British Heart Foundation

Protecting the brain

Impact of BHF support for cerebrovascular research

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Protecting the brain: Impact of BHF support for cerebrovascular disease research

By Professor Joanna Wardlaw and Professor Philip Bath

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1) Introduction

Cerebrovascular disease refers to a group of conditions that affect blood flow to the brain. It includes stroke, mini-stroke (transient ischemic attack, TIA), cognitive decline and dementia, aneurysms, blocked, burst and malfunctioning arteries. Stroke is a very common type of cerebrovascular disease. It occurs when there is a sudden disruption to the blood supply to the brain. This can be due to a blockage in the blood flow to the brain (ischaemic) or sudden bleeding in the brain (haemorrhagic). A stroke typically lasts more than 24 hours. If the symptoms last less than 24 hours then it is called a TIA. A TIA is a medical emergency since it can be a warning sign that a major disabling stroke is imminent, and this can be prevented by rapid identification of the cause and starting the appropriate prevention treatment.

In the last 60 years, our understanding of cerebrovascular disease, including stroke, has changed dramatically. Arguably, stroke has gone from being one of the least treatable brain diseases up to the early 1990s, to the most treatable in current times.

In this impact thematic review, we will consider all the diseases which affect blood flow and the blood vessels in the brain. These include:

- **Ischaemic stroke** – a blood vessel supplying the brain or in the brain, mostly an artery, gets blocked, representing around 80% of all strokes(1).
- **Haemorrhagic stroke** – a blood vessel in the brain bursts and blood leaks into the brain at pressure and damages the brain – this can lead to immediate death and most survivors are severely disabled, representing around 15% of all strokes(1).
- **Subarachnoid haemorrhage (SAH)** – a blood vessel inside the skull but outside the brain bursts and blood leaks into the cerebrospinal fluid that bathes the brain – this is at high pressure and very irritant so can lead to immediate death. SAH is usually due to an aneurysm (small outpouching from an artery where the wall is weak) bursting. They represent around 5% of all strokes(1).
- **Cerebral small vessel disease (cSVD)** – a disease of the tiny blood vessels in the brain which can cause stroke, cognitive impairment and dementia, mood and mobility problems.

- **Vascular cognitive impairment and dementia (VCI, VaD)** – since stroke damages the brain, as well as causing physical disability it can also cause problems with thinking and memory. This occurs in up to 34% of patients at one year after a stroke(2), but is most commonly due to small vessel disease.

The size and breadth of the problem of cerebrovascular disease

About one in four people will have a stroke at some point in their life[1]. Stroke is the second commonest cause of death worldwide, and the commonest cause of dependency in adults(3). There are about 12.2 million strokes per year worldwide, about one every three seconds, of whom about 6.5 million die from the stroke[2]. There are more than 100,000 strokes in the UK each year. That's a stroke every five minutes[3].

There are about 100 million stroke survivors around the world, of whom approximately a third will be dependent on others for essential daily support. In the UK, stroke is the single biggest cause of severe disability[4]. The cost of cerebrovascular disease is huge, to individuals, their families and society. The World Stroke Organisation estimates that the cost of stroke (not including VCI or VaD) to the global economy in 2017 was US$891billion (about 1.12% of global GDP)(4). A large proportion of strokes, perhaps as much as 90%, are linked to 10 major modifiable risk factors, offering substantial potential for prevention(5).

Vascular cognitive impairment and dementia

We now realise that disease of the brain's blood vessels can affect people more gradually and lead to subtle functional issues and problems with thinking and memory, and ultimately may cause vascular dementia.

There are around 47 million people living with dementia worldwide, although that is likely to be an underestimate since dementia may go undiagnosed in a close family setting(6), and the number does not include cognitive impairment that falls short of frank dementia. Alzheimer's disease is the commonest cause of dementia, followed by vascular disease (about 20% of dementias)(7).

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[1] https://www.world-stroke.org/assets/downloads/WSO_Global_Stroke_Fact_Sheet.pdf
[2] https://www.world-stroke.org/assets/downloads/WSO_Global_Stroke_Fact_Sheet.pdf
[3] https://www.bhf.org.uk/-/media/files/for-professionals/research/heart-statistics/bhf-cvd-statistics-uk-factsheet.pdf
[4] https://www.mynewsdesk.com/uk/stroke-association/documents/state-of-the-nation-stroke-statistics-54459

Cerebral small vessel disease (SVD) is the leading cause of VCI and VaD. In mixed dementias, which are more common in older people, cSVD is the most prevalent blood vessel disease, contributing to up to 45% of all dementias, either alone or in combination with other pathologies. In mixed dementias, the blood vessel damage makes the dementia symptoms much worse than Alzheimer's disease alone.

There is increasing evidence that common risk factors for blood vessel diseases, such as hypertension, diabetes, and poor diet are major risk factors for both cerebrovascular disease and Alzheimer's disease. This indicates that there is a strong vascular component in Alzheimer's disease, and raises the possibility that better prevention and treatment of cerebrovascular and cardiovascular risk factors and disease will also help reduce the risk of Alzheimer's disease.

The role of BHF

BHF, founded in 1961, has been funding research into stroke since its earliest days and more recently into vascular cognitive impairment. Indeed, the first ever grant funded by the BHF in 1963 was for research into stroke ['A study of certain aspects of cerebral vascular disease' was awarded to Dr Enid Joan Acheson at North Staffs Royal Infirmary]. BHF-funded research has complemented cerebrovascular research across the UK and internationally. Partnership has been key to this, and the BHF has partnered with several national and international funders in the field.

In total, BHF has funded over 160 grants to study blood vessel diseases and the brain, totalling over £75M since 1961.

2) Generating new knowledge

a) Control of cerebral circulation

Cerebral circulation is the movement of blood through a network of arteries and veins supplying the brain. Blood carries oxygen and nutrients to support brain function and removes waste. The cerebral circulatory system incorporates safeguards such as autoregulation of the blood vessels to prevent any interruption in blood supply to the brain, which can lead to damage. If these protective measures fail, it can result in a stroke.

i) Regulation of the cerebral circulation

In 2019, BHF funded Dr Alyson Miller and colleagues at the University of Glasgow to understand the roles of regulatory enzymes DDAH in the brain's circulation. DDAH enzymes are important for preserving the health of blood vessels around the body, they regulate the levels of a substance called ADMA in the body. ADMA has a number of damaging effects in the body, and high levels have been linked

to cerebrovascular disease. There is very little known about how ADMA and DDAH work in brain blood vessels. Using genetically modified mice that lack the DDAH enzymes, the team will determine how important these enzymes are for maintaining healthy brain blood vessels in normal conditions and after a stroke. This could lead to new medicines for the treatment of cerebrovascular disease, such as stroke.

ii) Studying the link between hypertension and Alzheimer's disease

Amyloid B peptide (Aβ) is a toxic substance that accumulates in the brain in Alzheimer's disease. It can cause blood vessels in the brain to narrow, making it harder for blood to flow through. The brain may respond by raising blood pressure to overcome the resistance. Studies in large groups of people have shown a link between middle-age high blood pressure and increased risk of developing Alzheimer's disease in later life(8). It has been assumed, because of the timeline of these observations, that the blood pressure leads to the brain damage.

With BHF support, Professor Seth Love and colleagues at the University of Bristol found in older people dying with Alzheimer's disease, that this potential blood pressure effect could be triggered by the brain and be mediated by a chemical known as endothelin-1. Professor Love's research suggests that the build-up of Aβ in the brain may cause high blood pressure (9-11). A similar theory that changes in the brain lead to high blood pressure has been proposed previously, although without providing a potential mechanism. These findings need to be repeated in people at earlier stages of Alzheimer's disease. If promising, this research could open the prospect of treatment of hypertension with drugs that block endothelin-1 receptors in the brain. However, caution is required when the hypertension may be protective and too aggressive treatment may make the brain blood flow worse. The work also suggest that drugs that block endothelin-1 receptors may be able to improve blood flow through the brain of people who are developing Alzheimer's disease and this has the potential to slow down the progression of the disease.

iii) Studying the link between atrial fibrillation and cerebrovascular disease

Atrial Fibrillation (AF) is a condition that causes an irregular and often fast heartbeat. AF is associated with a substantial risk of stroke, cognitive decline, and dementia. Understanding why AF leads to these conditions could help devise strategies to reduce the risk. One potential contributing mechanism is cerebrovascular dysfunction. With BHF funding, Dr James Fisher and colleagues at the University of Birmingham investigated whether brain blood vessels do not work properly in people with AF. Dr Fisher's previous work shown that the ability of the arm blood vessels to relax is impaired in AF patients, which led them to investigate whether the brain blood vessels are similarly altered in AF. The team found, in a small cross-sectional study, that the small brain blood vessels in

patients with AF may be less good at increasing brain blood flow in response to visual and similar stimuli compared to people of similar age without AF. These changes in the ability to match brain blood flow to demand may in part explain the increased risk of stroke in people with AF(12).

b) Genetics of stroke

Genetic factors can also affect the risk of stroke. These factors can be classified into two types: those caused by an abnormality in a single gene (monogenic) and those resulting from a combination of both genetic and environmental influences (multifactorial). In recent years, large-scale genome-wide association studies (GWAS) have enabled major progress in deciphering the genetic basis that increases the risk of stroke and its subtypes. Large collaborative efforts partly supported by BHF have contributed to this progress. This includes one of the largest published comprehensive stroke and stroke subtype GWAS meta-analysis to date (MEGASTROKE), which gathered over 67,000 stroke cases and discovered 22 new stroke risk loci (13). MEGASTROKE is now a part of GIGASTROKE. These insights can help to understand the causes of stroke, help to find new treatments, and identify those at risk of stroke.

i) Lacunar stroke

Cerebral small vessel disease (cSVD) is an umbrella term that covers a variety of abnormalities related to small blood vessels in the brain. cSVD is thought to cause around a quarter of strokes, so-called lacunar strokes. Despite its significance, there are currently very few treatments to prevent cSVD and there are no effective treatments to stop or slow the condition. To change this, researchers have worked to increase understanding of the pathophysiology of the disease, and one mechanism of doing this is through the study of genetics.

Professor Hugh Markus and his team at the University of Cambridge collected blood samples from around the world from people with lacunar stroke and identified genetic factors which increase the risk of SVD. The team have provided the first comprehensive genetic analysis of lacunar stroke and identified a number of novel genes predisposing to the disease(14). This has identified pathways that could be targeted therapeutically. Their GWAS study provides extremely useful data to apply further analytical techniques to look at causality in relationships and determine likelihood of successful therapeutic approaches. Professor Markus has received further BHF funding to continue this research. The team will now look to see whether genetics plays an important role in altering the risk of developing vascular dementia in people with SVD. By combining genetic data, brain scans and blood samples it will be possible to build a biological fingerprint of disease to help predict which patients are most likely to develop vascular dementia.

ii) Large vessel stroke

Large vessel stroke is caused by a blockage in one of the major arteries of the brain and accounts for up to 38% of acute ischaemic strokes. A variant in the Histone Deacetylase9 (HDAC9) gene has been associated with an increased risk of stroke (15), but researchers do not yet know why this is the case. BHF is funding Professor Hugh Markus and colleagues at the University of Cambridge who are trying to understand how variation of the gene HDAC9 increases the risk of stroke. The team are using stem cells from skin donated by people who've had a stroke and carry the HDAC9 stroke-prone variant. From the stem cells they have created blood vessel cells mimicking the patients' carotid arteries in the lab. They are studying how the variant changes the way blood vessel cells behave, compared to those carrying an unchanged HDAC9 gene. Their model has shown that HDAC9 overexpression causes dysfunction such as excess cell growth and impaired response to inflammation. They also found that the dysfunction can be reversed by treatment with HDAC inhibitors. The study has highlighted that the model is a useful tool for studying the effects of HDAC9 and could be applied to other genetic variants associated with stroke(16).

iii) Genetic risk and lifestyle

Lifestyle is an important modifiable risk factor for stroke. BHF-funded researcher Dr Loes Rutten-Jacobs investigated the association between genetic risk of stroke, lifestyle, and incident risk of stroke in over 300,000 people in a UK Biobank study. The study found that genetic and lifestyle factors were independently associated with risk of incident stroke. An unfavourable lifestyle was associated with a 66% increased risk of stroke compared with a favourable lifestyle, and this increased risk was present within any genetic risk category. These findings highlight the potential of lifestyle interventions to reduce risk of stroke across entire populations, even in those at high genetic risk of stroke(17).

iv) Telomere length and cerebrovascular disease

Telomeres are found at the ends of chromosomes and have a role in protecting chromosomes. Telomere length shortening is a known hallmark of cellular ageing and is associated with an increased risk of neurological and psychiatric disorders. BHF research has played a part in increasing understanding of the relationship between white blood cell (leucocyte) telomere length (LTL) and neuroimaging markers. A 2023 study using MRI scans of over 30,000 UK Biobank participants found that those with longer telomeres had larger grey matter volumes, and lower white matter hyperintensity volume, among other markers of vascular damage. Grey matter plays a crucial role in various brain functions such as memory, decision-making, and sensory perception. Whereas white matter hyperintensities are lesions that indicate blood vessel damage and an increased risk of cerebrovascular events and dementia. Longer telomeres were also associated with a lower risk of dementia but not stroke or Parkinson's disease,

suggesting a pathway by which longer LTL may confer protection against dementia(18). This study is the largest and richest study to date examining relationships between LTL and MRI markers of brain structure and function.

c) The role of inflammation in stroke

Stroke triggers a robust inflammatory response, which can cause further damage to the brain. With BHF funding, Professor Stuart Allan and colleagues at the University of Manchester have studied how a molecule produced by the body during inflammation, called interleukin-1 (IL-1), contributes to the inflammation and damage caused by stroke. The team investigated the role of central IL-1 (derived from the central nervous system) and haematopoietic IL-1 (derived from peripheral blood cells) in brain injury. They found that both central and haematopoietic sources of IL-1 added to ischaemic injury in mice. This provided the first evidence that central and peripheral IL-1 contribute to brain injury and suggested that inflammation and neuronal death after a stroke might be reduced by blocking peripheral IL-1 actions. These results may help to develop drugs targeted against the bad inflammation caused by IL-1 (19) (20), and IL-1 receptor agonists are now being tested in clinical trials in subarachnoid haemorrhage(21).

Dr Emmanuel Pinteaux and colleagues at the University of Manchester have also contributed to increased understanding of the role of IL-1 during post-stroke cerebrovascular inflammation. The team have studied the role of Pentraxin-3 (PTX3), a molecule produced by IL-1, that has important functions in repairing brain blood vessels. They found that PTX3 is a key regulator of new blood vessel formation (angiogenesis) in mice and is emerging as a promising target to improve repair of damaged blood vessels after stroke(22). The group also found that PTX3 regulates the movement of white blood cells (neutrophils) from blood into the brain during neuroinflammation, demonstrating the potential of PTX3 as a therapeutic target in neuroinflammatory conditions(23).

IL-1 is produced in response to a stroke as two different molecules – IL1 alpha and IL-1beta. Pinteaux's group are now investigating the specific role of these two molecules during post-stroke cerebrovascular inflammation using mouse models of stroke with the hope of developing new treatments.

d) Discovery of potential treatments for stroke and vascular dementia– animal studies

i) Restoring blood flow after a stroke – Avoiding the 'no-reflow' problem

A stroke can occur when a blood clot blocks a blood vessel in the brain (ischaemic stroke). Doctors can dissolve (thrombolysis) or physically remove some clots (thrombectomy), but sometimes, even after the clot has been removed, blood still may not flow properly into the brain blood vessels beyond the site of the clot, known as the 'no-reflow' problem. When this happens, the brain tissue

continues to suffer from a lack of oxygen and nerve cells can become further damaged, worsening the stroke and hindering recovery. Small contractile cells, called pericytes, may constrict the small blood vessels (called capillaries) and can cause no-reflow, but why they contract so persistently during and after stroke is not fully understood. With BHF funding, Dr Paolo Tammaro and his team at the University of Oxford have studied the mechanism by which pericytes contract, with the aim of finding ways to prevent 'no-reflow' from happening. They found that a protein called TMEM16A, that sits outside the pericyte and allows calcium in and out of the cell, is a crucial part of the way that pericytes may regulate normal brain capillary function, and may act abnormally after a stroke. TMEM16A may therefore be a potential therapeutic target for ischaemic stroke and other conditions of impaired blood flow, such as vascular dementia(24) and possibly even in Alzheimer's disease where brain blood flow is known to be reduced.

ii) Protective mechanisms of sulforaphane

When a person has a stroke caused by a blood clot in an artery in the brain, the clot can sometimes be broken down by clot-busting drugs. However, when this happens, molecules called free radicals travel into the blood-deprived part of the brain where they damage brain cells. Researchers from the King's College London BHF Centre of Research Excellence have been studying a molecule called sulforaphane, which is found in broccoli, to find out if it can be used to limit the harmful effects of these free radicals. Professor Giovanni Mann's team has discovered that sulforaphane can protect small blood vessels in rodent brains affected by stroke. They have shown that sulforaphane increases levels of the antioxidant protein Nrf2, which helps to mop up free radicals and thereby minimises tissue damage and protects the mouse brain(25). The team are now investigating a stabilised version of sulforaphane (SFX-01) in mice to better understand the drug's actions and give an idea of the best time to use the drug, whether that's before or after the stroke. The results of this research will be essential for the design of future clinical studies where sulforaphane could be tested in patients at risk of ischaemic stroke.

iii) Controlling von Willebrand factor as a treatment for stroke

Von Willebrand factor (vWF) is a molecule in the blood that is important for the formation of blood clots. Imbalances in vWF levels or activity can lead to excess bleeding or to too much clotting. To prevent unnecessary blood clots, the body uses a molecule called ADAMTS13 to control levels of vWF. Professor David Lane at Imperial College London and Professor Stuart Allan at the University of Manchester have investigated the possibility of ADAMTS13 as a treatment for stroke. They have discovered that ADAMTS13 needs a specific change to its structure to work efficiently. Studies using a mouse model of stroke have shown that the modified version of ADAMTS13 is more effective at breaking down blood

clots. These studies show that ADAMTS13 variants could be potential therapeutic options for the treatment of stroke.

iv) Repurposing blood pressure medication for vascular dementia

High blood pressure is a main modifiable risk factor for developing vascular dementia. However, the mechanism by which high blood pressure leads to vascular dementia has been unknown. In 2021, Dr Adam Greenstein and colleagues at the University of Manchester discovered that the blood pressure drug amlodipine could help restore blood vessel function in mice(26). This is because high blood pressure decreases the activity of the protein Kir2.1 that is present in cells lining the blood vessels and which increases blood flow to active areas of the brain. Amlodipine was found to restore the activity of Kir2.1 and improve blood vessel function which could protect the brain from the harmful effects of high blood pressure. It is thought that this protein could also be targeted by other drugs in the future, presenting a potential additional way to help prevent dementia. The results in mice are consistent with results of the TREAT-SVDs trial by Professor Joanna Wardlaw and colleagues that tested three blood-pressure lowering drugs in patients with cSVD who are at risk of VCI and VaD (amlodipine, losartan, atenolol). TREAT-SVDs showed that amlodipine improved brain small vessel reactivity compared with atenolol, as measured by the vascular response to inhaling 6% CO2 in air on Magnetic Resonance Imaging of the brain(27). This adds further support to continue the routine use of amlodipine and related drugs in clinical practice to treat high blood pressure on stroke and heart attack prevention, although it should be noted that benefit in terms of prevention of VCI and VaD has yet to be shown in large scale human trials.

e) Epidemiology

Around 1 in every 4 people will have a stroke at some point in their life. In addition, many people will develop 'silent' cerebrovascular disease that shows up on a brain scan but did not cause recognised stroke symptoms. For doctors and scientists to be able to prevent and treat stroke, and for government organisations to be able to plan health services, it is important to understand why stroke and cerebrovascular disease affects some people more than others.

The BHF has been funding important research into risk factors and causes of stroke and vascular disease since the 1980s. For example, we now know that around 50% of strokes and heart attacks are associated with high blood pressure[5]. Other studies focussed on the differences in the way that stroke affect people depending on sex/gender, ethnicity or socioeconomic backgrounds (29).

[5] https://www.bhf.org.uk/-/media/files/for-professionals/research/heart-statistics/bhf-cvd-statistics-uk-

Amongst these, BHF has funded large long-term ground-breaking studies such as the British Regional Heart Study, the British Women's Heart and Health Study (2006, 2009), the Caerphilly Study, and the Whitehall Study. The British Regional Heart Study (BHRS), funded by a number of BHF grants, began in 1978 and is a long-term cohort investigating the causes of cardiovascular disease in men in the UK. The study's aim is to find out why there was considerable variation in coronary heart disease, hypertension and stroke across the UK to better inform prevention strategies. The Whitehall II Study investigated the causes of social inequalities in health by recruiting 10,308 London civil servants aged 35-55 and has followed them up with regular health checks and questionnaires.

These studies have identified that factors such as smoking, lack of exercise, obesity (30, 31), diabetes and high blood pressure greatly increase the risk of developing blood vessel narrowing (plaque) and of having a stroke. In populations that are at high risk of stroke, e.g. in people whose parents moved to the UK from South Asia and who are at 1.5x higher risk of stroke compared to people whose parents were born in the UK, these factors can be far more deadly. They magnify the effect of each other (32). Diet(33), genetics(34), socioeconomics, health cultures, air pollution (35) and other factors are now known to play a role on both stroke and the risk of dementia(36, 37). This knowledge has led to better lifestyle advice(38), as well as new therapeutic approaches.

i. Identifying risk factors that predict future stroke risk

With BHF funding, Dr Alistair Webb and colleagues at the University of Oxford led a study that investigated ways to prevent stroke patients from experiencing another stroke, by identifying factors that could predict the likelihood of future strokes.

Researchers studied patients who had a minor stroke 5-years prior, who took part in the Oxford Vascular Study (OxVasc)[6]. Through OxVasc, participants underwent home and ambulatory blood pressure monitoring. Participants then had a series of follow-up tests, including brain imaging, measurements of arterial stiffness, and mental arithmetic. Dr Webb hoped that the study could identify factors that could predict abnormal blood vessel development, blood vessel brain injury and recurrent strokes.

The study found that arterial stiffness, cerebral pulsatility (39) (the pulsation of blood flow in the brain blood vessels) and blood pressure (40) variability are associated with both each other and an increased risk of vascular events. Through this study, researchers were able to identify potential targets to reduce the risk of recurrent strokes. In response to these findings, the Oxford team began

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factsheet.pdf?rev=98dd12be6bbf4e38b45678186f7d154e&hash=F2563B62CB96459E2A90E52F2AEF0CD7

[6] https://www.ndcn.ox.ac.uk/research/oxvasc

a clinical trial to assess the impact of vasodilating drugs on cerebral pulsatility and blood pressure variability. If successful, further trials could take place to assess the potential of these medications to prevent progression of the newly identified factors(41).

ii. Rates, Risks and Routes to Reduce Vascular Dementia (R4VaD)

BHF, along with the Stroke Association and Alzheimer's Society, is currently funding a large observational study (R4VaD) to understand the risk factors for post stroke cognitive impairment (PSCI)(42). Stroke is known to impact cognition, however risk factors for PSCI are not well defined at the individual patient level and mechanisms are not well understood. The study, led by Professor Joanna Wardlaw from the University of Edinburgh, recruited 2,441 patients within six weeks of stroke from 53 centres in the UK.

The study has two core objectives. The first is to determine rates of PSCI, study its progression, and develop better risk prediction models by investigating pre-stroke cognition, lifestyle, and socioeconomic factors, along with the medical history of participants. The second objective is to gain a better mechanistic understanding of PSCI, through the study of genetic and inflammatory blood samples and mechanistic sub studies, such as advanced neuroimaging and blood pressure monitoring. The research team are now in the final stages of completing follow-up and hope that their findings will highlight accurate cognitive trajectories up to two years after stroke as well as risk factors for cognitive impairment, and will inform future clinical service development.

3) Developing new technology

a) Advances in imaging techniques

Finding out what the blood vessels and organs look like, particularly at early stages in disease and how appearance changes as disease progresses, is crucial. This knowledge helps us to understand the causes of vascular disease, make early diagnoses, monitor disease progression and assess treatment effects.

Imaging techniques have significantly improved the diagnosis, understanding, and management of cerebrovascular disease, thanks in part to BHF-funded research.

i) Transcranial Doppler Ultrasound (TCD)

Transcranial Doppler (TCD) ultrasound is an imaging technique that uses sound waves to examine blood flow in the brain. It can be used to monitor a range of conditions including stroke.

Most strokes happen when blood clots, also known as emboli, lodge in an artery blocking the flow of blood to the brain. These emboli typically originate from furring up of arteries (atheroma) in the neck or the heart. TCD can be used to

detect emboli as they travel through the bloodstream. Professor Hugh Markus and colleagues at St George's University of London led a study to investigate whether the detection of emboli in the brain arteries by TCD could help predict stroke risk in patients who have carotid stenosis, but do not have symptoms. Carotid stenosis is a narrowing of a carotid artery resulting in reduced blood flow to the brain. The study found that TCD can be used to identify patients with this condition who are at a higher risk of stroke. This created a way of identifying patients who would benefit from having the atheroma surgically removed(43).

ii) Magnetic resonance imaging (MRI)

MRI uses a magnetic field and computer-generated radio waves to create highly detailed images of what's going on inside the body. The impact of BHF research into cardiovascular MRI has been covered in a separate impact report[7]. MRI has many different applications in the context of cerebrovascular disease. These include detecting vascular abnormalities, measuring blood flow in the brain and monitoring progression of disease.

MRI can be used to monitor the activity of atheroma. Atheroma goes through cycles of 'activity' during plaque formation due to several factors including inflammation. For example, when inflamed, the atheroma is more likely to rupture, triggering the formation of blood clots. These clots can then break away and travel through the bloodstream which may cause strokes. MRI can show atheroma at different stages in this cycle, as well as highlight clots in the blood vessels that might break off. Several BHF-funded studies have made improvements in the sensitivity of MRI to detect active atheroma. This includes work by Professors Peter Jezzard and Robin Choudhury in Oxford, and more recently Dr Alkystis Phinikaridou at Kings College London.

Work by Prof Steve Williams and colleagues at Kings College London are using MRI to identify heart changes related to atrial fibrillation (AF) in stroke patients. The underlying cause of stroke is often unknown, but it's important to identify whether AF is the cause. This is because future strokes caused by AF can be prevented by anti-clotting drugs. If abnormal heart structure is seen with AF, the team will use this information in a future clinical trial. The MRI results will guide doctors on which patients can benefit from anti-clotting drugs which could prevent repeat, potentially disabling, strokes.

iii) Positron emission tomography (PET)

Although MRI is commonly used in the clinic to diagnose carotid stenosis, not all of the important features of plaque activity are visible on MRI. Radio-isotope methods such as positron emission tomography (PET) imaging can detect subtle chemical reactions in the plaque, which serve as important indicators of its activity. BHF Professor David Newby and colleagues in Edinburgh have shown

[7] https://www.bhf.org.uk/impactofmri

that isotope tracers such as 18F-Fluoride can detect subtle signs of plaque activity that are not visible by other means(44-46). This includes detecting plaque activity in the aorta in people at risk of aneurysm rupture, and can help identify the cause of a stroke. They are now using 18F-Fluoride to determine the origin of blood clots in people with different types of stroke. This is important as it is often difficult for doctors to identify the source of the clot or to confirm a blood clot as the cause of a stroke. Professor Newby and colleagues are also exploring if isotope tracers that detect the glycoprotein IIb/IIIa receptors which are present on activated blood platelets in new blood clots, such as 18F-GP1, can identify the culprit blood vessel abnormality in patients with stroke where the cause is unclear(47).

iv) Computerised tomography (CT)

MRI and PET imaging are expensive and not available to vascular patients in every NHS hospital. In contrast, computerised tomography (CT) scanning is widely available. CT scans use a combination of X-rays and computer technology to produce images of inside the body.

BHF-funded research led by Professor Charalambos Antoniades (now BHF Professor of Cardiovascular Medicine) and colleagues at the University of Oxford, led to the development of a new CT imaging technique to identify vascular inflammation and vulnerable plaques(48). The technology uses artificial intelligence (AI) and deep-learning technology to produce a fat attenuation index score (FAI-Score®), which accurately measures inflammation of blood vessels in and around the heart. It allows the identification of people at high risk of a heart attack at least 5 years before it strikes. Professor Antoniades is also hoping to apply a similar technique to identify stroke risk. They have shown that by looking at the fatty tissue surrounding the atria (upper chambers of the heart) they can identify changes to the atria that can lead to onset of AF. This is important as AF significantly raises the risk of stroke. They hope that their technology, which analyses routine heart CT scans to identify these changes, will enable earlier detection of stroke. The team trained a deep-learning model to automatically quantify adipose tissue from CT scans. Findings revealed that automated assessment of fat tissue volume from CT scans is possible. The positive results from this study could allow doctors to make early, individualised assessments of stroke risk allowing people to receive preventative treatment and specific monitoring plans(49).

b) Data science and artificial intelligence in cerebrovascular research

Data science is a multidisciplinary field combining statistics, computer programming, and advanced analytics to uncover meaningful information from data. Data science is playing an increasingly significant role in many fields of research, including cerebrovascular. Also having a significant role, and closely related to data science, is artificial intelligence. AI refers to the spectrum of computer science that focuses on simulating human cognitive processes. More

specifically, machine learning (ML) refers to a group of tools that perform tasks such as classification, regression or clustering based on patterns or rules learnt directly from data. Several studies have already demonstrated the usefulness of AI tools in the analysis of large biological, imaging, and environmental data. BHF is funding several studies using data science and AI to improve the diagnosis of cerebrovascular disease.

i) Harnessing machine learning to diagnose stroke and predict outcomes

Professor Philip Bath at the University of Nottingham, funded by BHF, is leading a study that is assessing whether machine learning and statistical approaches can help improve the diagnosis of stroke and mini-stroke and predict the outcome after a stroke. Early diagnosis is essential in allowing patients to receive optimal treatment; however, diagnosis can be challenging, partly because symptoms of other conditions such as seizures and migraine are similar. These conditions, also known as 'stroke mimics', are frequently misdiagnosed as stroke. It is also challenging to predict complications and longer-term outcomes of strokes, such as whether stroke patients will be able to live independently or not. The statistical analysis techniques versus artificial neural networks for diagnosis and outcome prediction after acute stroke (SAVANNAS) study has collected information from trials involving 110,000 people with an acute stroke. It uses data such as age, sex, medical history, brain scans and post-stroke outcomes. If the machine learning and statistical analysis techniques provide accurate diagnosis and outcome prediction, they could be integrated into routine clinical care as apps on phones and computers. This could help ensure people receive the most appropriate treatment and lead to NHS savings.

Professor Konstantinos Theofilatos at Kings College London is also leading a study using machine learning to change the way we predict vascular diseases, including stroke. The most significant risk factors, such as blood pressure, smoking, and cholesterol, are used routinely to calculate heart attack and stroke risk. However, these 'traditional' risk factors fail to predict vascular disease in certain patients. The aim of this project is to use powerful computational tools to develop more comprehensive risk analysis and diagnosis algorithms that take more factors into account. Researchers will characterize distinctive 'fingerprints' in blood by combining cutting-edge technology with machine learning techniques. Results from this study could transform clinical practice for treating CVD patients, as there is currently no blood test that predicts heart attacks and strokes before they occur.

ii) Using large data sets to examine COVID-19 and the risk of vascular events

Professor William Whiteley and colleagues at the BHF Data Science Centre used large UK health registry data to track vascular disease, including stroke, during the COVID-19 pandemic. They examined the risk of vascular disease following a diagnosis of COVID-19 in 48 million adults in England and Wales. They found that the risk of vascular events was increased several fold particularly in the first week after COVID-19 infection and remained elevated up to 49 weeks after diagnosis particularly for arterial thrombotic events(50). They were also able to

track rates of cardiovascular complications in 46 million adults after different types of COVID-19 vaccination. In adults aged over 70 years, the rates of vascular complications were generally lower in vaccinated than unvaccinated individuals confirming the benefits of vaccination and safety of vaccines in this age group(51). In those aged under 70, there were increased rates of intracranial venous thrombosis and thrombocytopenia after ChAdOx1-S vaccination, but these were small compared to the benefit in reducing COVID-19 mortality.

iii) Data-driven retinal analysis of cSVD progression

BHF, alongside the Alan Turing Institute, is funding researchers at the University of Edinburgh who are using data science to investigate the onset and progression of cSVD. cSVD is difficult to detect and study because the vessels where the disease starts are too small to be visible with current brain imaging technology. However, the small blood vessels at the back of the eye – the retinal microvasculature – are closely related to the small blood vessels in the brain and can be seen in detail with high-definition retinal imaging cameras. A team led by Professor Miguel Bernabeu and Professor Joanna Wardlaw are applying data science methods to high resolution retinal images to discover what they can tell us about the onset and progression of cSVD. The team will develop mathematical and computational techniques to characterise the retinal microvasculature of people with cSVD and determine which vessels do not have adequate blood flow or have other abnormal characteristics. The researchers will then investigate how this data relates to blood flow in vessels of the brain and whether it can be used to predict the onset and progression of cSVD. This research could aid the development of a non-invasive technology that is much cheaper and can diagnose cSVD much earlier than current methods.

4) Influencing clinical practice

In the last 40 years, there have been major and rapid advances in the understanding of cerebrovascular disease. Arguably, stroke has gone from being one of the least treatable brain diseases up to the early 1990s, to the most treatable in current times. Up to the late 1980s, stroke was regarded with utter nihilism as to prevention and treatment. The brain was thought to 'die' immediately upon a vessel becoming blocked or bursting, with no hope for saving the tissue beyond the blockage or affected by the burst. Hence, typically patients with stroke were sent to hospital (if at all) in a 'slow ambulance' and often left unattended in the Emergency Department. Now, we know that the brain can survive for some hours, sometimes longer, but nonetheless every minute counts. For example, one estimate indicated that for each 15 minutes' less treatment delay, patients with ischaemic stroke gained an average of 1 month of additional disability-free life(52). Hence now, all types of stroke are handled as an ultra-emergency. All patients should go rapidly to a stroke unit. In ischaemic stroke, there are now highly effective drugs and procedures to remove clots

(thrombolysis and thrombectomy) and prevent more such strokes. In haemorrhagic stroke, recent clinical trial results show improved outcomes with a range of medical and surgical treatments that are close to being ready for clinical practice, and there is more knowledge about preventing brain haemorrhage. The aneurysms that cause subarachnoid haemorrhage are treated routinely with minimally invasive procedures. There is even hope for small vessel disease and vascular dementia with much better understanding of the causes and recent positive results from clinical trials(53).

The UK's contribution

The UK has made substantial contributions to the field of stroke, 'punching above its weight', and leading on diagnostic and mechanistic studies and clinical trials. This work has improved care of patients affected by cerebrovascular disease and changed clinical practice worldwide. There are many examples: the UK TIA trial, the European Carotid Surgery Trial, hospital Stroke Units, the International Stroke Trial, the Third International Stroke Trial, numerous epidemiological studies into the causes of all types of stroke, improvements in stroke prevention, evaluations of how best to use CT or MRI or ultrasound to diagnose the cause of the stroke, trials testing how to manage blood sugar and blood pressure in acute stroke, have all influenced clinical practice world-wide.

a) Treatment of acute ischaemic stroke

Acute ischaemic stroke occurs when a blood vessel, usually an artery carrying blood into the brain, becomes blocked. Originally, it was thought that the brain died immediately once the blood flow dropped, hence there was little scope for treatment. It was also thought that re-opening the artery and restoring blood flow would worsen the brain damage and cause a haemorrhage – also known as 'reperfusion injury'. However, we now know that it is better to reopen the artery as quickly as possible since the benefits of restoring blood flow to the brain outweigh the risk of any harm.

After pioneering trials with thrombolytic ('clot busting') drugs in the early 1990s, leading to large international clinical trials, the thrombolytic drug alteplase was licenced for treatment of acute ischaemic stroke up to 4.5 hours after onset.

Subsequent trials have focused on extending the time to treatment, trying different thrombolytic drugs or doses, and performing surgical interventions to remove the clot (thrombectomy).

i) Pre-hospital treatment

In 2014, BHF funded Professor Philip Bath and colleagues at the University of Nottingham to assess the safety and efficacy of the drug glyceryl trinitrate (GTN) in patients with stroke(54). Previous small trials had suggested that GTN, given as a skin patch, might improve functional and cognitive outcomes when given within 6 hours of stroke. The BHF-funded rapid intervention with glyceryl trinitrate

in hypertensive stroke trial-2 (RIGHT-2) was the first multicentre UK pre-hospital stroke trial with patients recruited and treated by paramedics in the ambulance. Patients in the RIGHT-2 trial were given GTN within 4 hours of showing stroke symptoms, with most patients treated by paramedics within 80 minutes of stroke onset. The trial did not find an improved outcome with GTN as compared with placebo treatment. And patients with intracerebral haemorrhage (ICH) appeared to have worse outcomes. Surprisingly, a patient with a diagnosis masquerading as a stroke, i.e. a mimic, appeared to do better with GTN. The results of RIGHT-2 could contribute to changes in clinical practice. This is because previously, GTN was used for blood pressure management following ICH. However, this trial has shown worse outcomes when GTN is used in ICH.

On a more positive note, the trial has highlighted the feasibility of paramedic delivered, ambulance-based trials in the UK.

ii) Are some drugs better than others?

In 2016, the BHF, together with the Stroke Association, funded Professor Keith Muir and colleagues at the University of Glasgow to undertake the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST-2). The trial is testing whether a newer thrombolytic drug, tenecteplase, is as good as or better than the current licenced thrombolytic drug alteplase. In previous studies, alteplase has been shown to improve functional outcomes after stroke without increasing harm. Administration with tenecteplase is more practical than alteplase as it is given as a single larger dose compared to alteplase which is given as a smaller dose with the rest infused over an hour. Tenecteplase therefore has the practical advantage of not needing an infusion pump or having to monitor an infusion. In addition, tenecteplase theoretically acts faster since all the drug is administered within a minute. In ischaemic stroke, every minute counts, therefore it was assumed that delivering treatment an hour faster could provide on average up to four months more of disability-free life(55). The more practical administration of tenecteplase could also help increase availability of thrombolysis treatment to more healthcare systems. The ATTEST trial is the largest trial so far to compare alteplase with tenecteplase and has the potential to influence clinical practice. Preliminary results from the study, presented at the 15th World Stroke Congress in October 2023, show that tenecteplase was non-inferior to alteplase in suitable ischaemic stroke patients[8].

iii) Treatment options for wake-up stroke

In 2018, BHF funded Professor Thompson Robinson and colleagues to run the UK part of the Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST), led from

[8] https://neuronewsinternational.com/tenecteplase-deemed-non-inferior-to-alteplase-in-suitable-ischaemic-stroke-patients/

Norway. The trial aimed to improve the treatment of people who have had a stroke in their sleep.

Many older patients live alone and can have a stroke while on their own, and in some cases while asleep. The usual treatment for stroke involves giving a clot busting drug within 4.5 hours of the onset of symptoms. However, where people have had a stroke in their sleep it often isn't known when exactly symptoms developed, and these patients are usually not offered clot busting therapy.

TWIST is part of increasing efforts to identify patients who are likely to benefit from clot-busting treatment when the timing of their stroke is not known(56). TWIST used CT brain scanning, the widest available imaging technique, to select 578 patients for tenecteplase or no tenecteplase treatment within 4.5 hours of waking with a stroke. The study did not find better outcomes with tenecteplase, but it did not find more harm either, having similar rates of poor outcomes to other trials where patients were selected using advanced imaging. Reasons for these results could be that the trial was not large enough to detect benefit in this group, or patients were receiving treatment much later after stroke onset. More trials like this are needed to ensure that the widest possible range of patients can benefit from these powerful treatments.

iv) Anticoagulants and atrial fibrillation

In 2011, BHF and The Stroke Association funded Professor David Werring and colleagues at University College London to understand the risks of treating AF patients with anticoagulants following a stroke.

Anticoagulants reduce the risk of stroke but increase the risk of intracranial haemorrhage (ICH), especially in people with small vessel disease. Werring and colleagues assessed whether microbleeds, which are indicative of SVD, could predict intracranial haemorrhage risk in AF patients receiving anticoagulation after stroke. They collected data from 1490 patients at 79 hospitals and followed up for two years. The team developed a risk prediction model to determine which factors could reduce recurrent stroke without increasing haemorrhage risk. The study found that the presence of microbleeds is linked to an increased risk of ICH(57). Werring's work has influenced opinions on the use of anticoagulants(58), the timing of anticoagulant treatment(59), and comparisons of different anticoagulant drugs(60). It has also influenced clinical guidelines(61). This work also led to additional data pooling initiatives to strengthen the findings on risk of ICH and ischaemic stroke, and to the BHF-funded OPTIMAS trial (OPtimal TIMing of Anticoagulation after Stroke) which aims to find the best timing to start anticoagulation drugs in patients with atrial fibrillation after a recent stroke[9].

[9] https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2019/september/new-trial-could-prevent-further-strokes

b) Treatment of cerebral small vessel disease

Cerebral small vessel disease (cSVD) is a disorder that affects the small blood vessels of the brain – arterioles, capillaries and venules. These small vessels are integral to supplying oxygen and nutrients to the brain, and are part of the system that removes waste and manages the pressure inside the skull. These processes are carefully balanced to keep the brain functioning optimally.

The damage to the small vessels themselves are visible under a microscope. But the effects of the disease on the brain can be seen with CT or MRI imaging as abnormalities in the deep grey and white matter of the brain. These abnormalities include white matter hyperintensities, lacunes, microbleeds, perivascular spaces, and acute small subcortical infarcts(62, 63). cSVD is often found on brain imaging performed for other reasons in persons with no history of stroke or cognitive problems (covert cSVD)(64).

cSVD can cause a stroke called lacunar stroke and can worsen the outcomes of other types of strokes. cSVD is the commonest cause of brain haemorrhage in older people, and can cause cognitive impairment. It is the most prevalent cause of vascular dementia and is common in mixed dementias with Alzheimer's disease.

Cerebral small vessel disease can be sporadic or occasionally genetic, and it is commonly seen in people with hypertension or diabetes. Although the precise causes vary, it is increasingly clear that the underlying pathology is not a 'small vessel atheroma'. This explains why usual stroke prevention treatments, such as antiplatelets, are ineffective (or hazardous) for cSVD, unless it has caused a stroke(52). Instead, there is a distinct problem in the endothelium (the lining of the small vessels) or in the membranes surrounding the vessels. The blood vessels do not widen as they should when more blood is needed, they become stiff and leaky.

The BHF has been instrumental in funding clinical studies and trials to improve outcomes of cSVD, as illustrated by the following examples.

i) Intensive blood pressure lowering

In 2011, BHF and The Stroke Association jointly funded Professor Hugh Markus and colleagues to determine how intensively blood pressure should be treated in patients with cSVD. Hypertension is the major cause of cSVD but once people have established cSVD, it is not known how intensively it should be treated. Participants in the PRESERVE trial were randomly assigned to two groups: one with standard blood pressure targets (Systolic blood pressure (SBP) 130–140 mmHg) and the other with intensive blood pressure targets (SBP <125 mmHg). The team measured changes in white matter using diffusion tensor imaging (DTI) over 24 months and looked at cognitive performance and cerebral blood flow. The trial found that blood pressure was reduced by –15.3 and –23.1 mmHg in the

standard and intensive groups respectively. There was no difference in recurrent stroke or cognitive impairment between intensive and standard blood pressure lowering(65). The trial demonstrated that intensive BP lowering in patients with cSVD is feasible and does not increase white matter damage. This is important as BP lowering not only protects the brain but also reduces the risk of cardiovascular disease.

ii) Repurposing drugs – gout

In 2014, BHF and The Stroke Association jointly funded Prof Jesse Dawson and colleagues in Glasgow to find out whether allopurinol, a drug commonly used to treat gout, can offer any benefit to patients who have suffered a stroke. Allopurinol helps to reduce the amount of uric acid the body produces, and has anti-inflammatory effects. Previous research suggested a link between uric acid and the risk of having a stroke, and having worse outcomes from a stroke. High levels of uric acid in the blood are also linked to increased blood pressure, an important risk factor for stroke.

The XILO-FIST trial recruited patients over 50 who had a stroke in the previous 30 days and followed them for two years. Patients were randomly assigned to receive allopurinol or a placebo. During and after treatment, the patients were monitored closely to look for any signs of stroke recurrence or decline in brain function. The trial did not find any benefit or harm from allopurinol, ruling out one possible cause of and treatment for cSVD and vascular cognitive impairment(66).

iii) Repurposing drugs – existing cardiovascular drugs

In 2018, BHF funded Professor Joanna Wardlaw, Professor Philip Bath and colleagues at the University of Edinburgh and University of Nottingham to find out whether two existing drugs usually used for angina and peripheral vascular disease could help prevent dementia following lacunar stroke.

The LACI-2 trial shown that isosorbide mononitrate and cilostazol, which are already used to treat other cardiovascular diseases, can safely and effectively improve outcomes following lacunar stroke, particularly when they're used in combination(53). The researchers investigated these drugs as they are thought to improve the function of the endothelium. Problems with the endothelium are thought to play a role in cSVD, as described above.

The trial included 363 people who had experienced a lacunar stroke. As well as their standard stroke prevention treatment, participants took either isosorbide mononitrate or cilostazol individually, both drugs together, or neither, for one year. The trial shown that participants that took both drugs were nearly 20% less likely to have problems with their thinking and memory compared to the group that did not take either drug after one year. They were also more independent and reported a better quality of life.

The positive results mean that the two drugs could be available as a treatment for lacunar stroke within five years. The LACI-2 team is now starting to test these drugs in a large Phase 3 trial, LACI-3, which will test the two drugs for longer (18 months) in patients with lacunar stroke aiming to report in 2028. LACI-3 is currently the only large Phase 3 trial testing drugs to prevent VCI and VaD in the world. Importantly, LACI-3 will be set up to ensure that if it confirms the results of LACI-2, then the licence for one or both drugs can be extended to include prevention of VCI and VaD, which is a major clinical impact.

Importantly, if the two drugs tested in LACI-2 work in cSVD, then they should also work in other types of cSVD. Therefore Professor Joanna Wardlaw, Professor Philip Bath and colleagues in the LACI trials collaboration are also looking to test whether the drugs are effective in different conditions linked to cSVD, such as VCI and VaD. The LACI-2 trial is included within the 2024 European Stroke Organisation (ESO) guideline on cSVD(67).

c) Prevention of cerebrovascular disease

i) Can statins reduce stroke risk?

BHF-funded research has helped to test whether statins can reduce risk of stroke. In the 1970s, it became clear that high levels of cholesterol were associated with an increased risk of having a stroke. In the 1980s, cholesterol-lowering drugs, called statins, became available. And shortly after, BHF Professor Stuart Cobbe and colleagues in Glasgow led a study looking at the effect of statins on over 6,000 men who had high cholesterol. Participants were followed up 10 and 15 years after the trial. Early results suggested statins reduced stroke risk(68), but in the long term, it proved non-significant(69). In the 2000s, BHF Professor Rory Collins and colleagues in Oxford tested if statins could help people with 'normal' cholesterol levels or with diabetes. The BHF/MRC Heart Protection Study involved over 20,000 people and ran for five years. The results, published in 2004, showed that statins reduced the risk of having a ischemic stroke by a third in both groups of people.

In 2007, Mr Peter Kirkpatrick at Cambridge University Hospitals set out to investigate whether the benefits of statins could help protect the brain after a subarachnoid haemorrhage (SAH). The BHF funded Mr Kirkpatrick's global 'Simvastatin for Aneurysmal Subarachnoid Haemorrhage' (STASH) trial, which recruited 803 participants with SAH. Half of the participants were given statins, and half received a placebo. The trial concluded that statins had no impact on the short-term or long-term outcomes of patients with subarachnoid haemorrhage(70). The outcome of this study was disappointing when compared with earlier encouraging trials. Researchers argued that subarachnoid haemorrhage is less common and suggested that a mega-trial would be necessary in showcasing the benefits of statins.

ii) Are three antiplatelet drugs better than two at preventing early recurrent stroke?

Antiplatelet drugs prevent blood clot formation by stopping platelets sticking to atheromatous plaque. These plaques can cause clots that may break off (embolisation) and block downstream blood vessels. The carotid arteries and aortic arch are typical places for blood clots to form and cause ischaemic strokes through embolisation. Sometimes a tiny bit of clot breaks off and causes a warning TIA or minor stroke; many research studies have shown that starting the antiplatelet rapidly after the TIA or minor stroke can help prevent a major disabling stroke. Other trials have shown that giving two antiplatelet drugs is more effective than giving one. Professor Philip Bath and colleagues at the University of Nottingham tested whether three antiplatelet drugs (aspirin, dipyridamole and clopidogrel) were better than either clopidogrel alone or aspirin plus dipyridamole when given for 30 days after the TIA or minor stroke. The Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS(71)) trial found that three antiplatelet drugs was not better than giving one or two drugs at preventing recurrent stroke - the tendency for ischaemic stroke to be reduced was offset by more bleeding.

iii) Should antiplatelet drugs be restarted after a haemorrhagic stroke?

In 2013, BHF funded the first multicentre study into whether antiplatelet drugs are safe to prescribe to patients who have just had a brain haemorrhage. Antiplatelet drugs, such as aspirin, are used to help prevent blood clotting. More than one third of adults who have a brain haemorrhage are taking antiplatelet medication at the time of their stroke.

Doctors often stop prescribing antiplatelet drugs immediately after a brain haemorrhage due to the risk of further bleeding in the brain. But there has been significant uncertainty surrounding whether antiplatelets should be restarted once patients have recovered.

Professor Rustam Al-Shahi Salman and colleagues at the University of Edinburgh led a clinical trial to answer this question. The RESTART trial recruited over 500 patients who had been taking antiplatelets such as aspirin at the time of having a brain haemorrhage. Around half were told to avoid antiplatelets and half were restarted on antiplatelet therapy within 24 hours of having a brain haemorrhage. Participants were observed for up to five-years.

The results of the study suggested it is safe for people who have had a stroke caused by bleeding in the brain to restart antiplatelets without raising their risk of another brain bleed(72). The results suggested that these drugs might even reduce the risk of a further brain bleed. The trial provided a crucial foundation, proving that further larger studies should take place. Presently, researchers from the RESTART trial are continuing to follow up patients to identify any emerging evidence, and are about to start a large confirmatory trial (ASPIRING) which will include UK and international centres. The findings of RESTART and ASPIRING

could have major implications for the treatment and management of people who have suffered a haemorrhagic stroke(72).

iv) Blood pressure medication and stroke risk

In 2000, BHF funded a study led by Professor Christopher Bulpitt at Imperial College London to investigate whether it was safe to prescribe blood pressure medication to patients above the age of 80. The HYVET trial recruited over 3,500 participants from several countries. The trial was stopped early when an analysis of the data showed that people receiving blood pressure medication had significantly lower death rates and, most importantly, these patients tolerated blood pressure lowering medications well.

Whilst the focus of the study was treating blood pressure in patients over 80, additional observations found that active treatment of high blood pressure resulted in a 30% reduction in the rate of fatal or non-fatal stroke, and a 39% reduction in the rate of death from stroke. Findings from the study strongly suggest that blood pressure medication is equally effective at preventing strokes and vascular death, regardless of age(73).

5) Improving patients' lives

Over the last decade, stroke incidence in the UK has been rising steadily, with 136,839 hospital admissions for stroke in 2022. Whilst admissions have risen, there has been a decline in mortality, with an estimated 33,796 deaths in 2022 compared to 40,282 deaths in 2013[10]. BHF-funded research has contributed to improve the lives of patients with cerebrovascular disease.

People who have had a stroke are at increased risk of suffering from a recurrent stroke, which tends to be more disabling and have poorer outcomes than the first stroke(74). BHF has funded research to identify factors that could predict the likelihood of future strokes.

There is no cure for VCI or VaD and by 2050 it's predicted that the number of people in the UK living with this condition could double. Promising results from the LACI-2 trial show that cardiovascular drugs have the potential to prevent dementia in cSVD, including after lacunar stroke.

6) Partnerships

BHF works together with other national and international funders to support innovative cardiovascular research. Partnership enables the joining up of different research communities, increases available funds, supports interdisciplinary research and projects with a broader reach, and ultimately

[10] https://www.bhf.org.uk/what-we-do/our-research/heart-statistics/heart-statistics-publications/cardiovascular-disease-statistics-2023

maximises the impact of research funding efforts. Cerebrovascular disease is a significant global health concern and therefore benefits from partnership to improve prevention, diagnosis, and treatment strategies. BHF has created partnerships dedicated to increasing funding for cerebrovascular research.

BHF has partnered with other key cerebrovascular funders in joint funding calls, this includes the Stroke Association. BHF and the Stroke Association previously ran an annual joint call for clinical study grants in stroke research with a vascular focus. Since 2009, 7 grants have been funded through this partnership worth more than £7 million. This includes major trials such as ATTEST and XILO-FIST. A separate joint funding call with Stroke Association and Alzheimer's was established in 2016 focussing on vascular dementia. Three projects were funded through this initiative worth more than £2 million, including the 2441 patient R4VaD study (see earlier).

In 2017, BHF partnered with The Alan Turing Institute to create a joint funding opportunity promoting multidisciplinary research to generate data science solutions to key cardiovascular problems. The partnership has included two projects relating to cerebrovascular disease, one using an algorithm to identify properties that may increase risk of heart attack or stroke (Dr William Astle, University of Cambridge). And another studying the eye to improve detection of SVD in the brain (Professor Miguel Bernabeu and Professor Joanna Wardlaw, University of Edinburgh).

Cardiovascular diseases are a global problem, which is why BHF partners with funders worldwide. Since 2018, BHF has been part of a funding scheme alongside the German Centre for Cardiovascular Research (DZHK) and the Dutch Heart Foundation (DHF). The International Cardiovascular Research Partnership Awards fund cardiovascular research projects where the cross-national dimension enables work of greater ambition and higher potential impact than can be carried out nationally. There have been five rounds of the competition, which has included one project related to cerebrovascular disease worth more than £1 million. The project, led by Professor Hugh Markus at the University of Cambridge, uses advanced brain imaging to determine the nature of the dysregulated immune response, and how it is related to cerebrovascular disease progression.

BHF is part of the Global Cardiovascular Research Funders Forum (GCRFF), a coalition of major international funders of cardiovascular clinical research established in 2018. GCRFF's Multinational Clinical Trial Initiative aims to help researchers in different countries collaborate on multinational clinical trials that might not be feasible in a single country or with support from a single funder. The initiative provides a way for investigators to submit a single Expression of Interest (EOI) for a multinational cardiovascular clinical trial for consideration by GCRFF members for endorsement. The endorsement of an EOI by the GCRFF is an indication of strong support by the GCRFF members for the proposed trial.

Investigators can then seek funding to support the trial through relevant national funding schemes (including those of GCRFF and non GCRFF member funders). There have been ten EOIs in the field of cerebrovascular disease, and three have been endorsed. One project has received funding from four funders across the globe, including BHF. The 'Antiplatelet Secondary Prevention International Randomised trial after INtracerebral haemorrhaGe' (ASPIRING) will be led by Professor Rustam Salman from the University of Edinburgh. ASPIRING will investigate whether using a single antiplatelet therapy is more effective in reducing adverse cardiovascular events for adults with a history of stroke due to bleeding in the brain, compared to avoiding antiplatelet therapy. Over 4,000 patients will be recruited in Australia, Canada, The Netherlands, and the UK.

In 2023, BHF developed two new initiatives enabled by partnerships. This includes the Stroke Data Science Catalyst and the BHF-UKDRI Centre for Vascular Dementia Research. The Stroke Data Science Catalyst is a five-year partnership between the BHF Data Science Centre, Health Data Research UK (HDR UK), Stroke Association, and BHF. The initiative will enable researchers to securely access, link and analyse existing UK health data, speeding up the search for better stroke prevention, treatments and care. Led by stroke expert Professor Will Whiteley, the Stroke Data Science Catalyst enables approved research teams to use data from a range of real-world settings, including hospitals, general practices and pharmacies. The initiative hopes that this will generate valuable insights and improve understanding of the causes and consequences of stroke.

The BHF-UK DRI Centre for Vascular Dementia Research results from a partnership between BHF and UK Dementia Research Institute (UK DRI). BHF has committed to investing £7.5 million into the centre, which will be the UK's flagship investment for vascular dementia research and will bring together world leading expertise in biomedical and translational dementia research. UK DRI has pledged to contribute £1.5 million towards the centre and will also provide access to its cutting-edge technology and research centres. The partnership builds on UK DRI's standing as the UK's leading research institute dedicated to studying a range of neurodegenerative diseases, including vascular dementia. Following its launch in early 2024, the Centre appointed Professor David Attwell at University College London as its Director. It is currently seeking four new group leaders to join the UK DRI's three existing vascular dementia research focused group leaders (Professor Joanna Wardlaw, Dr Axel Montagne, Dr Bianca Diez Castro all at the University of Edinburgh) that will work across key preclinical and translational areas of vascular dementia research. The unique combination of over 60 years of BHF breakthroughs in heart and circulatory diseases and the in-depth neuroscience expertise and resources provided by the UK DRI, could transform the research landscape for this devastating condition.

7) Conclusion

When the BHF was founded in 1961, the very first research project funded was to support Dr Enid Acheson to identify the causes of stroke. Little was understood about the condition at this time. There was no CT or MRI brain imaging and most information about causes of stroke came from postmortems. It was very hard to know what was really going on. Since then, BHF has grown to become one of the largest independent funders of stroke and cerebrovascular diseases research in the UK. In part thanks to BHF funding, stroke has gone from being one of the least preventable or treatable type of brain disease to one of the most preventable and treatable.

Many recent breakthroughs in the field have been due in part to BHF funding. In the last 10 years alone BHF research has started to identify better treatments and prevention for haemorrhagic stroke. Treatments to prevent small vessel disease worsening or to prevent vascular dementia are also beginning to emerge. It is interesting that some of the most promising treatments for small vessel disease in the brain are drugs that have been used for many decades to treat symptoms of ischaemic heart disease.

In BHF's strategy to 2030, there is an emphasis on addressing stroke and vascular dementia, with a specific focus on treatment and prevention. Despite the many advances in prevention and treatment, stroke and vascular dementia are not about to disappear. Our population is ageing, increasing the number of people at risk of stroke, and stroke is increasing in younger people for reasons which are not yet well understood.

Looking ahead, it will be crucial to have a better understanding of various elements such as genetic factors, early life influences, socioeconomic and dietary factors, vascular risk factors, lifestyle and other environmental exposures. These factors manifest at different stages across the life-course and play a critical role in optimising prevention of stroke and vascular dementia in the future. Undoubtedly a multipronged approach is essential, incorporating diverse approaches such as epidemiology, leveraging 'big data' and health data registries, utilising imaging technologies, employing experimental medicine approaches and exploring genetics. With the new UK Centre for Vascular Dementia Research jointly supported by the BHF and UK DRI, the UK should be well-placed to continue 'punching well above its weight' in the quest for better prevention and treatment of stroke and vascular dementia.

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