# Protecting the brain

## Impact of British Heart Foundation support for cerebrovascular research

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British Heart Foundation

# Contents



This review was led by Joanna Wardlaw, Professor of Applied Neuroimaging, University of Edinburgh and Philip Bath, Professor of Stroke Medicine at the University of Nottingham.

# Message from our Chief Scientific and Medical Officer

Since British Heart Foundation (BHF) was founded in 1961, it has funded pioneering research that has improved the lives of the millions of people affected by heart and circulatory diseases. Powered by our supporters and volunteers, BHF-funded researchers have made fundamental discoveries and translated promising science into revolutionary breakthroughs.

To crystalize the impact of this research, we are producing reviews that showcase the impact of BHF-supported research in specific areas of cardiovascular medicine. We highlight key research leaders whose work has advanced knowledge, developed new technologies, and improved clinical practice, with the aim of improving the lives of patients living with, or at risk of cardiovascular diseases.

The following pages focus on cerebrovascular disease, encompassing conditions such as stroke and vascular dementia. Over the last 60 years, BHF-led research has significantly contributed to the prevention and treatment of strokes, reducing their long-term damage. Moreover, our investment into the new Centre for Vascular Dementia Research I hope will provide new insights and opportunities to prevent and treat this devastating condition. Our continued investment lays a strong foundation for tackling the growing challenges posed by cerebrovascular disease.

I look forward to seeing BHF's continued progress in the decades to come.

**Professor Bryan Williams OBE MD FMedSci**
Chief Scientific and Medical Officer,
British Heart Foundation

# What is cerebrovascular disease?

**Cerebrovascular disease is a term for conditions that affect the blood vessels and blood flow to the brain. These conditions include stroke and vascular dementia.**



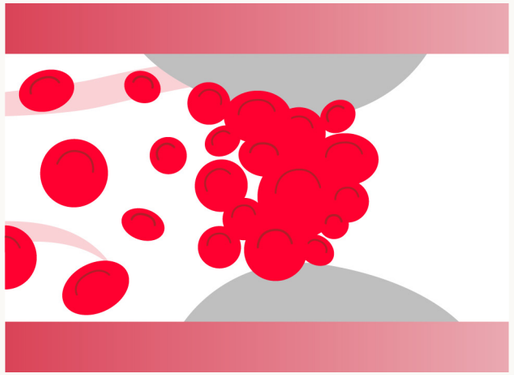
## Stroke

Stroke is the most common type of cerebrovascular disease and is one of the main causes of severe disability in the UK. A stroke happens when the blood flow to part of the brain is cut off, which can cause brain cells to become damaged or die. A stroke can be due to a blockage in the blood flow to the brain (ischaemic stroke) or bleeding in the brain (haemorrhagic stroke).

The symptoms of a stroke typically last more than 24 hours. If the symptoms last less than 24 hours, then it is called a transient ischemic attack (TIA) or mini stroke.

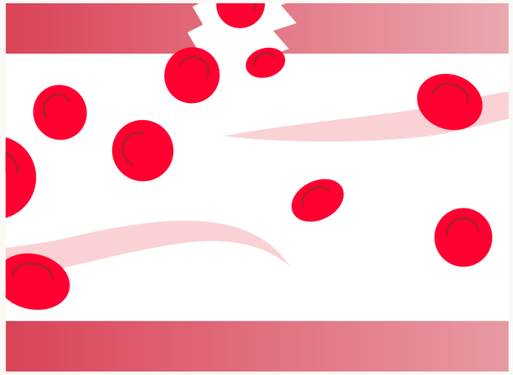
A stroke can affect people in different ways, depending on where in the brain is affected, and how big the damaged area is. Stroke can cause changes to someone's speech, thinking and movement.

**There are more than 100,000 strokes in the UK each year. That's someone having a stroke at least every five minutes.**



### Ischaemic stroke

An ischaemic stroke happens when an artery that supplies the brain with blood is blocked by a blood clot.



### Haemorrhagic stroke

A haemorrhagic stroke happens when a blood vessel in the brain, or on its surface, bursts and bleeds into the brain.

## Vascular Dementia

Vascular dementia is a condition caused by poor blood flow in the brain, resulting in symptoms like memory loss, confusion, and thinking difficulties. It can happen after a stroke, or more gradually if the small blood vessels in the brain are not working properly.

Vascular dementia is a progressive and incurable disease, lifechanging for both the person diagnosed and those closest to them.

Vascular Dementia is estimated to affect at least

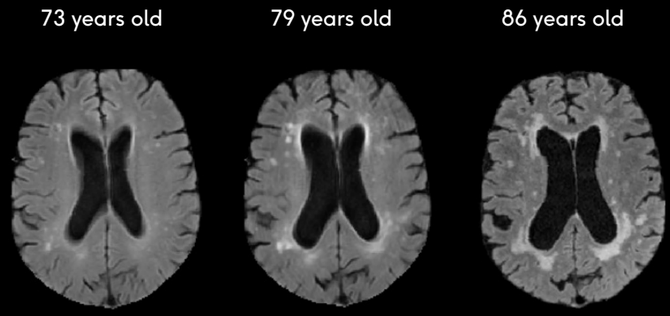
**150,000**

people in the UK



## Cerebral Small Vessel Disease (cSVD)

cSVD is the most common cause of vascular dementia. It is a disease where the small blood vessels deep within the brain become damaged and stop working properly. cSVD can cause a type of stroke called lacunar stroke and can worsen the outcomes of other types of stroke.



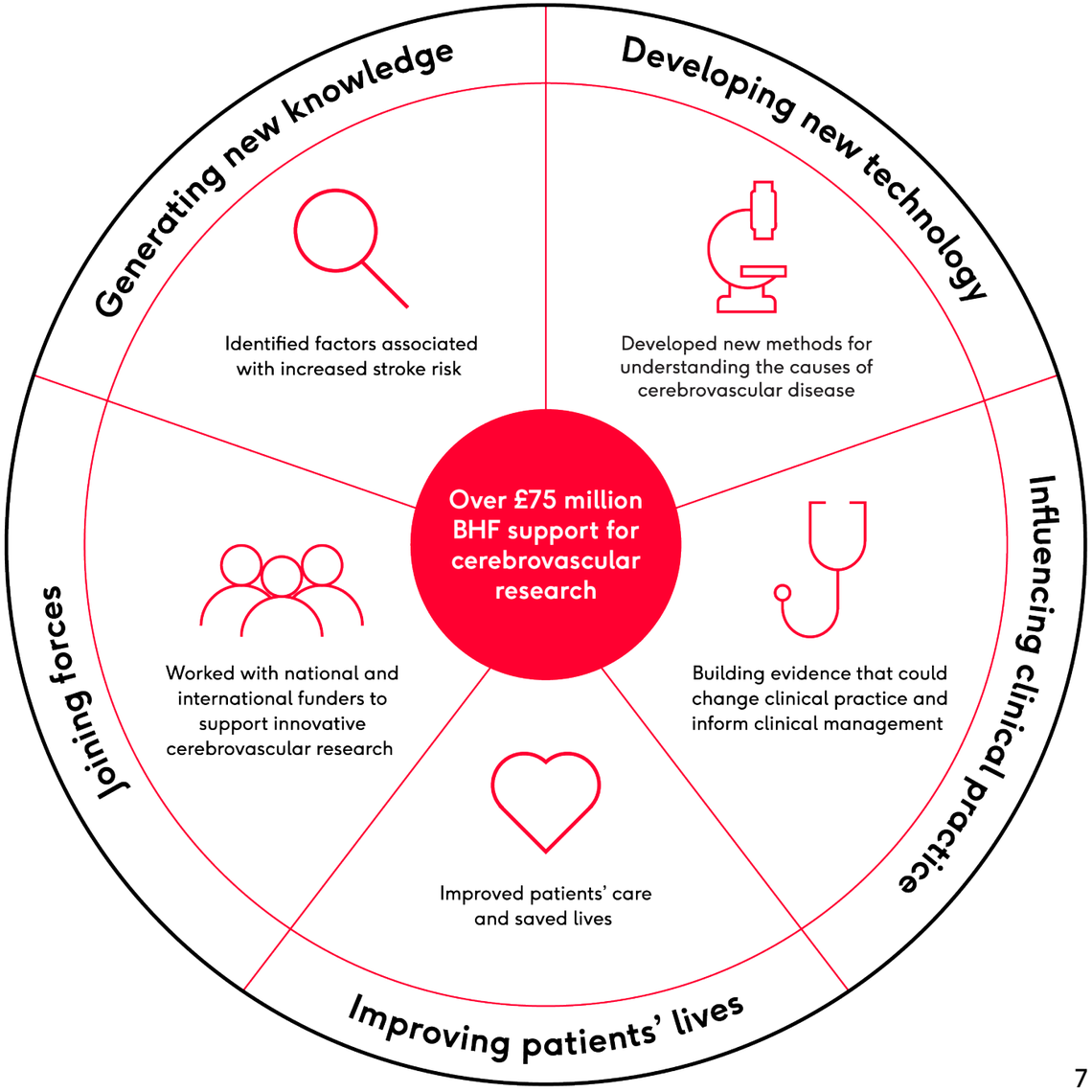

White matter hyperintensities (WMH) are bright spots seen on brain MRI scans. They indicate changes in the brain's white matter, which are associated with cSVD. Image shows how WMHs increase as a person ages.

# Our support for cerebrovascular research

The very first research project funded by BHF in 1963 focused on stroke, and was awarded to Dr Enid Joan Acheson. Since then, BHF has grown to become one of the largest independent funders of stroke and cerebrovascular disease research in the UK. Whilst research has led to improvements in the prevention and treatment of cerebrovascular disease, there is still a long way to go. BHF is supporting vital research in the quest to find better prevention and treatment of stroke and vascular dementia.

Over **160** grants worth more than **£75 million**

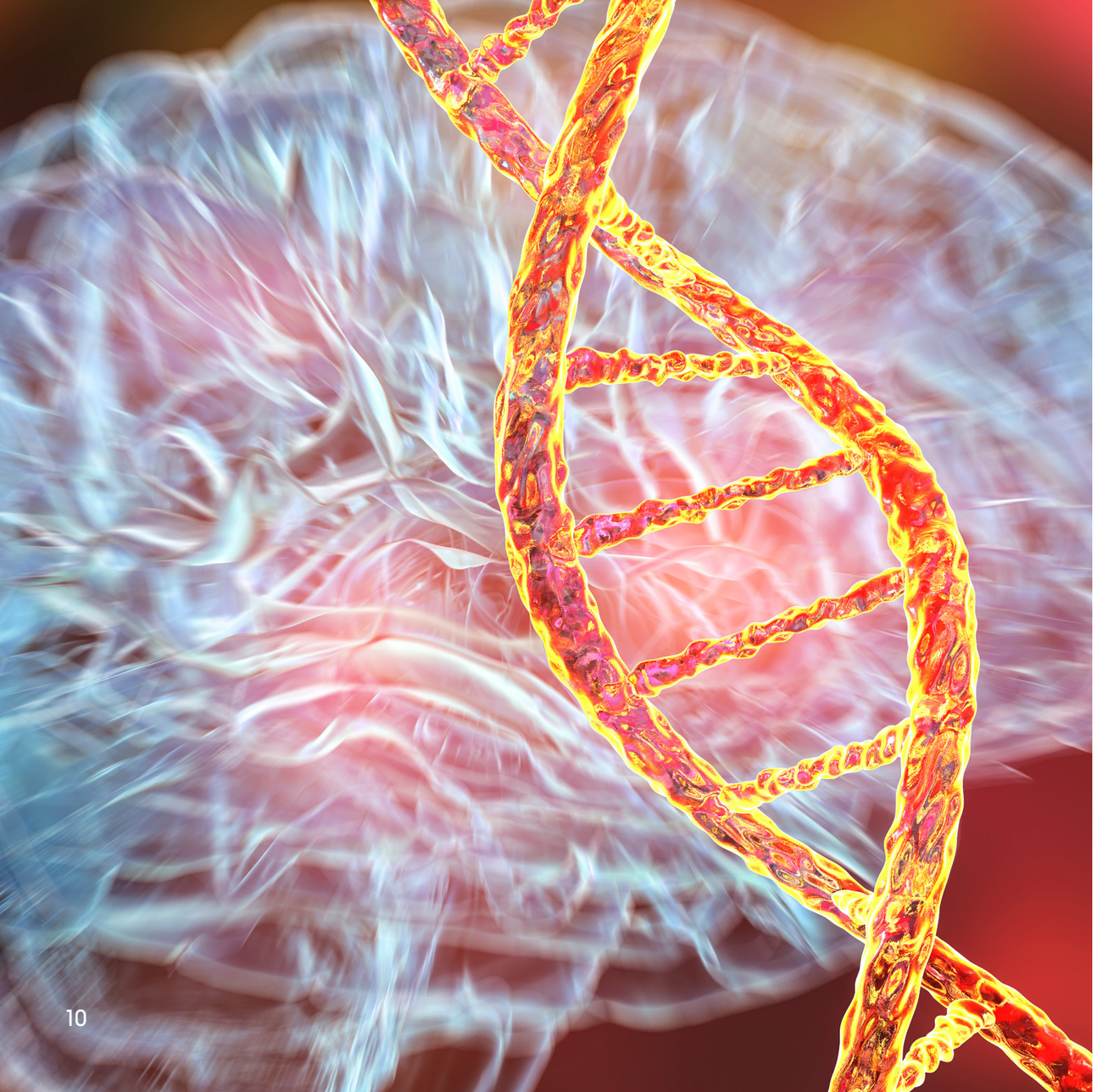
Supporting the training of more than **40 researchers**



# Generating new knowledge

**Over the past 60 years our understanding of cerebrovascular disease has substantially improved. BHF-funded research has been instrumental in increasing our knowledge in this area by:**

- Identifying differences in the risk of stroke depending on gender, ethnicity or socioeconomic backgrounds.
- Contributing to the largest stroke genetics analysis, which discovered 22 new genetic regions linked to an increased risk of stroke.
- Identifying genetic factors that increase the risk of small vessel disease, which has revealed new potential targets for treatment.
- Finding a potential therapeutic target in brain cells to prevent the ‘no-reflow’ problem following stroke, where blood flow to the brain’s small blood vessels is not restored properly even after treatment, hindering recovery.



# Genetic clues point to new treatments for lacunar stroke

Cerebral small vessel disease (cSVD) is a group of conditions that affect the small vessels of the brain. It can cause a type of stroke called lacunar stroke, which account for about a fifth of all strokes. Lacunar strokes put people at an increased risk of developing vascular dementia.

There are currently no effective treatments for lacunar stroke. To change this, BHF has funded research to understand more about cSVD, including through the study of genetics.

With BHF funding, Professor Hugh Markus and his team at the University of Cambridge carried out the first in-depth study into genetic factors which increase the risk of lacunar stroke. The team compared the genetic code of 7,338 patients who had a lacunar stroke with 254,798 people who had not. They discovered changes to 12 genetic regions in the DNA of people with lacunar stroke. Many of the regions were involved in maintaining the neurovascular unit – the part of the brain that separates the blood vessels from the brain and ensures that nerves function normally. These genetic changes are thought to make the small blood vessels 'leakier', causing toxic substances to enter the brain, and meaning that messages travelling around the brain slow down or don't arrive at all.

The team now plans to test whether new treatments can correct these abnormalities on brain cells in the lab. They hope to begin human clinical trials in the next ten years. Professor Markus and his team have received further BHF funding to continue this research and will investigate whether genetics play an important role in altering the risk of developing vascular dementia in people with cSVD.

# Developing new technology

**BHF-funded research has helped to advance technologies and methods for understanding the causes of cerebrovascular disease, helping to speed up early diagnosis, monitor disease progression and assess treatment outcomes. Examples include:**

**Transcranial Doppler Ultrasound (TCD)**

Helping to establish TCD as an effective way of detecting blood clots in the brain's arteries, which could help predict stroke risk. TCD uses sound waves to examine blood flow in the brain.

**Magnetic Resonance Imaging (MRI)**

Improving the sensitivity of MRI to monitor the activity of fatty deposits in the blood vessels, highlighting fatty deposits that are at risk of rupturing and could cause a stroke.

**Positron Emission Tomography (PET)**

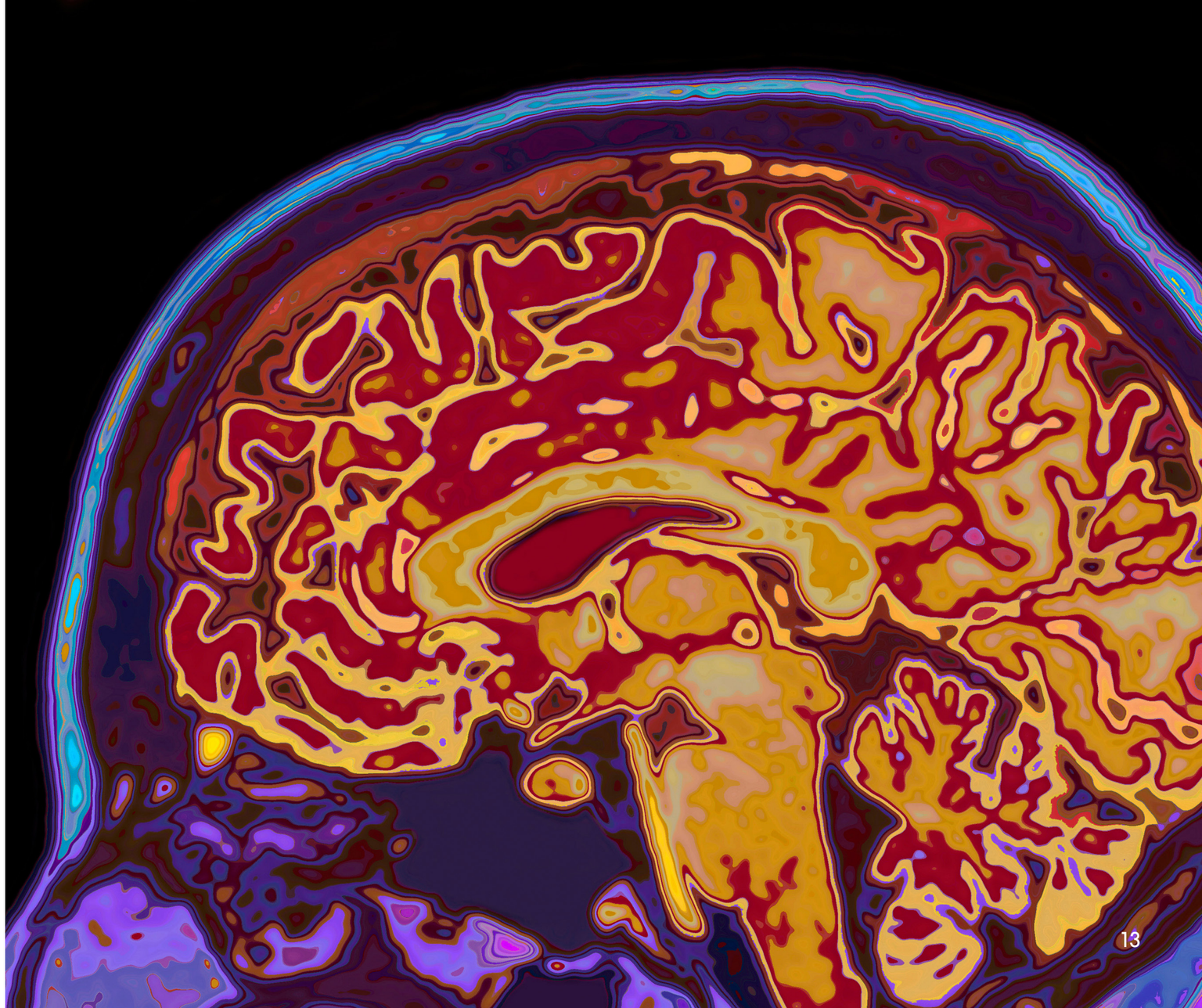
Highlighting that radioactive tracers such as 18F-Fluoride can detect subtle signs of plaque activity that are not visible by other means. Detecting changes in plaque activity could help identify patients at risk of stroke.

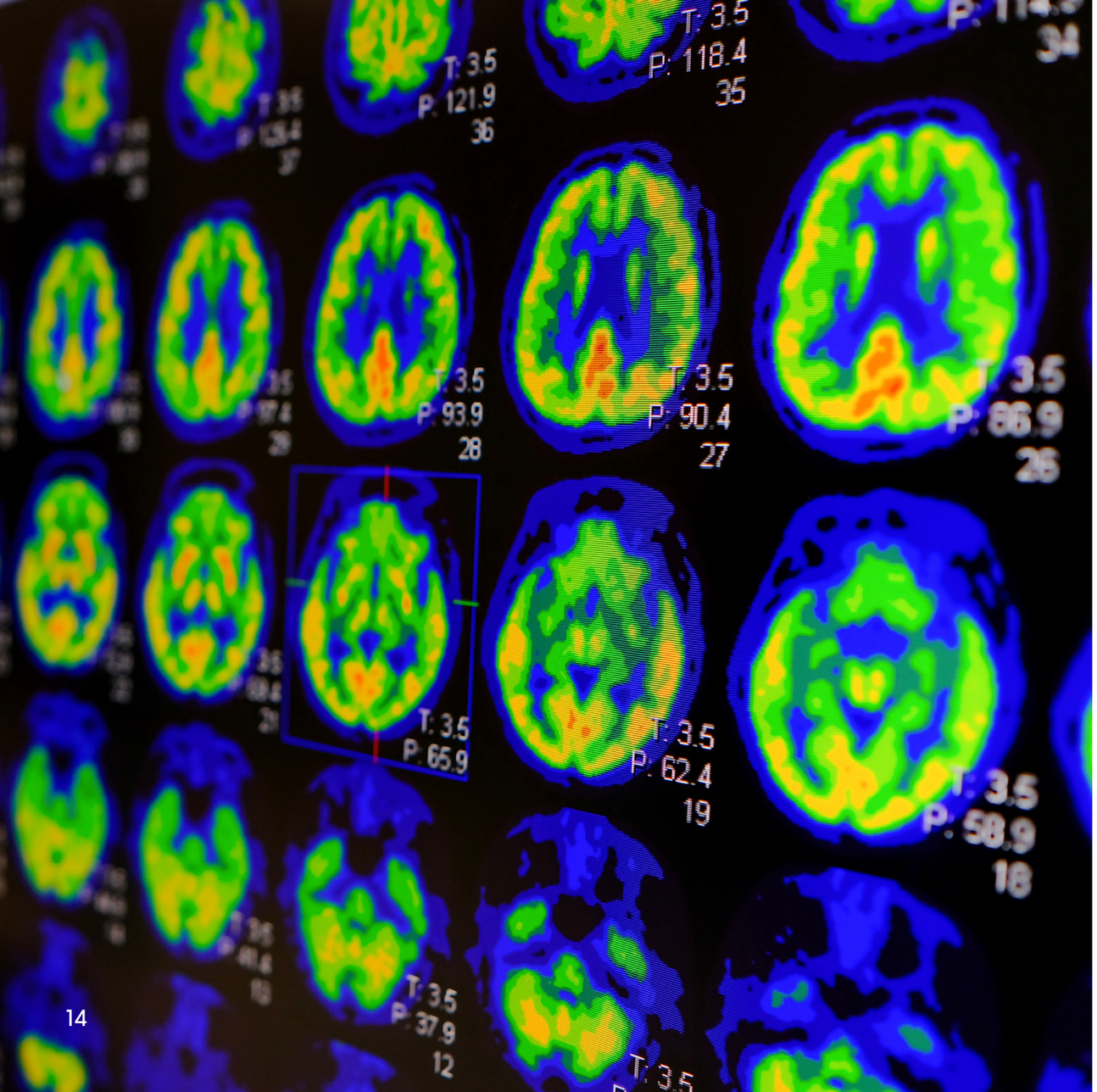
**Computerised Tomography (CT)**

Integrating a new CT imaging technique with artificial intelligence (AI) and deep learning to identify stroke risk.

**Data science and AI**

Assessing the potential benefit of machine learning and statistical approaches to help diagnose and predict the outcome of stroke.








# New scanning techniques to detect dangerous plaques

The most common type of stroke is an ischaemic stroke. An ischaemic stroke occurs when a blood clot blocks the flow of blood and oxygen to the brain. Blood clots typically form in areas where arteries have become narrowed or blocked by fatty deposits, called plaques. If a piece of plaque ruptures, it can cause a blood clot to form and block the blood supply to the brain.

BHF-funded research led by Professor David Newby and colleagues at the University of Edinburgh has been investigating new scanning methods to monitor plaque activity that could lead to a stroke.

The team are using PET scanning - a technique that creates detailed 3D images of the inside of the body. Images are created by detecting the radiation produced by a radiotracer, which is injected into the arm and accumulates in different parts of the body, including the blood vessels.

Their research has shown that specific tracers, such as 18F-Fluoride, can detect subtle signs of changes to plaque activity, which can't be seen by any other scan. This means that plaques that are likely to break apart and cause a stroke can be detected.

It is often difficult for doctors to identify the source of a blood clot or confirm that a blood clot has caused a stroke. The team are now using this new type of PET scan to help solve these issues. This will help improve the accuracy of stroke diagnosis.

# Influencing clinical practice

**In the past 40 years, there have been major advances in the treatment of cerebrovascular disease. The UK has made substantial contributions to the field of stroke that has changed clinical practice worldwide. BHF-funded research is contributing towards building the evidence that could change clinical practice.**

**BHF has already funded research that has:**

- Showed that reducing blood pressure is feasible in patients with cSVD without causing harm to the brain.
- Discovered that two existing drugs show potential to prevent dementia following lacunar stroke.
- Revealed that restarting antiplatelet drugs after a haemorrhagic stroke is safe and might be beneficial.
- Demonstrated that blood pressure lowering drugs are safe to prescribe to patients over 80, and also reduce the risk of having an ischaemic stroke by a third.
- Investigated the effectiveness of a newer clot busting drug called tenecteplase for stroke treatment.

**BHF is currently funding research that is:**

- Testing if a device can help reduce the risk of stroke during a procedure used to treat heart valve disease.
- Understanding the rates of and risk factors for changes in thinking and memory that can happen after a stroke.

# Should antiplatelet medication be restarted after a haemorrhagic stroke?

Antiplatelets drugs, such as aspirin, are used to prevent blood clotting. More than one third of adults who have a brain haemorrhage are taking antiplatelets at the time of their stroke. When someone has a brain haemorrhage, doctors will often stop prescribing antiplatelet drugs immediately to reduce the risk of further bleeding in the brain. However, there has been uncertainty and a lack of evidence surrounding whether antiplatelets should be restarted once patients have recovered.

In 2013, BHF-funded Professor Rustam Al-Shahi Salman and colleagues at the University of Edinburgh led the first multicentre clinical trial that compared restarting and avoiding antiplatelet drugs among survivors of brain haemorrhage.

The trial showed that it seemed safe for people who have had a haemorrhagic stroke to restart taking antiplatelet drugs, without increasing their risk of another brain bleed. In fact, the results suggested that antiplatelets might even reduce the risk of a further brain bleed.

Building on these findings, the team are now leading a larger, international clinical trial called ASPIRING. ASPIRING is one of the first trials to have been endorsed by the GCRFF Multinational Clinical Trials Initiative, which was set up by a group of international research funders (led by BHF) to help researchers carry out important clinical trials across multiple countries.

**4% of patients**

taking antiplatelet medication had another intracerebral haemorrhage, compared with

**9% of patients**

not taking antiplatelet medication.

# Improving patients' lives

**Whilst research into cerebrovascular disease is showing the potential of new treatments, stroke is still the single biggest cause of severe disability in the UK, and around two thirds of stroke survivors will leave hospital with a disability.**

A significant amount of research funded by BHF aims to find treatments for stroke, but preventing strokes is just as important, and BHF-funded researchers have made great strides in this area. In the 1990s and through to the 2000s, BHF-funded landmark clinical trials that helped show that statins, a type of cholesterol-lowering medicine, reduce the risk of stroke. Thanks in part to this research, statins prevent 80,000 heart attacks and strokes every year in the UK.

Between 2015 and 2035 the number of strokes in the UK per year is projected to increase by 60%, and the number of stroke survivors is projected to more than double. BHF-funded research is more important than ever to keep building the knowledge that will help improve the lives of people at risk of or affected by cerebrovascular disease.

The estimated annual long term care cost of stroke in the UK is around
**£2.2 billion**

Statins prevent
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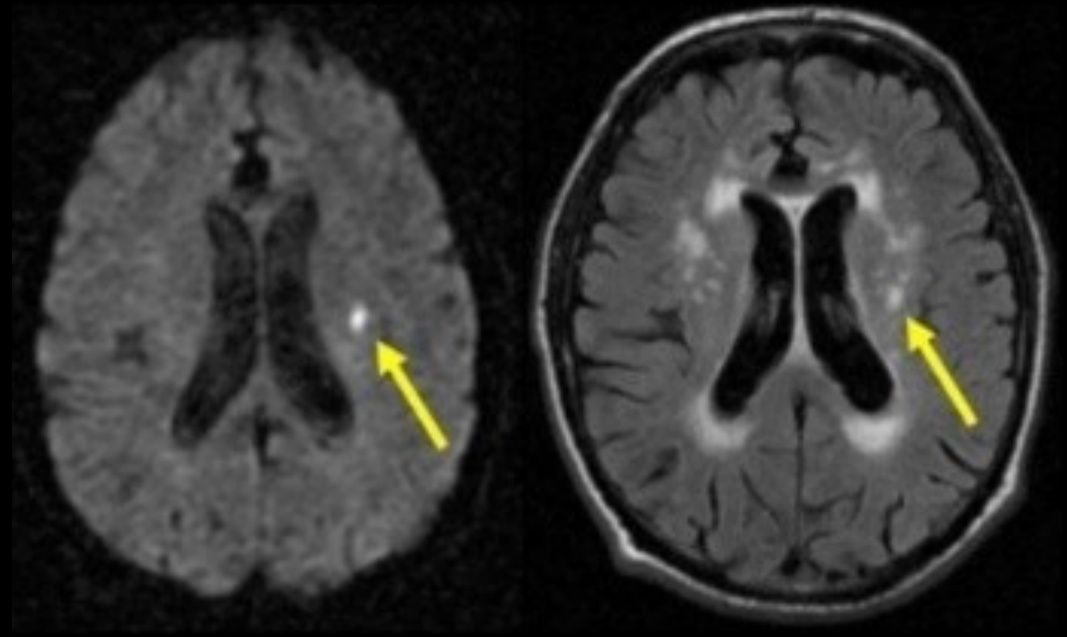


Brain MRI scans with arrows indicating a lacunar stroke.



# Ian's story: The LACI-2 trial

Ian Reynolds, from Edinburgh, suffered a lacunar stroke in 2020.

Ian was among the 363 people who took part in the BHF-funded LACI-2 clinical trial led by Professor Joanna Wardlaw and colleagues at the University of Edinburgh. The trial showed that two existing drugs, isosorbide mononitrate and cilostazol, show potential to improve outcomes and help prevent dementia following lacunar stroke.

"Far too many are living with the after-effects of this type of stroke, so finding a treatment would be fantastic." Ian says.

Ian was part of the group that took cilostazol on its own. Two and a half years after his stroke, he still has numbness and weakness in his left arm and leg. Despite this, he was able to return to work as a driver six months after his stroke.

"I'm determined that this will not stop me living my life" Ian says. "My experience could have been very different, and I realise just how lucky I have been. It looks like the drugs have helped a lot of people, which can only be good news."

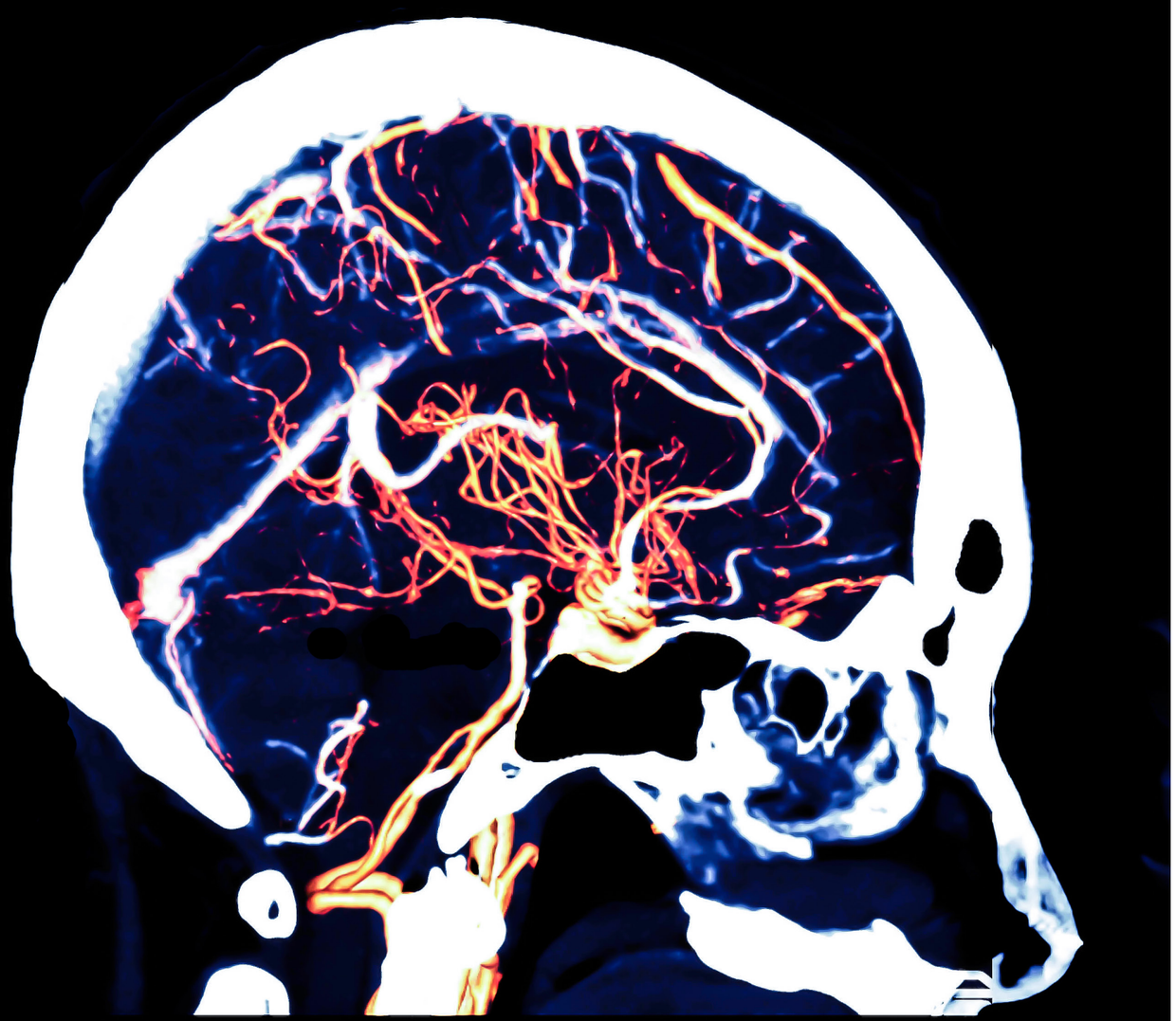
The LACI-2 team are now testing the drugs in a larger four-year trial (LACI-3). They are also hoping to test whether these drugs are effective in treating other conditions linked to cSVD, such as dementia.

# Joining forces

**BHF works with other national and international funders to support innovative cerebrovascular research. Partnerships allow for the joining up of different research communities, increase available funding, and ultimately maximise the impact of research funding efforts.**

In the past 15 years, BHF has partnered with the following organisations to combat cerebrovascular disease:

- Stroke Association
- Alzheimer's Society
- The Alan Turing Institute
- Global Cardiovascular Research Funders Forum
- BHF Data Science Centre
- German Centre for Cardiovascular Research
- Health Data Research UK
- UK Dementia Research Institute
- Dutch Heart Foundation



# Launching the UK's first Centre for Vascular Dementia Research

BHF has partnered with the UK Dementia Research Institute (UK DRI) to establish the UK's first research centre dedicated to finding new treatments to prevent, halt and ultimately cure vascular dementia.

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 experts in the field and unite them under a single virtual 'roof'.

Whilst it's possible to modify risk factors of vascular dementia, such as high blood pressure, there is no cure or treatment that can halt or reverse its progression. The centre will play a pivotal role in tackling this condition.

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. Scientists at the institute are studying all areas of dementia, focusing on understanding the underlying causes of the disease, including how problems with the brain's circulation can lead to neurodegeneration.

The unique combination of over 60 years of BHF-funded 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.

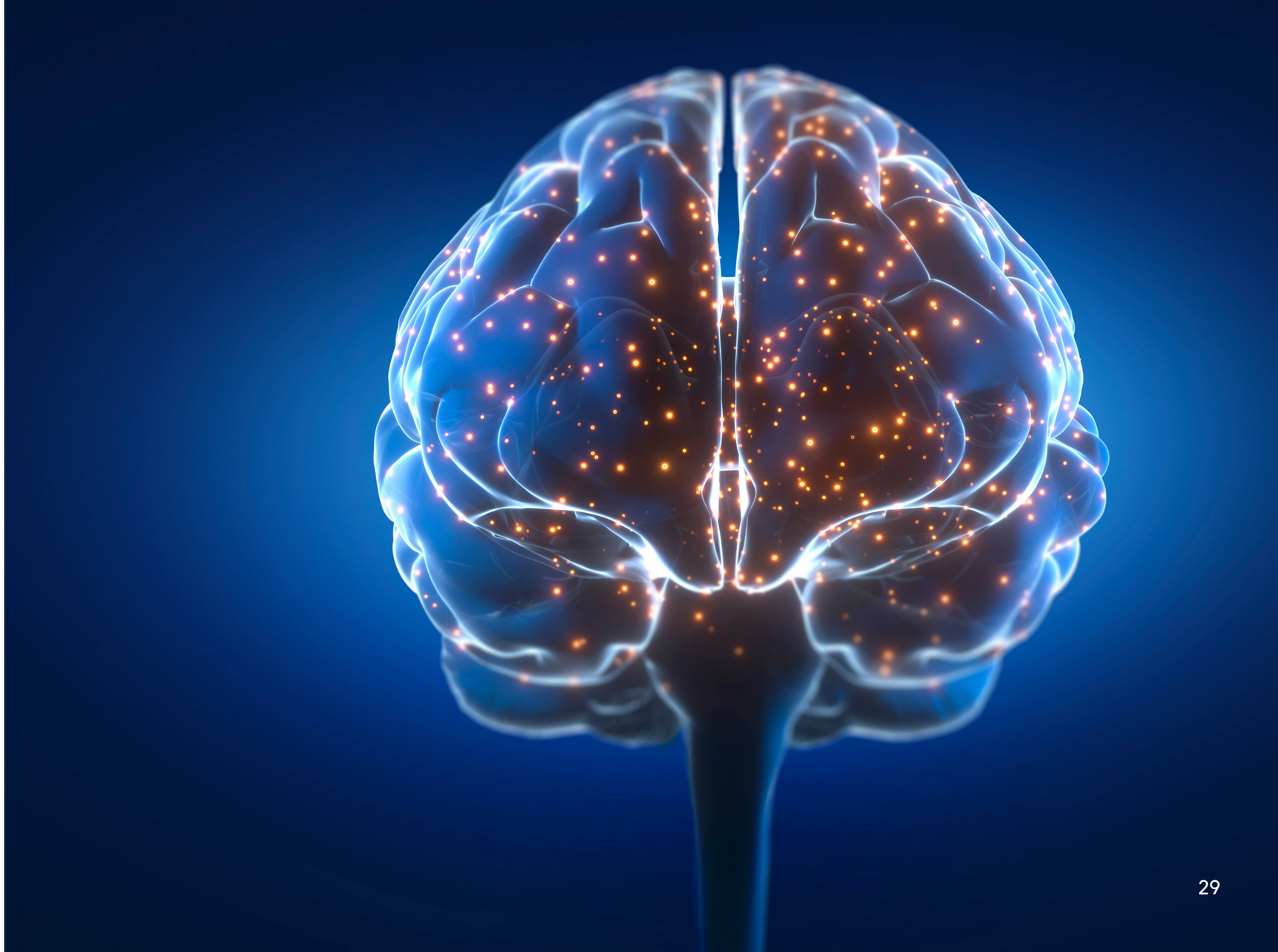
# Looking to the future

When BHF was founded in 1961, there was little understanding of cerebrovascular disease and no effective treatments. Since then, BHF has grown to become one of the largest independent funders of stroke research in the UK.

BHF has played a leading role in increasing knowledge about cerebrovascular disease and identifying ways to prevent it. BHF-funded research is helping to identify promising therapeutic avenues to treat these devastating conditions.

Looking ahead, it's important to have a better understanding of factors that can be modified to optimise prevention of stroke and vascular dementia. These include genetic factors, early life influences, lifestyle factors and environmental exposures. This will require a range of different approaches like studying health data, using advanced imaging technologies and exploring genetics.

**For references, supplementary information and more on the impact of BHF-funded research into cardiovascular surgery please visit bhf.org.uk/impactofstroke**



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