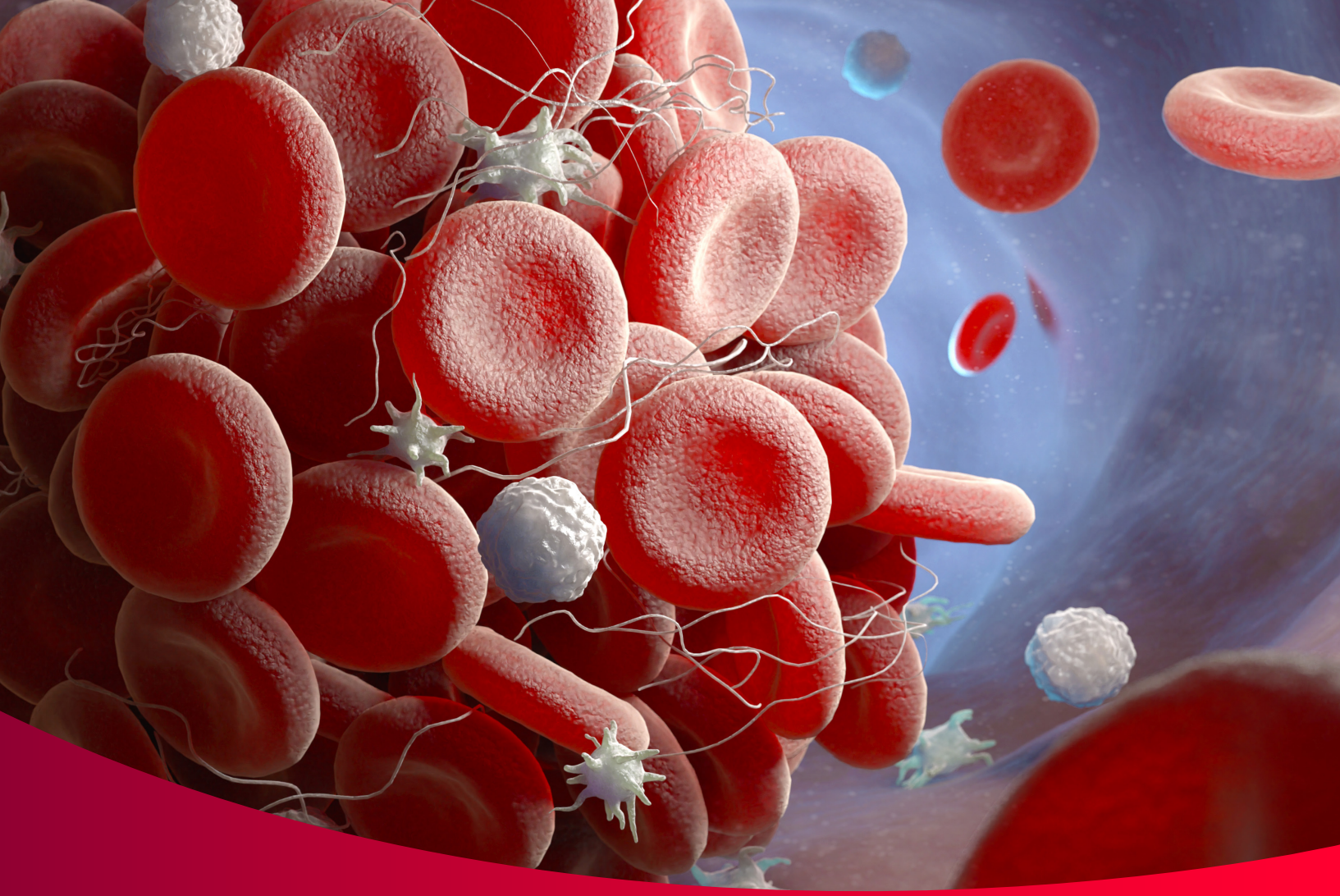

Sticking together

Impact of British Heart Foundation support for haemostasis and thrombosis research

Impact Thematic Review Series | Volume 3 | January 2023

British Heart Foundation

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This review was led by Steve Watson, BHF Professor in Cardiovascular Sciences and Cellular Pharmacology, University of Birmingham; Robert Ariëns, Professor of Vascular Biology, University of Leeds; and Rob Storey, Professor of Cardiology, University of Sheffield.

Message from our Medical Director

At British Heart Foundation (BHF), we fund research to save and improve the lives of the millions of people living with or at risk of heart and circulatory diseases, in the UK and worldwide. We focus our efforts on supporting underpinning research and turning discoveries into lifesaving medical advances.

Working with research leaders, we are producing a series of compelling reviews that articulate the impact arising from the support of BHF in specific fields of research, in each case assessing impact all the way from generation of new knowledge to improving patients' lives.

The following pages illustrate the lasting impact of our research funding on thrombosis and haemostasis – the processes underpinning the development of blood clots - which play such a crucial role in many heart and circulatory diseases including heart attacks and strokes.

None of these achievements could have been realised without the generosity and dedication of our supporters, and the passion and perseverance of our researchers. I hope they inspire you as much as they inspire me.

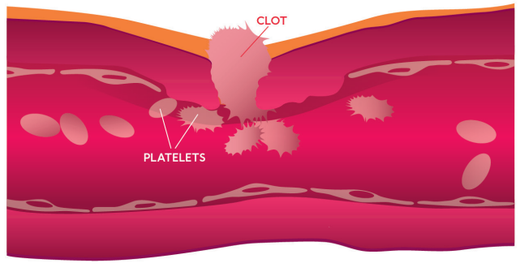
Professor Sir Nilesh Samani,
Medical Director, British Heart Foundation

What are haemostasis and thrombosis?

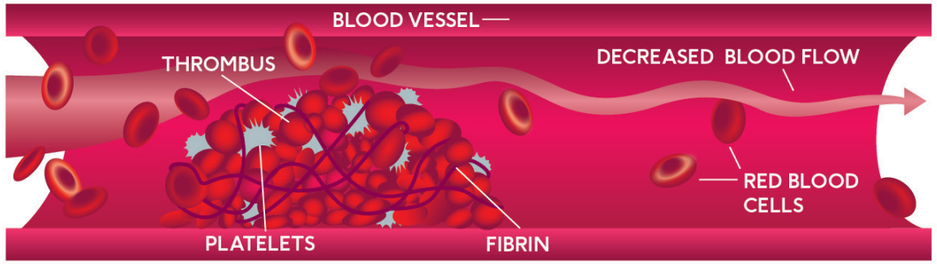
Haemostasis is the body's natural response to injury which stops bleeding from damaged blood vessels by forming a blood clot. Small cells in the blood, called platelets, are activated to clump together at the injury site and form a plug. At the same time, the process of blood clotting is triggered, strengthening the plug with a mesh of filaments of a protein called fibrin. Red blood cells are also trapped in the clot.

Blood clots protect us from excessive bleeding, but abnormal blood clotting can cause many health problems. Sometimes clots form where they shouldn't, some people form clots too easily, and in others the clots don't break down like they should as the injury heals.

When a blood clot blocks a vein or an artery, the clot is called a thrombus and the process is known as thrombosis. A thrombus that forms in an artery, particularly one of the arteries supplying the heart or the brain, is dangerous and can cause a heart attack or a stroke. Blood clots in the veins can break off and travel to the lungs, causing pulmonary embolism, another serious condition.



Haemostasis



Thrombosis

The prevention and treatment of blood clots involves several different types of treatments that aim to prevent and break down dangerous blood clots.

Some definitions

Antithrombotic drug

A drug that reduces the formation of blood clots. The two types of antithrombotic drugs are anticoagulants and antiplatelet drugs.

Anticoagulant

A drug that slows down blood coagulation, preventing clots from forming and growing, often referred to as a blood thinner. An example would be warfarin.

Antiplatelet drug

A drug that stops platelets from sticking together. Aspirin, which has been used to relieve pain for more than 100 years, was first used to help patients with heart disease over 75 years ago and in 1970 was shown to work by blocking platelet activation.

Fibrinolytic drug

Also known as thrombolytics, clot-busting drugs are used to break up or dissolve blood clots.

Our support for haemostasis and thrombosis research

BHF has supported research into platelet biology, haemostasis and thrombosis since it was founded in 1961. Over the last 60 years, there have been many remarkable advances in the prevention and treatment of thrombosis. Important changes over this period include the recognition of smoking as a major cause of heart disease, advances in surgical procedures, and the introduction of drugs such as antiplatelets and anticoagulants.

This is due to the many advances that have come from research into the mechanisms of thrombosis and both its prevention and treatment.

1000 grants worth more than £150M

Supporting the training of >130 PhD students and the career development of >90 fellows.

Generating new knowledge

Over the last 60 years, our understanding of platelet biology and the mechanisms underlying clotting has increased dramatically, thanks in part to BHF-funded research. BHF has funded ground-breaking discoveries, including:

- Discovering that most heart attacks are caused by thrombosis occurring in a coronary artery.
- Identifying platelet surface proteins (called receptors) responsible for platelet clumping and formation of blood clots. Drugs that block one of these receptors are now used worldwide to prevent thrombosis occurring in patients undergoing percutaneous coronary intervention (PCI) to open up blocked arteries.
- Supporting large-scale genetic screening in patients with inherited blood disorders to identify genes involved in haemostasis, some of which are targets for the development of new antithrombotic drugs.
- Understanding the mechanisms of thrombo-inflammation, a key process in the development of heart and circulatory diseases.
- Establishing the molecular mechanisms by which warfarin, a commonly prescribed blood-thinner, inhibits clotting.
- Developing a prototype that led to the development of the antiplatelet drug cangrelor.

Developing new and improved antiplatelet drugs

Antiplatelet drugs are commonly used to reduce the risk of heart attack. They work by preventing blood cells from sticking together and forming a blood clot. During clot formation, activated platelets release molecules that further stimulate the activation of more platelets. This leads to more platelets sticking together. The antiplatelet aspirin works by inhibiting one of these activating molecules, called thromboxane A_2.

In the late 1990s, a new drug was developed, called clopidogrel, which inhibits platelet activation by blocking a platelet receptor called $P2Y_{12}$. However, clopidogrel is not an ideal antiplatelet as it is irreversible – its effects cannot be stopped, except by transfusing platelets. Clopidogrel can lead to excessive bleeding, which is a concern in patients who need to undergo surgery.

In the early 1980s, BHF supported the work of Dr Noel Cusack, who developed a series of new molecules targeting $P2Y_{12}$ to create a reversible inhibitor of platelet activation.

The antiplatelet drug ticagrelor is now used worldwide

The prototype from these studies led directly to the development by AstraZeneca of cangrelor, a reversible antiplatelet delivered by infusion, which entered the clinic in 2015 and is mainly used in patients undergoing coronary stenting or bypass surgery. This work also catalysed a discovery programme that led to the development of the first oral reversible inhibitor of the $P2Y_{12}$ receptor, ticagrelor, which entered the clinic in 2010. In combination with aspirin, ticagrelor is now used worldwide as a daily pill to prevent future heart attack or stroke in patients who have already suffered from either.

Developing new technology

BHF-funded research has supported the development of methods and technology that have helped researchers and clinicians around the world to understand the biological mechanisms of haemostasis and thrombosis and develop novel treatments, including:

- Developing a high throughput screening study for use in the NHS to identify genetic mutations in patients with bleeding disorders.
- Application of fluorescent-based imaging techniques used to monitor clot formation in real time.
- Generation of platelets in vitro from stem cells. It is anticipated that with further technical development this will be used to produce a large-scale supply of platelets for transfusion into patients at high risk of bleeding.
- Developing novel anticoagulants that minimise the risk of excessive bleeding.

Reducing the risk of excessive bleeding

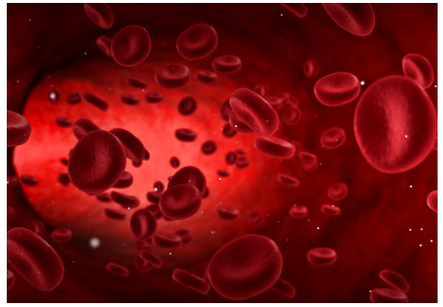
People who are diagnosed with heart and circulatory diseases receive multiple drugs to prevent them from developing blood clots and reduce the risk of thrombotic events such as heart attacks and strokes. However, it can be difficult to balance the benefits of preventing clots with the potentially dangerous side effects of these drugs, which include excessive bleeding.

Professor Helen Philippou and Dr Richard Foster from the University of Leeds have identified a new way to stop blood from clotting that has less risk of causing bleeding.

With funding from British Heart Foundation, the team have focussed on the inhibition of activated Factor XII, a clotting factor that plays a role in thrombosis, but not in the stemming of bleeding (haemostasis). Individuals who lack Factor XII do not exhibit any abnormal bleeding.

This work has led to the creation of the spin-out company LUNAC Therapeutics, which is developing drug candidates targeting activated Factor XII.

The best of these has the potential to become the first-in-class, next generation anticoagulant that can eliminate the risk of increased bleeding, improving the management of thrombosis.



Flow of red blood cells in an artery

Influencing clinical practice

An increase in understanding about how and why the body creates and degrades blood clots leads to new clues on how to treat pathological clots. BHF-funded research has contributed to changing how we treat and manage thrombosis today by:

- Demonstrating the efficacy of clot-busting drugs to treat heart attacks.
- Contributing to the development of new anticoagulants, now known as direct oral anticoagulants (DOACs).
- Supporting clinical trials evaluating the safety and efficacy of clot-busting drugs alteplase and tenecteplase in patients who have recently suffered a stroke.
- Supporting a clinical trial which found that taking antiplatelets after a brain haemorrhage is safe.
- Supporting the Antithrombotic Treatment Trialists' Collaboration (ATTC) which led to internationally adopted clinical guidelines for the use of aspirin.

Clinical trial collaboration reveals benefits of aspirin

Supported by British Heart Foundation, the ATT Collaboration was set up in the 1990s to conduct worldwide meta-analyses of randomised trials of antithrombotic therapy, drugs that reduce the formation of blood clots. The objective was to provide reliable information about the benefits and risks of these drugs in different groups of patients.

The ATT Collaboration found that long-term antiplatelet therapy, for example with aspirin, reduces the yearly risk of serious heart problems by a quarter in patients who have suffered heart and circulatory problems such as a stroke or heart attack. However, any benefit of the use of aspirin to prevent heart attacks or strokes in people who don't have evidence of cardiovascular disease is likely outweighed by the increased risk of excessive bleeding.

These findings have changed international clinical guideline recommendations for the use of aspirin in people at risk of a heart attack or stroke.

The 2002 ATT Collaboration meta-analysis reviewed 287 studies involving 212,000 patients

Influencing Policy

Over the last 60 years, BHF has helped raise awareness of certain conditions, behaviours and unhealthy environments that increase the likelihood of developing heart and circulatory diseases. BHF-funded research has shown that smoking and air pollution affect how our blood works, which has led to changes in policy. Some examples include:

Highlighting that smoking cigarettes causes the build-up of fatty material and plaque formation leading to thrombosis and blockage of major blood vessels in the heart and brain. In the early 2000s, BHF played a major role in anti-smoking campaigns and in driving government policy that led to an increased recognition of the dangers of smoking, changes in advertising and bans on smoking in indoor public places across the four nations of the UK.

Highlighting air pollution as a critical health issue in cardiovascular disease and a target for global health policy. BHF-funded researchers were among the first to show how exposure to air pollution damages the heart and blood vessels by encouraging blood to clot, leading to thrombosis.

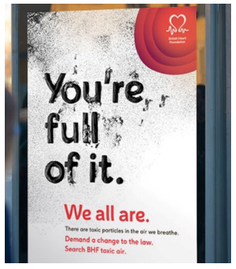
Protecting our health from air pollution

Air pollution takes an estimated six months off the average life expectancy in the UK and is associated with up to 11,000 heart and circulatory deaths every year.

In 2005, BHF funded Professor David Newby and his team at the University of Edinburgh to investigate the effects of air pollution from diesel vehicles on the heart and blood vessels. The team found that breathing in diesel fumes at the level of polluted cities stops blood vessels relaxing and encourages blood to clot.

Newby and colleagues have written influential reviews in this area, including systematic reviews on the link between air pollution and stroke, air pollution and heart failure, as well as an expert position paper of the European Society of Cardiology.

BHF has highlighted these findings to Government to ensure a better understanding of the link between exposure to PM2.5 (small particles particularly prevalent in diesel fumes) and poor heart and circulatory health. In 2020 we launched a campaign called ‘We’re full of it’ calling for the World Health Organization’s (WHO) guideline limits for PM2.5, which are stricter than our current limits. There has been good progress with Government introducing new, tighter limits, but BHF will continue to call for adoption of the WHO’s health-based guidelines as soon as possible.



BHF ‘We’re full of it’ campaign 2020

Improving people's lives

It is estimated that 1 in 4 deaths worldwide are linked to blood clots. When a blood clot forms in an artery or vein it can lead to heart attack, stroke, or a pulmonary embolism. It is therefore vital that we discover ways to prevent dangerous blood clots from forming and find treatments to combat clots.

BHF-funded research has contributed to the development of new prevention strategies and treatments to improve the outcomes of patients with or at risk of dangerous blood clots. Some examples include:

- Driving an increase in survival after a heart attack thanks to the use of clot busting drugs in the 1960s. ISIS 2 and other trials suggested that for every 1,000 patients with a heart attack, rapid administration of a clot-buster would save an average of 29 lives.
- Investigating new target treatments for Deep Vein Thrombosis (DVT) that have less side effects.
- Preventing heart attack and stroke in high-risk patients. Aspirin reduces the yearly risk of heart problems by a quarter in those who have previously suffered heart and circulatory problems.
- Reducing the thrombotic risks of passive smoking by driving the implementation of smoking bans. Research in Scotland showed that one year after their smoking ban came into force, hospital admissions for heart attacks decreased by 17% in nine hospitals. Additionally, exposure to second-hand smoke was reduced by almost 40%.

In 2020/21, 98% of people who were discharged from hospital following a heart attack in England, Wales and Northern Ireland were prescribed aspirin.

Proving the benefits of clot-busting drugs

Clinical trials of clot-busting drugs have had a profound impact on the survival chances of patients presenting to hospital with thrombotic conditions such as heart attack, stroke and pulmonary embolism. Patients presenting with these conditions can now expect better prognosis due to huge research efforts.

BHF supported the pivotal ISIS-2 study, the first large scale trial of clot-busting drugs in thousands of heart attack patients, led by BHF Professor Peter Sleight and Dr Rory Collins (now BHF Professor Sir Rory Collins). The trial assessed the impact of the clot-busting drug streptokinase alone as well as in combination with the antiplatelet aspirin in patients presenting to hospital with a major heart attack.

The study found that giving streptokinase and aspirin together decreased deaths after a heart attack by around 40%. The trial also found that the earlier this combination of medicines was given after a heart attack, the better outcome for the patient. This remarkable outcome helped to kickstart a revolution in heart attack treatment in the 1990s and transformed survival rates.

In 1987, only 2% of doctors said that they routinely used clot-busting therapy for most heart attack patients. But by 1989, 68% had switched to routine administration of the drugs. Thanks to the spirit of these pioneers of medical research, and with support from BHF, a revolution in emergency cardiac treatment was under way.

Although the use of clot-busting drugs during a heart attack has widely been superseded by the more recent development of angioplasty, they are still important for the emergency treatment of stroke. In addition, ISIS-2 provided the evidence for use of aspirin in the acute management of a heart attack, a practice that is now global.

Looking to the future

BHF-funded research has helped to improve our understanding of the mechanisms which lead to blood clotting and has paved the way for the development of new treatments to combat thrombosis.

Research into haemostasis and thrombosis remains a highly active field and there are many challenges ready to be tackled. These include understanding the role of platelets in inflammation, discovering mechanisms of thrombosis related to Covid-19 and other infections, identifying further novel targets for safe anticoagulation, and more. We confidently expect that new ground-breaking science and technical advances, building on previous BHF-funded research, will lead to further success in the prevention and treatment of thrombosis.

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

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bhf.org.uk