, salt intake, age, ethnicity, gender, and family history. High BP can often be prevented or reduced by eating healthily, maintaining a healthy weight, taking regular exercise, drinking alcohol in moderation and not smoking.

The diagnosis and management of hypertension is crucial for preventing its complications and improving patients' lives. Treatments range from lifestyle modifications to medications such as ACE inhibitors, angiotensin-2 receptor blockers, and calcium channel blockers.

BHF has been at the forefront of research into hypertension for over 60 years, supporting studies that have advanced our understanding of the mechanisms, risk factors, diagnosis, treatment, and prevention of high BP and its consequences.

2) Generating new knowledge

a. Blood pressure regulation and hypertension mechanisms

Several organs are involved in the control of blood pressure, including the brain, the adrenal glands, the kidneys, and the blood vessels. These systems are highly interlinked. Dysfunction in any of these systems can lead to consistently high BP. BHF-funded research has contributed to generating knowledge of the various mechanisms involved in BP regulation and hypertension and how these are affected by BP lowering drugs.

i. The baroreflex

The baroreflex is a mechanism for the rapid regulation of BP in response to a changing environment, for example suddenly standing up from a sitting position. Gravity causes blood to pool in the legs, leading to a drop in BP. Some specialised proteins in the carotid arteries and aortic arch (part of the aorta directly connected to the heart), called baroreceptors, can detect the change in BP by sensing how stretched blood vessels are. Baroreceptors can send signals to the brain, which then responds by sending instructions to the heart and blood vessels, regulating their functions to control BP.

BHF-funded researchers have studied how the baroreflex is affected in hypertension since the 1960s/70s in the hope of identifying new therapeutic targets.

BHF-funded Professor Peter Sleight at the University of Oxford, who later became BHF Chair of Cardiovascular Medicine, and Dr Jennifer Angell-James at St Bartholomew's Hospital in London have extensively studied the mechanisms of the baroreflex. They showed a decreased baroreflex and baroreceptor sensitivity in experimental models of hypertension and in hypertensive patients[4]. Professor Sleight also studied how BP lowering drugs, including beta-blockers, affect the baroreflex. It is now known that many approved anti-hypertensive treatments affect the baroreflex, because of the high interlink between all the BP control mechanisms.

But while the baroreflex has been extensively studied by BHF-funded researchers and other researchers throughout the world, it is not currently being directly targeted by anti-hypertensive treatments. However, research is underway around the world to test baroreceptor activation therapy (BAT), which uses an implanted device to stimulate pressure sensors in the neck and help lower blood pressure[5].

ii. The carotid body

Recently, the role of the carotid body in the pathophysiology of hypertension has gained considerable interest. The carotid body is a sensory organ located at the point where the common carotid artery splits in the neck at the base of the skull. The carotid body detects changes in the composition of arterial blood flow, such as amount of oxygen and carbon dioxide in the blood and relays this information to the brain triggering physiological responses to maintain homeostasis. Professor Julian Paton, based at the University of Bristol received BHF support to study the role of the carotid body in regulating BP, and its therapeutic potential[6].

Professor Paton's research indicated that carotid bodies are a cause of high BP and offer a new target for treatment. They found that removing one carotid body from some patients with hypertension caused an immediate and sustained reduction in BP[7]. The trial demonstrated that the carotid bodies in patients who responded to the treatment had raised carotid body activity. Paton's research also discovered a receptor responsible for carotid hypersensitivity – the P2X3 receptor - and has worked to develop a novel small molecule to block it, which showed promising results in rats with high BP[8].

iii. Adrenaline/noradrenaline pathway

In the 1970s, BHF supported the research of Professor Colin Dollery at Hammersmith Hospital in London, working with many other researchers, including Professor Peter Lewis. Their research has contributed to advancing our knowledge of the mechanisms underlying the development and maintenance of hypertension. Their work highlighted the importance of the central nervous system in BP regulation, especially the role of the sympathetic system. Often referred as the 'fight or flight' system, the sympathetic system is mainly controlled by the neurotransmitters noradrenaline and adrenaline.

Drugs blocking the action of adrenaline and noradrenaline, called beta-blockers (e.g., propranolol), were developed in the 1950s to treat angina. In 1969, researchers showed beta-blockers could also be used to treat hypertension, however their mechanisms were not well understood. In 1973,

BHF-funded research by Professor Dollery showed that propranolol lowered BP in pre-clinical models of hypertension by blocking the activity of beta-adrenoreceptor at the level of the central nervous system[9], also confirmed by BHF-funded by Professor Anthony Smith at the University of Sheffield[10]. Since then, many other BHF-funded studies have looked at deciphering the mechanisms of action of beta-blockers, specifically looking at their effect on the central and peripheral BP control, with 'central' meaning control by the nervous system and 'peripheral' referring to all mechanisms outside of the central nervous system.

From the mid-1970s, Professor William Littler, who was appointed the Sir Melville Arnott BHF Chair of Cardiovascular Medicine at the University of Birmingham in 1975, tested the effect of various beta-blockers in human studies. He looked at how effective different drugs were at reducing BP, and for how long, but also their effects on circulating levels of noradrenaline[11-13]. Some of the drugs he studied are still in use today (e.g., atenolol, acebutolol).

iv. The renin-angiotensin-aldosterone system

The renin–angiotensin–aldosterone system (RAAS), primarily controlled by the kidneys, is a complex hormonal system that is essential for the regulation of BP and fluid balance in the body. The system is manly comprised of three hormones – renin, angiotensin II, and aldosterone. In the 1970s, Drs John Ledingham and Michael Lee at St Thomas' Hospital Medical school developed a method for measuring the activity of the plasma enzyme renin[14], and showed elevated renin activity in a pre-clinical model of hypertension[15], adding further evidence for the crucial role of the RAAS in hypertension.

Also in the 1970s and with BHF funding, Dr Malcolm Waite developed assays to measure the levels of renin and angiotensin I and II in the blood[16, 17] and found a six-fold increase of these proteins in the blood samples of patients with chronic renal failure and hypertension. Dr Waite found these protein levels fall after bilateral nephrectomy (the removal of both kidneys), with the extent of the decrease related to a reduction in BP. At the time, the mechanisms of the increased BP in chronic renal failure were not fully established and the findings suggested an involvement of the renin-angiotensin system[18].

Today, several classes of drugs targeting the RAAS system are now routinely used to treat hypertension, including:

- ACE inhibitors: developed in the 1980s/90s, they prevent an enzyme (called angiotensin-converting enzyme) in the body from producing angiotensin II which can narrow blood vessels and increase BP. Lowering production of angiotensin II results in lower BP.

- Angiotensin receptor blockers (ARBs): developed in the 2000s/2010s, they reduce the action of angiotensin II by blocking the receptors angiotensin II acts on, which are found in the heart, blood vessels and kidneys. Blocking the activity of angiotensin II receptors can lower BP.

v. The role of calcium in blood pressure control

Calcium plays a variety of crucial roles in the body. In the early 1960s, research demonstrated that calcium controls muscle contraction; this includes the contraction of the heart and blood vessels, which is key for BP regulation[19].

BHF-funded researchers have contributed to the wealth of knowledge describing the role of calcium in the regulation of blood vessel contraction. They have also studied the effect of calcium channel blockers, drugs commonly prescribed to treat hypertension, which reduce blood vessel contraction by reducing the amount of calcium entering cells of the heart and blood vessel walls.

In the 1980s, BHF funded Dr Tony Raine and Dr John Ledingham at the University of Oxford, as well as Professor John Swales at the University of Leicester who found correlations between BP and abnormalities in calcium handling in a range of blood cells (red blood cells, immune cells, platelets)[20]. It was then hypothesised that these different blood cell types reflected a global variability of cell membrane capacity at regulating the transport of calcium in and out of the cells, including in blood vessels. Raine and Ledingham also found that in patients with chronic kidney failure, the concentration of calcium inside certain blood cells (platelets) was increased and was associated with an increase in BP. However, patients treated with the calcium channel blocker nifedipine did not show elevation in intracellular calcium in platelets, nor in BP[21] . Their research contributed to better understanding the BP lowering effect of calcium channel blockers, as well as further evidencing the intricate links between various mechanisms involved in BP regulation.

vi. The nitric oxide pathway

Nitric oxide (NO), a substance produced naturally by the body, plays a significant role in regulating BP through its effects on blood vessels. BHF research has generated new insights into the synthesis and action of NO as well as its association with raised BP.

In 1986, NO was identified as the factor released by endothelial cells that induces relaxation of blood vessel smooth muscle. BHF Professor Andrew

Henderson in Cardiff contributed significantly to the identification of this factor as NO[22]. It was subsequently discovered that NO was generated from the amino acid arginine by the enzyme nitric oxide synthase[23]. NO dilates blood vessels by activating the enzyme guanylate cyclase (sGC), which in turn produces a molecule called cGMP[24]. These discoveries were rewarded with the Nobel Prize for Medicine or Physiology in 1998.

In 1992, Professor Patrick Vallance discovered that asymmetric dimethylarginine (ADMA) inhibits NO synthase, the enzyme responsible for producing NO[25]. In 2003, work by BHF-funded researchers Professor Vallance and Professor James Leiper at University College London showed that an increase in ADMA produces adverse cardiovascular effects in humans, including an increase in BP[26]. Normally, the majority of ADMA is eliminated through active metabolism by dimethylarginine dimethylaminohydrolase (DDAH). In 2007 the team investigated the DDAH gene and showed for the first time that the loss of DDAH activity leads to reduced NO production and may cause heart and circulatory disease[27]. These findings are likely to be important in the search for new ways to optimise the health of our blood vessels.

vii. Novel pathways

More recently, BHF-funded researchers have studied novel mechanisms involved in the regulation of BP, identifying potential new therapeutic targets that could lead to the development of a new generation of BP lowering drugs.

Professor Tomasz Guzik, formerly at Emory University and then the University of Glasgow, discovered clear roles for one blood cell type (T cells) and inflammation in the development of hypertension[28]. In 2022, BHF funded Professor Guzik and Dr Sophie Saxton at the University of Manchester, who are both studying the role of interleukin-33, a molecule with inflammatory actions on T cells. Professor Guzik wants to find out whether interleukin-33 plays an active role in the development and/or vascular complications of hypertension, offering a potential new therapeutic target to decrease BP or the complications associated with hypertension. On the other hand, Dr Saxton is studying the potential beneficial effect of interleukin-33 in pre-clinical model of obesity-mediated hypertension. Both projects will help better understand the role of this molecule in hypertension.

Professor Rhian Touyz, who was BHF Chair of Cardiovascular Medicine at the University of Glasgow until 2021, has been studying the role of the Nox5 enzyme in hypertension, which she found to be partly responsible for producing higher levels of free radicals in blood vessels, causing inflammation[29]. She also showed that Nox5 expression is increased in arteries from hypertensive patients[30]. A better understanding of how Nox5 affects blood vessels and its

role in the development and/or complication of hypertension could help identify new ways of treating it.

b. Risk factors for high blood pressure

In most cases, there isn't a single specific cause of high BP. However, there are factors that can increase risk of high BP, including lifestyle, genetics or medical conditions. BHF has funded research to understand why some people are at a greater risk of high BP, which plays a crucial role in prevention efforts.

i. Diet

Over the years, evidence has built supporting a close relationship between diet and hypertension, with a particular focus on salt intake. Since its inception, BHF has funded research to understand how specific dietary factors, including salt, affect blood pressure.

In the early 1980s, BHF funded Dr Julian Tudor-Hart at his practice in Glyncorrwg, Wales, the first GP practice in the UK to be recognised as a research practice. Dr Tudor-Hart was interested in understanding whether a family history of hypertension represented a greater sensitivity to sodium-induced high BP. He compared salt (sodium chloride) intake between the children of hypertensive and normotensive parents. His research found that individuals with high BP in their families are more likely to have higher systolic pressure, but their sodium intake and kidney function related to sodium handling were not significantly different from those without a family history of high BP[31]. He also studied the effect of sodium restriction in those with and without a family history of high BP and found no differences in BP in either of the groups, providing evidence that those with a family history of high BP aren't more susceptible in their BP response to dietary sodium[32].

Other BHF-funded studies have helped strengthen the evidence linking high salt intake to hypertension. One notable example is the INTERSALT study from the late 1980s, which involved 10,079 participants across 32 countries. The study found a clear association between sodium intake (or urinary sodium excretion) and age-related increases in blood pressure, suggesting that higher sodium consumption contributes to rising blood pressure over time[33].

BHF-funded research has also highlighted that changes in diet could improve blood pressure. A BHF funded clinical trial at Queen Mary University of London provided the first evidence that drinking beetroot juice daily could reduce BP in patients with hypertension[34]. The level of reduction was similar to that from

some forms of BP medication. The effect is caused by the high levels of nitrates, which are found in high quantities in beetroot and other leafy green vegetables. A study on many more patients is needed before this approach can become a recommended treatment for high BP.

BHF also part-funded a meta-analysis of over 70,000 participants, linking increasing alcohol consumption with cardiovascular conditions including fatal hypertensive disease, caused by long-term high blood pressure[35].

In addition to funding research on the health impacts of diet, BHF has also funded behavioural studies aimed at changing shopping habits to improve cardiovascular health. In 2017, BHF funded Professor Susan Jebb at the University of Oxford to develop a smartphone app to encourage healthier grocery purchases. In initial testing with 947 hypertensive people, offering lower-salt swaps led to a significant reduction in salt content in their shopping [36]. This success led to the development of the SwapSHOP app. The app allows users to scan UK supermarket products to better understand the nutritional information and receive healthy swap suggestions. A 2024 pilot study showed users reduced sugar and saturated fats in their shopping through SwapSHOP[37]. However, there appeared to be reluctance to reduce salt. Despite this, high engagement suggests SwapSHOP could be scaled as a low-cost tool to help reduce hypertension and other cardiovascular risks.

ii. Ethnicity

Ethnicity has been identified as a significant factor influencing the risk of developing hypertension[38], contributing to health inequalities. The reasons behind this connection are complex and not fully understood. BHF has supported several projects that investigate the relationship between ethnicity and hypertension to help tackle health inequalities.

The Southall and Brent Revisited (SABRE) study led by Professor Nish Chaturvedi, investigated the health of a group of nearly 5,000 people of European, South Asian, African and African Caribbean backgrounds. This work revealed ethnic differences in hypertension rates[39], blood pressure control, and medication use[40].

The AIM HY (Antihypertensive Investigation of Medicines in Hypertension) study was co-funded between BHF and the Medical Research Council in 2015. The results found higher aldosterone levels in Africans in Europe than White Europeans, possibly due to differences in potassium intake. Aldosterone could contribute to the higher ventricular mass and greater hypertension risk observed in Africans in Europe[41]. More recently, the AIM-HY programme has explored differences between Black, South Asian and White participants in responses to single-drug and dual-combination antihypertensive therapies. This could go on

to inform clinical recommendations, towards more personalised and effective blood pressure treatment.

In 2024, BHF awarded a fellowship to Dr Lydia Simpson at the University of Bristol to investigate why Black African Caribbean (BAC) women are more at risk of high BP than White women, contributing to greater risk of hypertension-related mortality[42]. In this project she will study why BP is higher in BAC women during stress and what effect stress has on the brain blood vessels and tissues. If successful, this research will shed light on the underlying mechanisms of BAC women's high BP and could lead to better management of risk in BAC women – a big step forward in addressing health inequalities in the UK.

iii. The influence of sex

Blood pressure is partly controlled by how much the muscle cells in the blood vessel walls contract, narrowing the vessels. With BHF funding, Professor Iain Greenwood's team at St George's University of London found that a protein called a Kv7 potassium channel helps keep muscle cells relaxed, allowing vessels to stay open[43]. In male rats with high BP, these channels were degraded, leading to narrower vessels. However, in female rats the channels were less degraded and functioned more normally. A BHF-funded PhD project in 2018 explored why this sex difference exists. It found that kv7 channels behave differently depending on biological sex and vary across the female oestrus cycle [44, 45]. These findings reveal important sex-dependent aspects of artery control that may have implications for disease onset and therapeutics.

iv. Genetics

Genetic factors are thought to contribute to approximately 30-60% of BP variation between individuals[46]. There are many genes that have been identified as potential contributors to hypertension, many of which BHF has had a role in discovering.

Genome-wide association studies

Genome-wide association studies (GWAS) scan entire genomes of large numbers of subjects to help to identify genes associated with a particular trait or disease.

Over the past 20 years, there have been substantial advances in understanding the genetic basis of hypertension through GWAS. Several notable studies have been supported by BHF including:

- A 2011 GWAS in 200,00 individuals[47], part-funded by BHF (15 grants), identified 16 novel loci associated with blood pressure. Six of these contained genes previously known or suspected to have a role in regulating BP, including loci related to the renin-angiotensin system. The other ten provided new clues into BP physiology, for example, two had connections to BP via genes implicated in renal physiology or kidney disease.
- A 2018 GWAS of over one million people (the largest of its type)[48] identified 535 novel BP loci using data from the UK Biobank (a resource co-funded by BHF). The study also identified several BP associated loci that are also associated with lifestyle traits.
- In 2021, research led by Professor Maciej Tomaszewski at The University of Manchester led to the discovery of 179 kidney genes contributing to risk of hypertension, with around 80% of these never before associated with hypertension[49]. Some of these genes can be targeted by existing medicines, creating new opportunities to treat the condition. Professor Tomaszewski is now utilising a new method of prediction of kidney gene activity, and will use new analytical methods to understand how these genes lead to some groups of people having a greater risk of high BP. His research group also plan to identify if the hypertension-related genes could be a therapeutic target, leading to the development of new BP lowering medications.

These GWAS studies have led to a greater understanding of how genetics influences hypertension risk. These insights could be used in spotting those at higher risk of developing hypertension, helping to identify new therapeutic targets to treat hypertension and informing a personalised approach to the treatment of high BP.

Rare-variant analyses

Genetic studies of blood pressure have mainly analysed common genetic variants. In 2020, BHF-part-funded research based at the University of Cambridge and around the world studied the genetic make-up of 1.3 million people with diverse ancestries, and found 106 new regions of DNA and 87 new rare genetic variations associated with BP[50]. The importance of the work is illustrated by the finding that six of the genes identified in this study, four of which contain rare variants, are already drug targets for heart and circulatory conditions. This suggests that the other genes identified may also be good targets for developing new drugs.

Predicting drug responsiveness

Since 2006, BHF has funded Professor Sandosh Padmanabhan's team at the University of Glasgow, who have focussed their research on the genetic determinants of BP response. The team have a particular interest in the gene that codes the hormone uromodulin, which is thought to play a part in controlling BP through its effects on the kidney. Working alongside Professor

Dame Anna Dominiczak and Dr Lesley Graham, the team identified two crucial novel pathways that are potential targets to modify uromodulin action on salt transport and consequently blood pressure[51]. In 2016, BHF funded a clinical trial led by Professor Padmanabhan to find out if people with uncontrolled hypertension who have a genetic variant in the uromodulin gene respond better to a class of drugs called loop diuretics than those without the variant. In 2024, the study reported that after treatment with torasemide (a common loop diuretic), participants with two copies of the genetic variation experienced a 5% reduction in BP. Those with only one copy of the variation, or no variation at all, saw a smaller 2.3% reduction[52].

These results offer hope that personalised BP treatment based on a patient's genetic profile could be key to helping people with uncontrolled hypertension in the UK. Now larger trials are needed to confirm whether torasemide and other loop diuretics could be a significant new tool to combat uncontrolled hypertension.

v. Early life influences

Knowing more about how a mother's health affects her child's health could help women planning a pregnancy or who are pregnant, to make the best decisions for themselves and their child's health.

A growing body of evidence shows that obesity during pregnancy affects long-term cardiovascular health of the children. In 2010, BHF awarded an Intermediate Basic Science Research Fellowship to Dr Anne-Maj Samuelsson who studied the developmental origins of hypertension in offspring of obese rodents. Dr Samuelsson found that maternal obesity leads to hypertension in young offspring prior to their own obesity[53]. This was linked to a surge of leptin, the hormone produced by fat cells, in early postnatal life. She also found that the central melanocortin system plays a key role in the early origins of hypertension[54], presenting a possible new target for intervention.

In 2011, Professor Paul Leeson at the University of Oxford was awarded a Senior Clinical Research Fellowship to investigate how early life influences, such as being born prematurely, could affect heart health later in life. Previous research found that young adults who were born prematurely because their mothers had severe problems with their BP during pregnancy have higher BP themselves[55]. Work by Professor Leeson and BHF Intermediate Basic Science Fellow Dr Adam Lewandowski discovered that the offspring of hypertensive pregnancies have abnormalities in their blood vessels, and their hearts develop differently, particularly if born early, so as adults they have smaller thickened hearts[56]. These insights could help spot those at risk of hypertension and design interventions to reduce their risk.

c. High blood pressure and pregnancy

i. Hypertensive pregnancy

For one in ten people with high BP, a specific cause can be found and removed: a Conn's syndrome nodule[57]. Conn's syndrome, or primary aldosteronism, describes a benign nodule in one of the adrenals glands that sit on top of the kidneys and produce steroid hormones, including aldosterone. This hormone boosts salt retention by the kidneys, raising BP. As a result, Conn's syndrome typically leads to drug-resistant hypertension and raises the risk of stroke and heart attacks compared to other high BP cases.

A study part-funded by BHF and led by Professor Morris Brown at Queen Mary University of London discovered a new type of primary aldosteronism caused by the coincidence of a unique pair of new genetic variants which always occur together[58]. The patients are women, who present with sudden onset of high BP and low blood potassium in the early months of a pregnancy. It also emerged that the new gene variants switch on a protein in the adrenal gland cells which recognises the pregnancy hormone Human Chorionic Gonadotropin (HCG) - the hormone measured in routine pregnancy testing - and that the protein triggers a surge of aldosterone production. As mentioned, aldosterone raises blood pressure by increasing salt retention.

Pre-eclampsia

Pre-eclampsia is a very serious condition in pregnant women, where a severe rise in BP is accompanied by the presence of proteins in the urine. Pre-eclampsia affects up to one in 25 pregnancies in the UK. Research suggests that the condition doubles the risk of coronary heart disease, stroke and heart attacks[59] and quadruples the risk of high BP later in life[60]. BHF has been funding research to understand how pre-eclampsia develops, to try to discover new treatments.

Research has shown that endothelial cells do not function properly in women with pre-eclampsia. With BHF funding, Professor Paul Leeson and his team at Oxford are looking into the role of a molecule called BH4 which is important for the normal function of endothelial cells. Their previous research demonstrated that a deficiency in BH4 can induce pre-eclampsia in pregnant mice. They also identified that elevating BH4 levels through dietary supplementation with 5-MTHF, a form of folate metabolised into BH4 by the body, can restore endothelial cell function and maintain normal BP levels[61]. BHF is currently funding a small clinical trial to test whether giving 5-MTHF to pregnant women with pre-eclampsia can protect the endothelial cells and help control their BP by stabilising BH4 levels. The researchers also aim to determine to what extent the

stabilisation of BH4 levels during pregnancy influences foetal endothelial cell function. These results have the potential to revolutionise pre-eclampsia prevention and treatment, reducing the risk to mother and baby both during pregnancy and in later life.

After women with pre-eclampsia give birth, their BP can remain high for weeks or months, and the damage in their body can be long-term. These women are at higher risk of cardiovascular diseases in later life[59, 60]. In 2017, Professor Leeson's team showed that giving new mothers a BP monitor to take their own readings for the first month or two after the birth, together with a smartphone app that advises what medication to take in response to the readings, results in lower BP six months after the birth compared to those who received usual care[62]. Following up these women four years later, the team reported in 2021 that this sustained reduction in BP remained for up to four years[63]. They found that diastolic BP was on average 6.8 mmHg lower in women who had self-managed than those who received usual care. A larger 2023 study, involving 220 new mothers who had experienced hypertensive pregnancies, found that daily self-monitoring and personalising medication doses led to lower BP and fewer hospital readmissions compared to usual care[64]. A larger trial is set to assess how best to deliver BP self-monitoring to more women after a hypertensive pregnancy across the NHS.

d. The risks of high blood pressure

High BP puts extra strain on the blood vessels, heart and other organs, such as the brain, kidneys and eyes. Persistent high BP can increase the risk of a number of health conditions, such as heart failure, atrial fibrillation, chronic kidney disease, heart valve diseases, aortic syndromes, and dementia, in addition to coronary heart disease and stroke.

BHF supported the Prospective Studies Collaboration, a collaborative meta-analysis of 61 prospective studies of vascular risk factors and cause-specific mortality. The study, published in 2002, found that BP is a major risk factor for ischaemic heart disease, stroke and other vascular causes of death both in middle and in old age, with about a halving in risk for every 20 mmHg lower usual systolic (or 10 mmHg lower diastolic) BP[65].

Other BHF studies in this area include work by Professor Kazem Rahimi from the University of Oxford, who found that long term exposure to elevated BP is associated with an increased risk of valvular heart disease[66]. In Glasgow, BHF-funded work by Dr James McLenachan looked at the role of hypertension in ventricular arrythmias[67].

In 2023, BHF-funded research led by Professor Tomasz Guzik at the University of Edinburgh, identified specific brain regions damaged by high BP that may contribute to cognitive decline and dementia[68]. Using brain scans and genetic

data, the team found that high BP affects brain areas like the putamen and white matter, regions responsible for crucial functions such as regulating movement and learning. This may be how high BP increases the risk of developing conditions like vascular dementia and Alzheimer's disease. These findings suggest that scanning these regions of the brain could help identify those at higher risk and lead to more personalised treatments, better protecting cognitive function in patients with high BP.

3) Influencing clinical guidelines and practice

a. Diagnosing hypertension

i. A new tool for diagnosing drug resistant hypertension

Conn's syndrome is the most common single cause of hypertension, accounting for 10% of all cases[57] and 20% of treatment-resistant hypertension[69]. Despite its prevalence, it's estimated that fewer than 1% of patients are identified and fully investigated due to the invasive nature of the standard test, known as adrenal vein sampling. It's a difficult and complex procedure which often fails to confirm the diagnosis.

In 2007, BHF funded research at the University of Cambridge to develop a new imaging technique to simplify the diagnosis of Conn's syndrome. Building upon work previously done by Swedish researchers, BHF-funded researchers developed a simple, non-invasive PET-CT scan using a radiotracer that lights up and identifies the responsible tumours[70]. The scan was tested in a clinical trial to compare the new test with adrenal vein sampling. Results from the study confirmed that the scan was as accurate as the old catheter test, but quick and painless. Researchers also found that, when combined with a urine test, the scan detected a group of patients who could come off all their BP medication after treatment[71]. This new 10-minute scan has the potential to save lives by identifying the nodules causing high BP so they can be removed.

b. Treating high blood pressure

i. Personalised approaches to hypertension treatment

People with high BP are commonly prescribed up to three types of different medications to lower their BP. However, it isn't always clear which drugs or

combination of drugs are best suited to each patient, with many still experiencing 'uncontrolled' BP. Several researchers across the UK, including Professor Morris Brown from Queen Mary University London and Professor Bryan Williams, BHF's first Chief Scientific and Medical Officer, came together to design a series of clinical trials to tackle this problem. The PATHWAY trials, funded by BHF, aimed to develop new, more personalised approaches to treating high BP.

From 2009 to 2014, the trials addressed several different issues surrounding the treatment of hypertension. PATHWAY-1 explored whether initiating treatment with a combination of BP lowering drugs was more effective than starting with a single drug. The trial concluded that beginning treatment with multiple drugs led to quicker and effective BP control without increased side effects[72]. PATHWAY-2 aimed to find the best 'add-on' treatment for people with uncontrolled high BP who were already on high doses of all three of the recommended types of BP medication. The trial found that spironolactone, a cheap diuretic, was by far the most effective 'add-on' medication[73]. PATHWAY-3 explored the use of a type of diuretic which does not cause potassium to be lost from the body, as there were concerns that diuretics may increase the risk of diabetes. The trial found that a combination of two diuretics – one that does lead to potassium loss, and one that doesn't – was more effective at reducing high BP compared with either drug alone[74].

The results of these three trials have influenced European and US guidelines for the management of hypertension. It is hoped that resulting changes in practice will help to improve the speed and efficiency of BP control in people at risk of heart attacks and strokes.

ii. Blood pressure medication in the over 80's

Previous hypertension treatment trials excluded people over the age of 80 because of concerns that the risk of side effects from these drugs outweighed the benefits. This resulted in unclear guidelines for doctors to follow.

Professor Christopher Bulpitt at Imperial College London was part funded by BHF to determine whether it was safe to prescribe BP medication to patients in this age group. The 'Hypertension in the Very Elderly Trial' (HYVET) study was the first of its kind and recruited over 3,500 participants, taking place in 195 centres across 13 countries[75]. The trial randomly assigned participants to take either BP lowering drugs or a placebo. The study was stopped early in 2007 due to strong and promising results.

The results showed that the people receiving BP medication had a clear reduction in the rate of stroke and death from any cause. Treating hypertension in this age group was associated with a 30% reduction in the rate of fatal or nonfatal stroke; a 21% reduction in the rate of death from any cause; a 23%

reduction in the rate of death from heart and circulatory events; and a 64% reduction in the rate of heart failure. Importantly, Professor Bulpitt showed that there was no increase in drug side effects within this age group.

The HYVET trial helped to shape clinical guidelines for doctors in the UK and worldwide, and provided a safe, effective treatment option for patients who are over 80. It was also named 'Trial of the year 2008' by the Society for Clinical Trials, recognised for its major impact in "providing the basis for a substantial and beneficial change in healthcare".

iii. What is the best time of day to take anti-hypertensive drugs?

BHF funded Professor Tom Macdonald at University of Dundee who led a trial to definitively test whether the time BP medication is taken impacts its effectiveness in preventing cardiovascular events.

BP levels naturally follow a daily cycle, falling during sleep at night and rising again in the morning. However, people with high BP might not experience a fall in BP during the night. Those without a normal pattern of BP variation between the day and night are thought to be at a higher risk of a cardiovascular event. This concern led to the hypothesis that taking BP tablets at night, rather than in the morning, could help restore a natural BP rhythm and reduce the risk of cardiovascular events. Whilst some studies have explored this, more conclusive evidence was needed.

Professor Macdonald's trial involved over 20,000 people taking at least one medication to lower their BP. Half were asked to take their medication in the evening and the other half in the morning. Participants were monitored for five years. The trial found that BP medication was equally effective at helping to prevent heart attack, stroke and vascular death whether it was taken in the morning or evening[76]. The results of this study mean that the many people taking these medications can be confident that they are helping to protect their health, whatever time of day works best for them to take their tablets.

c. Preventing high blood pressure

i. Long term use of paracetamol and its impact on blood pressure

In 2014, Professor David Webb at the University of Edinburgh led a study investigating the effect of acetaminophen, more commonly known as paracetamol, on BP. Anti-inflammatory drugs (NSAIDs), such as ibuprofen, can increase BP and increase the risk of having a heart attack or stroke. As a result, patients with hypertension are advised against taking them. Paracetamol was

often suggested as a safer alternative to NSAIDs and is the most used painkiller worldwide. However, previous observational studies have reported associations with increased cardiovascular events.

Due to decreasing confidence in paracetamol benefits and increasing concerns about it exacerbating high BP, there was a need for data that could effectively address this safety concern. BHF funded Professor Webb to lead a study that compared the effect of paracetamol versus a placebo on the BP of patients with hypertension. The trial ran from 2014 to 2019 and recruited 110 participants who were on at least one anti-hypertensive medication. Participants were randomly assigned to either receive regular doses of paracetamol or receive a placebo.

The study produced some concerning results, highlighting that after 2 weeks of taking paracetamol, hypertensive participants had a clear increase in their BP. The rise was comparable to NSAIDs effects and might be expected to increase the risk of heart disease or stroke by around 20%[77]. Dr Webb's study was successful in identifying the relationship between paracetamol and BP, with the results urging doctors to be more cautious when recommending paracetamol, especially to those who have hypertension or increased cardiovascular risk.

4) Innovating healthcare delivery

Improving the detection and management of high BP in the UK has been a focus of BHF, and much of its work has influenced UK policy. Nationally, NHS England work is heavily influenced by BHF-led work. As such, BP testing and management is also an ongoing priority for NHS England, and for the National Clinical Director (NCD) for cardiovascular disease (CVD) prevention.

i. Blood Pressure Award Programme

In 2017, BHF created the Blood Pressure Award Programme[78] to gain insights and ideas for how the UK could improve identification and care of patients with hypertension. BHF awarded £1.5m to 14 sites across the UK, from local councils to clinical commissioning groups (CCGs) and public health collaboratives. Funding went to sites that demonstrated evidence of unmet need locally, such as high rates of cardiovascular disease, premature mortality, or health inequalities. Hypertension must also be a local priority within these sites.

The aim of providing funding was to:

- Increase detection and management of people with undiagnosed hypertension.
- Improve access to BP testing in the community.

- Strengthen support for patients to manage their high BP.
- Empower people to test their BP routinely.
- Add to the evidence base on the detection and management of hypertension and how new ideas are adopted.

The Blood Pressure Award Programme consisted of two rounds, the first consisted of £700,000 awarded to 7 sites and ran from 2017 to 2021, the second ran from 2019 to 2021. The programme ended in 2021 due to the pandemic.

With a focus on local community delivery, the programme has improved access to BP testing across the UK, particularly in underserved populations. The programme evaluation showed that over 31,529 people had their BP checked[79], with around 5080 people found to have high BP. Subsequently, at least 258 of these went on to receive a formal diagnosis of hypertension. Also, 9725 referrals were made by the programme sites to behavioural change interventions, including smoking cessation services, cookery clubs and weight loss groups. The programme had a positive impact on participants, by increasing awareness and confidence around BP. And for medical staff and services, the programme increased awareness of potential hypertension cases and knowledge of managing high BP.

The programme has directly influenced national policy, as reflected in the new community pharmacy contract, which includes government payment for BP testing and diagnoses. The establishment of the NHS England Blood Pressure @home initiative, which has seen over 220,000 home BP monitors distributed since October 2020, has also been delivered in close collaboration with the BHF[80]. The programme also inspired NHS England's community pharmacy-based BP testing, known as the 'hypertension case finding service'. This programme is now rolled out nationally, aiming to carry out 2.5 million BP checks a year[81].

In Scotland, the success of phase one sites led to the Scale Up BP initiative, expanding remote BP monitoring in partnership with the Scottish Government (2019-2021). Over 30,000 people joined the app-based programme, increasing remote monitoring reach in Scotland from 1.6% to 5% of those with hypertension, and successfully reduced average BP[82]. The approach also saved an estimated £629,000 in appointments. Dr Janet Hanley was funded by BHF to investigate patient experiences, providing additional evidence that BP telemonitoring improved access to routine care and motivation to self-manage hypertension during the COVID-19 pandemic[83]. BP testing and management remains an ongoing priority for NHS England, NHS 24 (Scotland), and for the NCD for CVD prevention.

ii. New resources on high blood pressure

Since early 2022, BHF has created a suite of resources about high BP targeted at a range of audiences, including patients and healthcare professionals. The resources include statistics on the prevalence of high BP in their local region and included recommendations on how to improve the detection and management of hypertension. BHF produces and distributes these resources on a request basis and has sent over 10,000 copies so far, allowing GP surgeries to better understand the prevalence of high BP in their communities and help ensure the detection and management of high BP is a priority for primary care staff. BHF has produced two more versions of this resource, one sent to 42 Integrated Care Boards (ICB), and one sent to all 533 English MP's, which was used for policy engagement during the 2022 Conservative and Labour conferences.

5) Influencing policy

i. Reducing the UK's salt intake

Working-age adults in England consume an average of 8.4g of salt per day, which is 40% above the UK's recommended maximum intake of 6g per day, and almost 70% over the World Health Organization's (WHO) 5g per day recommendation[84]. A 2023 poll by YouGov on behalf of BHF showed that 65% of British adults are not confident estimating their daily salt intake[85].

BHF is strongly advocating for the adoption of the World Health Organisations (WHO) recommended daily salt intake of 5g. In 2022, BHF commissioned a report that investigated what would happen if every adult in the UK met the WHO's salt consumption guidelines by 2030[84]. The report published groundbreaking findings, including predictions that there would be 1.4 million less cases of high BP and approximately 450,000 more years living in perfect health. Meeting these targets could prevent 135,000 people from developing coronary heart disease and more than 48,000 people from developing strokes. The study proceeded to investigate the effects of less salt consumption on the UK economy. It was estimated that the UK could save £11.4 billion by 2035 if people consumed less salt. £6.7 billion could be direct healthcare cost reductions, with 70% linked to hypertension. People would need the NHS less and the public would be more productive, because of better health and fewer needing to care for loved ones.

ii. Supporting the sugar tax

Just as excess salt contributes to high BP, so too does excess sugar, primarily through its role in driving obesity. Obesity accounts for around 26% of hypertension cases in men and 28% in women[86]. To tackle this, BHF works in partnership with the Obesity Health Alliance to prevent obesity and improve public health.

BHF-funded research played a key role in the introduction of the UK's sugar levy. In 2016, Associate Professor Peter Scarborough and his team in Oxford demonstrated how reducing sugar—especially in soft drinks—could lower obesity and heart disease rates[87]. Their findings helped shape the decision to introduce the Soft Drinks Industry Levy (SDIL). The levy came into effect in 2018, incentivising companies to reduce sugar in soft drinks, lowering sugar in diets across the population[88].

In 2023, BHF joined a major new campaign, Recipe for Change, calling for UK government to build on the success of the SDIL by introducing a levy on unhealthy food to encourage businesses to make products healthier, and invest the revenue in children's health and access to good food.

6) Improving people's lives

Up to 90% of adults will develop hypertension over their lifetime, representing a huge public health burden[89]. If left untreated, hypertension can lead to life-threatening complications, with around 50% of heart attacks and strokes in the UK associated with high BP [3]. BHF-funded research, healthcare innovation and influencing work is helping to advance how we prevent, diagnose, and manage high BP, for better health outcomes in the UK and beyond.

Increasing detection

Hypertension is common - in the UK, around 1 in 3 adults currently have high BP, and around 30% of these cases are undiagnosed[3]. If hypertension is detected early, timely changes can be made to lifestyle and medication to reduce the risk of heart attacks, strokes and cardiovascular deaths. BHF has played a key role in improving access to blood pressure checks, supporting over 30,000 people through community-based programmes like the Blood Pressure Award Programme[78]. More recently, BHF has funded research into technological innovations that could predict hypertension early. BHF-funded researchers at Imperial College London have developed AI-enhanced ECGs that can identify patients at risk of hypertension and further complications[90]. This approach could be applied in healthcare settings to identify patients who would particularly benefit from further monitoring and behavioural intervention recommendations, to reduce their risks of cardiovascular events. There has been no national increase in diagnosis of hypertension reported in those

unaware of their condition between 1994 and 2019[91] but BHF's efforts across community testing and novel diagnosis technologies have the potential to reduce underdiagnosis for years to come.

Reducing risk: prevention and management

BHF-supported research has shown that lowering blood pressure can significantly reduce the risk of strokes, heart attacks, and heart failure. Combining research from 48 randomised clinical trials of 344,716 participants, a meta-analysis part-funded by BHF found a 5 mmHg reduction of systolic BP reduced the risk of major cardiovascular events by around 10%, even in those without diagnosed hypertension[92]. A 10 mmHg reduction in BP could reduce the risk of heart attacks by 20%, strokes and heart failure by 27-28%, and death from any cause by 13%[93].

BHF supports risk reduction through public awareness, clinical resources, and behavioural tools. It's programmes have increased community knowledge and confidence, including through the Blood Pressure Award Programme[78] and resource sharing with over 10,000 GP surgeries. Innovations such as the SwapSHOP app[37], developed by BHF-funded research[36, 94], have the potential to support healthier food choices. Across its initiatives, BHF has built the confidence and knowledge of medical professionals and the public, empowering them to reduce risks of high BP and manage high BP if this does develop, towards decreasing their risk of cardiac events.

BHF is passionate about fair treatment of cardiac conditions, with recent funded research focused on supporting groups at high risk of hypertension, including Professor Leeson's work to tackle hypertension management in pregnant women and new mothers [61-63], and Dr Simpson's new project investigating mechanisms of increased hypertension risk in Black African Caribbean women.

Towards more effective and personalised treatments

BP lowering medications are among the most widely prescribed in the UK. In 1940s-1950s, high BP medications had undesirable side effects, such as fainting[95]. BHF has played a pivotal role in generating knowledge of the various mechanisms involved in hypertension and how these are affected by a range of now widely used anti-hypertensive medications, including beta-blockers, ACE inhibitors and Angiotensin Receptor Blockers (ARBs)[9-18]. BHF research has also informed which drugs should be given to which patients. BHF-funded clinical trials helped to change treatment guidelines, by showing the benefits of treating high BP in very elderly people through the HYVET trial [75]. Whilst for resistant hypertension, the PATHWAY-2 trial found an effective 'add-on' treatment, spironolactone[73]. These breakthroughs have transformed the way hypertension is treated worldwide.

Recognising that no two people are the same, BHF-funded researchers are now focused on personalising treatment strategies, developing new ways to identify and treat underlying causes of high BP tailored to each person's unique biology and lifestyle. BHF-funded research found that patient genetics can inform how effective certain drugs will be in treating high BP, in this case linking the uromodulin gene variant with efficacy of torasemide treatment[52]. Personalised treatment approaches like these promise more effective BP control and better long-term health outcomes for millions of people.

7) Conclusion

Over the past six decades, BHF-funded research has transformed our understanding of high BP, from uncovering its complex biological mechanisms to pioneering more effective and personalised treatments. Partly thanks to BHF, we are seeing blood pressure burden decreasing in Western Europe, with approximately 3% decrease in loss of years of healthy life (disability-adjusted life years, DALYs) due to high systolic pressure per year (2000-2021)[96] , with a slight reduction (1.5%) in hypertension cases in England between 1994 and 2019[91]. Across England's population, average systolic BP has dropped by around 8.5 mmHg and diastolic BP by 4 mmHg since 2000, and to greater extents in those diagnosed with hypertension, with average drops of 12 mmHg systolic and 4 mmHg diastolic[91]. Improvements in BP control may have contributed to the decrease in cardiovascular events in the UK, with a 46% reduction in hospital admissions for coronary heart disease between 2004 and 2024[97]. Together, these reductions in hypertension burden have been reached through innovative approaches to hypertension prevention, diagnosis and management which have been partially fuelled by BHF research.

Yet, despite this progress, high systolic pressure remains in the top two contributors to loss of years of healthy life (DALYs) in Western Europe and worldwide[96]. Hypertension continues to be one of the most significant and preventable causes of heart attacks and strokes, with up to 8 million people living with undiagnosed or uncontrolled hypertension in the UK today[3]. The World Health Organisation estimates that increasing people whose hypertension is under control to 50% could prevent 76 million deaths globally by 2050[98]. BHF is proud to be contributing to this global effort.

With continued focus on research, innovation and influencing, BHF is working towards a future where high blood pressure is detected earlier, treated more precisely, and prevented more widely, for longer and healthier lives.

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